Biomech Model Mechanobiol (2012) 11:291–302
DOI 10.1007/s10237-011-0317-z

REVIEW

Multiscale modeling and mechanics of filamentous actin cytoskeleton

Hidetaka Yamaoka · Shinji Matsushita · Yoshitaka Shimada · Taiji Adachi

Received: 9 November 2010 / Accepted: 8 May 2011 / Published online: 26 May 2011

Abstract The adaptive structure and functional changes of the actin cytoskeleton are induced by its mechanical behavior at various temporal and spatial scales. In particular, the mechanical behaviors at different scales play important roles in the mechanical functions of various cells, and these multiscale phenomena require clarification. To establish a milestone toward achieving multiscale modeling and simulation, this paper reviews mathematical analyses and simulation methods applied to the mechanics of the filamentous actin cytoskeleton. The actin cytoskeleton demonstrates characteristic behaviors at every temporal and spatial scale, and mathematical models and simulation methods can be applied to each level of actin cytoskeletal structure ranging from the molecular to the network level. This paper considers studies on mathematical models and simulation methods based on the molecular dynamics, coarse-graining, and continuum dynamics approaches. Every temporal and spatial scale of actin cytoskeletal structure is considered, and it is expected that discrete and continuum dynamics ranging from functional expression at the molecular level to macroscopic functional expression at the whole cell level will be developed and applied to multiscale modeling and simulation.

Keywords Actin filament · Multiscale modeling and simulation · Coarse-grained modeling · Computational biomechanics · Molecular dynamics · Continuum dynamics · Mechanobiology · Biomechanics

H. Yamaoka · S. Matsushita · Y. Shimada · T. Adachi
Computational Cell Biomechanics Team, VCAD System Research Program, RIKEN, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan

H. Yamaoka · S. Matsushita · T. Adachi
Department of Biomechanics, Institute for Frontier Medical Sciences, Kyoto University, 53 Kawahara-cho, Shogoin, Sakyo, Kyoto 606-8507, Japan

S. Matsushita · T. Adachi (✉)
Department of Micro Engineering, Graduate School of Engineering, Kyoto University, Sakyo, Kyoto 606-8501, Japan
e-mail: adachi@frontier.kyoto-u.ac.jp

Y. Shimada
Department of Mechanical Engineering and Science, Graduate School of Engineering, Kyoto University, Yoshida-honmachi, Sakyo, Kyoto 606-8501, Japan

1 Introduction

The adaptive structure and functional changes of the actin cytoskeleton play important roles in the mechanical functions of various cells and are usually understood to be the results of complicated interactions at the molecular level. Biochemical factors—protein molecules that build structural systems and related signal molecules—form multiscale temporal and spatial fields, which are also mutually related to mechanical factors. As an example of such multiscale behavior, we focus on the actin cytoskeleton, which plays a significant role in alterations of cell morphology and cell movement.

For instance, cell migration, which is driven by the dynamics of the actin cytoskeleton, occurs through the repetition of multiple biochemical processes, each of which starts with the protrusion of the cell front in the direction moved (cell protrusion), effected by growing actin filament structures (Lauffenburger and Horwitz 1996; Mitchison and Cramer 1996; Goldberg 2001). Depending on their shapes, these protrusions are called filopodia or lamellipodia. The filopodia are long, thin projections containing parallel actin filaments cross-linked into bundles, while lamellipodia contain a

two-dimensional actin mesh. Actin polymerization, the process responsible for the formation of these filopodia and lamellipodia, plays a key role in the generation of the protrusive force for cell migration, and its mechanism has been elucidated in various experiments (Pollard and Borisy 2003; Pollard et al. 2000; Schmidt and Hall 1998), and various numerical models were proposed and simulated (for details, see Pollard and Berro 2009 and references therein).

The actin cytoskeleton not only has a biochemical function as a protein but also functions as a structural material supporting the intracellular membrane from the inside and as a mechanosensor that can sense the surrounding dynamic environment (Wang et al. 2001; Riveline et al. 2001; Geiger and Bershadsky 2001; Hayakawa et al. 2008). To clarify the dynamic characteristics of cells and their adaptability to their physical surroundings, various experiments have been carried out to evaluate the tensile rigidity of actin filaments, which is one of their basic mechanical properties (Gittes et al. 1993; Kojima et al. 1994; Tsuda et al. 1996).

As shown in Fig. 1, the mechanical behavior of the actin cytoskeleton has been observed at various temporal and spatial scales. For example, the atomic structure of the actin molecule changes every picosecond (Suda and Saito 1994; Matsushita et al. 2010a,b), while actin molecules at the nanometer scale can undergo repeated polymerization, depolymerization, and severing at intervals of a millisecond and several seconds; this explains how actin filaments can dynamically change their structure from the nanometer to the micrometer scales (Pollard and Cooper 1986). In addition, the actin cytoskeleton can also form actin networks at the micrometer scale by branching or bundling (Winder and Ayscough 2005; Nemethova et al. 2008), thus supporting cells by acting as a structural material (Wang et al. 2001) and powering cell movement as an element of the mechanism generating driving force (Theriot and Mitchson 1991; Zigmond 1993; Lee et al. 1994; Mogilner and Oster 1996; Inoue and Adachi 2011). Thus, the actin cytoskeleton demonstrates characteristic behaviors at every temporal and spatial scale.

In this article, we review mathematical models and simulation methods applied to each level of actin cytoskeletal structure ranging from the molecular level to the network level, and also discuss future possibilities of the models, especially the multiscale modeling. In fact, MD simulations of proteins have been attempted to apply elastic models of their filaments and networks (Park et al. 2006; Lyman et al. 2008). Such multiscale modeling is often based on concept of coarse-graining method, and schemes for multiscale modeling of biomolecular systems are categorized into serial and parallel approaches in Ayton et al. (2007). Here, we focus on molecular dynamics, coarse-grained, and continuum dynamics modeling and simulations for actin filaments and networks.

2 Molecular level: actin monomers to filaments

2.1 Molecular dynamics approach

Ever since the MD method has been proposed by Alder and Wainwright (1957), the scope of its application has spread with the availability of advanced computer systems, from simple particle systems in which the molecular populations are also spherically symmetric to systems with even more complex structures, such as ions, water, and polymers. The first ever MD simulation of proteins was performed by McCammon et al. in (1977); today this method is applied to the analysis of a range of biomolecules, such as proteins, nucleic acids, and lipid bilayer membranes, and they help to clarify the structures and functions of various atom groups.

In 1990, Holmes et al. succeeded in clarifying the molecular structure of actin filaments by the X-ray crystallographic analysis of oriented F-actin gels (Holmes et al. 1990). Later, many other molecular structures of actin filaments were successfully analyzed, such as actin molecules with ATP, ADP, and actin-binding proteins (Narita and Maeda 2007; Oda et al. 2009) allowing analysis of molecular dynamics, taking into account various states such as the surrounding solvent and the addition of dynamic forces (Pfaendtner et al. 2009).

As shown in Fig. 2, actin filaments have a double-helix structure consisting of twin strands of a monomeric protein called G-actin (globular actin). Within the cytoplasm, the constituent atoms in the actin filaments fluctuate thermally, and as a result, the molecular structure of the actin filaments changes at various temporal and spatial scales, from the molecular scale, such as a change of amino acid residue, to the filamentous scale, such as a change in the double-helix structure. This dynamic behavior of the molecular structure is the source of the diverse functions of actin molecules. Thus, detailed observation of changes in the molecular structure of actin is the key to clarifying the functions of actin cytoskeleton.

In addition, it is also desirable to understand the microscopic behavior of actin molecules at the atomic level, and one means of doing this is using the molecular dynamics (MD) method. This method, which uses atoms as the minimum unit, allows observation of molecular behavior with femtosecond (10^{-15} s) time resolution and angstrom (10^{-10} m) spatial resolution, as shown in Fig. 1a, b. An MD method with such high resolution is useful for the close observation of the detailed behavior of actin molecules.

2.2 Application to actin monomers

This section introduces the analysis of actin monomers, which form actin filaments, based on MD. As shown in Fig. 2b, the actin monomer consists of four sub-domains, with clefts between sub-domains 1 and 3, and between

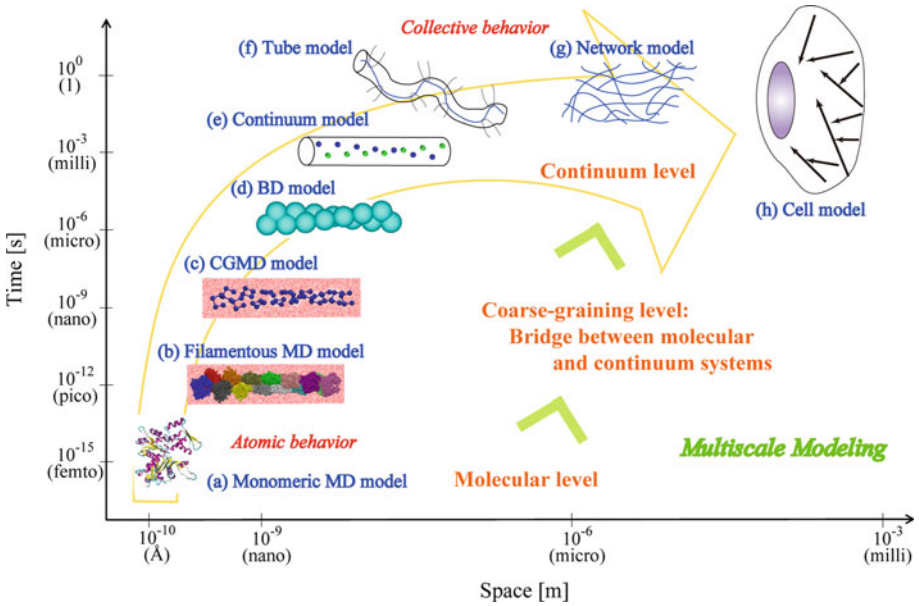

Fig. 1 Various temporal and spatial scales of actin filament structures. Molecular dynamics approach (**a**, **b**) is applied to the investigation of mechanical behaviors at the atomic scale, while continuum dynamics approach (**e**, **f**, **g**) is done to investigate the collective behaviors of filaments. Many coarse-grained approaches (**c**, **d**) are proposed as techniques bridging between molecular and continuum systems

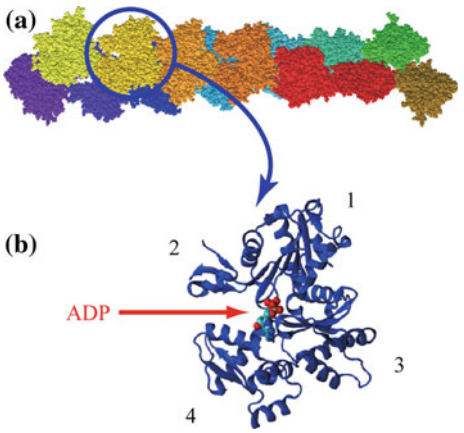

Fig. 2 The molecular structure of actin filaments. **a** Double-helix structure of a half-pitch of actin filament consisting of 14 actin monomers. The total protein size is 80,836 atoms. **b** Single monomer of nucleotides (ADP/ATP) binding to the cleft between its sub-domains

sub-domains 2 and 4. Furthermore, at the deepest part of the clefts, nucleotides (ATP or ADP) bind to the surrounding amino acid residues by hydrogen bonding or ion binding. This nucleotide binding is considered an important factor in the reconstruction of the actin cytoskeleton, because without it actin molecules degenerate rapidly, changing the molecular structure (Dalhaimer and Pollard 2008). Various studies have been conducted to elucidate the structure and activities of actin molecules affected by nucleotide binding (Wriggers and Schulten 1997; Oda et al. 2009). Since nucleotide binding changes the structure of actin molecules, phenomena occurring at the atomic scale should ideally be analyzed, which is why MD has been applied to the analysis of microscopic structural changes and atomic interactions.

In the analysis of the structure and functions of biomolecules, it is also important to consider mechanical factors, such as tensile and shear forces, because these induce structural changes to regulate protein functions. Schulten and coworkers proposed the steered molecular dynamics (SMD) method (Israelewitz et al. 2001) as a means of applying an external force locally. The advantages of the SMD method include the ability to forcibly induce changes in the molecular structure by the direct control of atoms and molecules, and the ability to simulate the experimental conditions of material testing. Today, it is used extensively to analyze the dynamics of static binding and disassociation of biomolecules and their elastic characteristics (Lu et al. 1998; Vogel and Sheetz 2006).

Wriggers and Schulten (1999) employed SMD to investigate the behavior of actin phosphate. They applied tensile force in one direction to the phosphate in the ATP (Fig. 3) and measured the force at which phosphate is released from the actin. They found that the amino acid residue His73 in actin forms a salt bridge with HPO_4^{2-}, which blocks the release of P_i from inside the actin.

2.3 Application of MD method to actin filaments

The MD method is useful for investigating changes in the structure of actin monomers. Modern computer systems allow the MD method to be applied even to gigantic groups such as actin filaments. The contributions of actin filaments to the mechanical strength of the cytoskeleton in functions such as maintaining cell shape, generating the driving force to power cell motility, and inducing changes in cell shape, such as those that occur during cell division, are related to mechanical deformations such as pulling, bending, and twisting. This

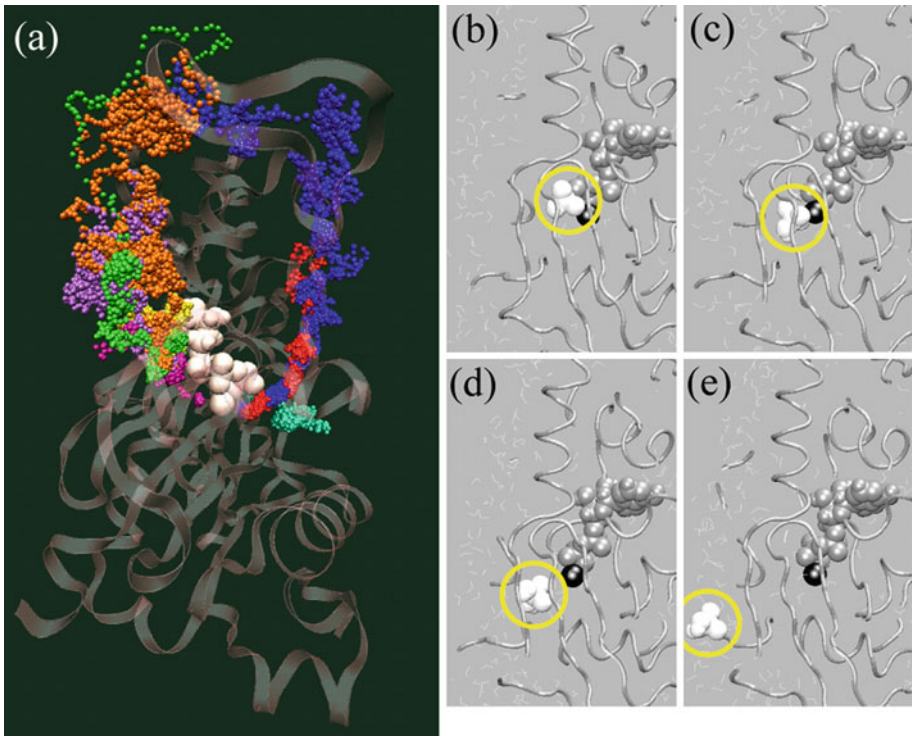

Fig. 3 Actin monomers visualized by MD simulations. **a** Actin monomer with ADP (represented by white van der Waals spheres). **b–d** Release of phosphate from ATP. Tensile force is exerted on the phosphate. The figures are modified from Wriggers and Schulten (1997) (Copyright 1997 Biophysical Society) and Wriggers and Schulten (1999) (Copyright 1999 Wiley-Liss, Inc.)

section introduces a study evaluating the stiffness of actin filaments to such mechanical deformation using MD simulation (Matsushita et al. 2010a).

To reconstruct actin filaments in the same conditions as those occurring within the cell, Matsushita et al. (2010a) arranged water molecules with Na and Cl ions in the vicinity of the molecular structure of the actin filament created from the Protein Data Bank (PDB code: 1MVW) (Holmes et al. 1990; Chen et al. 2002), and carried out equilibrium simulation of the structure. They then analyzed the thermal fluctuations of actin filaments in the thermal equilibrium state and evaluated tensile and torsional stiffness per unit length of the actin filament (Fig. 4). Their results showed that both tensile and torsional stiffness depend on the analyzed duration Δt evaluated on the basis of MD simulation, and that the tensile and torsional stiffness of actin filaments over small time scales are greater than the values determined in experiments. With increasing analyzed duration Δt, however, the stiffness evaluated on the nanosecond scale gradually decreases and exhibits a trend to converge to a value that is close to the experimental value. Hence, evaluations of stiffness by MD can be used to calculate stiffness appropriate for the time scales of intracellular activities.

Matsushita et al. (2010b) also tracked changes in torsion over time of actin filaments and observed how the torsion angle decreased with the application of tensile force. This decrease in the torsion angle is considered to be due to the existence of coupling between the motions of elongation and twisting (Yamaoka and Adachi 2010a) because of the geometric shape of the right-handed double-helix structure of actin filaments. Such analysis of the mechanical behavior of actin filaments should deepen our understanding of their biochemical characteristics. In fact, there are increasing numbers of experimental reports of associations between the mechanical behavior and biochemical characteristics of actin filaments (Tsuda et al. 1996).

Furthermore, the results by MD simulations including positions of atoms building proteins and evaluated stiffness of proteins are directly applied to elastic network model of proteins (Cascella et al. 2008). In Bathe (2008), MD data are used to define the protein volume, effective mass density, and boundary conditions. Additionally, the mechanical properties of actin filament rearranged by MD simulation were investigated based on the normal mode analysis (Deriu et al. 2011). In contrast, the knowledge from MD was often applied to various coarse-grained models for a large amount of calculation. The idea and technique of the coarse-graining approach are discussed in the next section.

3 Coarse-grained level: bridge between molecular and continuum systems

3.1 Coarse-graining approach

The branching and bundling of actin filaments to form higher-order structure is affected by the processes of molecular diffusion, polymerization, depolymerization, and severing, which

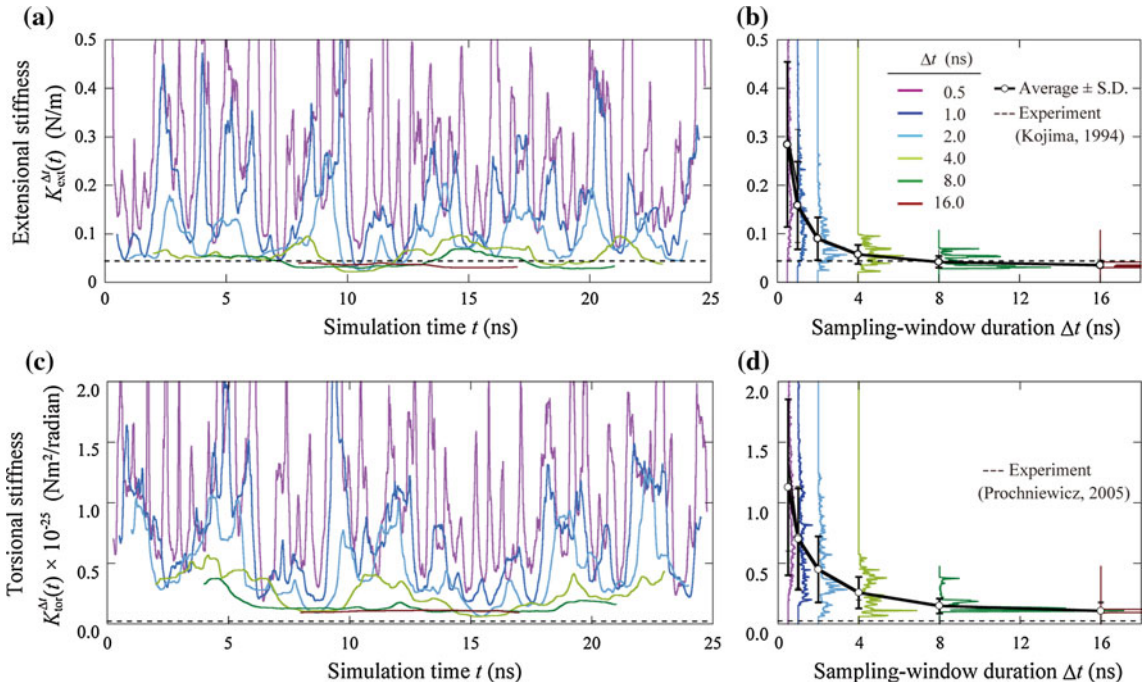

Fig. 4 Fluctuations in stiffness of actin filaments. **a** Tensile stiffness $K_{\mathrm{ext}}(t)$ per unit length of an actin filament and **b** its distribution for sampling window duration Δt = 0.5, 1.0, 2.0, 4.0, 8.0, and 16.0 ns. **c** Torsional stiffness $K_{\mathrm{tor}}(t)$ per unit length of an actin filament and **d** its distribution for sampling window duration Δt = 0.5, 1.0, 2.0, 4.0, 8.0, and 16.0 ns. The *dashed lines* are the stiffness experimentally measured, respectively, by Kojima et al. (1994) and Prochniewiez et al. (2009)

are smaller in scale than filaments. In general, the behavior of the actin cytoskeleton observed at various scales is influenced by phenomena occurring at even smaller scales. It is therefore important to extract and simplify critical factors from among such smaller-scale behaviors. Such an approach is called coarse-graining, and simulation method based on this approach is called coarse-grained simulation.

The application of coarse-grained simulation to the analysis of the behavior of the actin cytoskeleton is considered extremely significant, as the actin cytoskeleton demonstrates characteristic behaviors at a broad range of scales, as shown in Fig. 1c, d. This section discusses research in which coarse-grained simulation was applied to actin cytoskeletons. Section 3.2 reviews the coarse-grained MD (CGMD) method, which treats a significant molecular group as one particle according to its mechanical behavior, and Sect. 3.3 discusses the Brownian dynamics (BD) method, a mesoscale simulation method that treats inter-particle solvent as a continuum and considers the effects of solvent on solute particles as both a random and a dissipative forces.

3.2 Coarse-grained model based on MD simulation

The basic mechanical properties of filaments are apparent at the molecular scale, so it is extremely important to analyze their dynamic behavior from a microscopic perspective. In focusing on the relation between the molecular structure of actin filaments and their dynamic behavior, the temporal scale at which their molecular structure changes according to atomic motion is very small compared with that at which characteristics such as macroscopic stiffness appear. Thus, to analyze such relations, Chu and Voth (2006) proposed the coarse-grained MD (CGMD) method, which treats the atoms making up one molecule as one particle. Here, coarse-grained actin molecules are joined to construct the filament model.

As shown in Fig. 2b, actin molecules comprise four subdomains, which are atomic aggregates. As shown in Fig. 5, the four sub-domains are modeled as coarse-grained particles D1 to D4. Interactions between the coarse-grained particles are expressed by three bonds connecting D1 with D2, D1 with D3, and D3 with D4, two angles defined by three particles connecting D2-D1-D3 and D1-D3-D4, and a dihedral angle defined by four particles. The filament model was constructed by joining coarse-grained actin molecules prescribed in this way (Fig. 5).

With this model, interactions between molecules are chosen such that the fluctuation values of the filament match those obtained by the MD method. The stiffness and persistence length of this coarse-grained model show good agreement with experimental results (Isambert et al. 1995; Kojima et al. 1994). As shown by this example, the construction of coarse-grained models allows analysis of mechanical

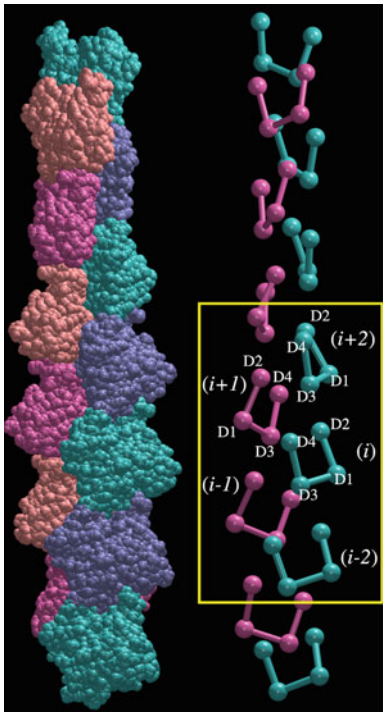

Fig. 5 A coarse-grained model of an actin filament. Each actin monomer has four sites denoted as D1, D2, D3, and D4. Actin monomers are denoted by *italic numbers*. The figure is modified from Chu and Voth (2006) (Copyright 2006 Biophysical Society)

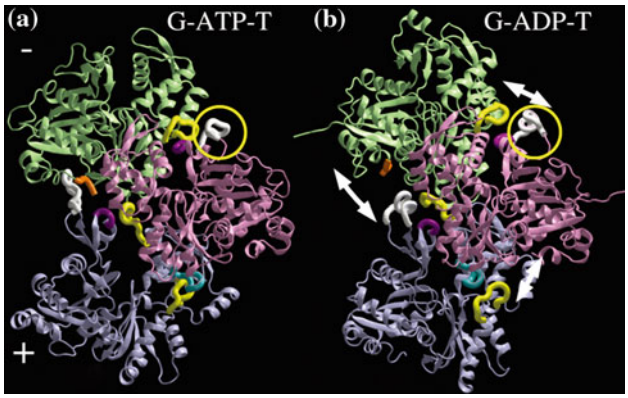

Fig. 6 The conformation of a G-actin trimer at the ATP and ADP states. Schematics of a snapshot during the MD simulation of (**a**) ATP-actin trimer and (**b**) ADP-actin trimer. The figure is modified from Chu and Voth (2005) (Copyright 2005 National Academy of Sciences, USA). The DB loops shown colored *white* are marked by *yellow circles*. The *white arrows* in the *right* figure indicate that the DB loop and plug-in loop (shown *colored yellow*) in ADP-actin trimer separate farther compared to that in ATP-actin trimer shown in the *left* figure, which shows the widening of the groove structure because of the decay of DB loop/plug-in loop interaction

behaviors on the macroscopic scale, such as stiffness and persistence length, while also including molecular scale interactions and fluctuation effects.

CGMD is useful for the analysis of the mechanical behaviors of molecular structures because the method is able to express the structural characteristics of the molecules. In the case of actin molecules, because CGMD is also able to express cleft structures, Chu and Voth (2005) applied it to the analysis of the effects on filament stiffness of structural changes inside actin molecules resulting from bonding with related proteins.

Inside cells, the bonding of ATP, ADP, and binding proteins changes the internal structure of actin molecules. For instance, as shown in Fig. 6, X-ray analysis demonstrates that the area of the actin molecule known as the DNase-I-binding loop (DB loop) does not have a fixed secondary structure in the ATP state (Fig. 6a), but has a spiral shape in the ADP state (Fig. 6b) (Graceffa and Dominguez 2003; Otterbein et al. 2001). Chu and Voth (2005) also analyzed the influence of internal structural changes of molecules due to ATP and ADP binding on the mechanical behaviors of filaments using the CGMD method, in which the model shown in the right figure in Fig. 5 was applied. In this model, actin sub-domains represented by balls are bound to form the *U*-shaped conformation, which is exactly the cleft structure of the actin molecule and evaluated in both cases.

The results clarified that interactions inside the molecule weaken and the groove structure widens when the DBloop has a spiral structure. In addition, the persistence length is longer with the ATP-binding filament. These results show a good match with experimental data (Isambert et al. 1995). In this way, the application of CGMD was shown to enable analysis of the relation between the structural changes and mechanical behaviors of filaments.

3.3 Coarse-graining of solute/solvent

The temporal and spatial scales at which dynamic structural changes occur in actin filaments due to polymerization, depolymerization, and severing are exceptionally large compared with the scale at which solvent atoms and molecules move. The following introduces a coarse-grained method focusing on this scale for investigating the cytoskeletal structural changes of actin filaments dispersing in the solvent.

Shimada et al. (2009) applied the BD model proposed by Bossis et al. (1982) for the analysis of the dynamic structural changes of actin filaments. As the behavior of each solvent atom and molecule is not tracked with this method, it allows analysis at spatial scales from several tens to several hundred nanometers and temporal scales of milliseconds.

If actin molecules are represented as spherical particles, actin filaments can be represented using the serial spring models of particles bound by a linear spring and bending spring (Fig. 7a and b). Polymerization is thought to occur when the distance between the tip of the filament and the actin monomer is below a certain value, and then they appear

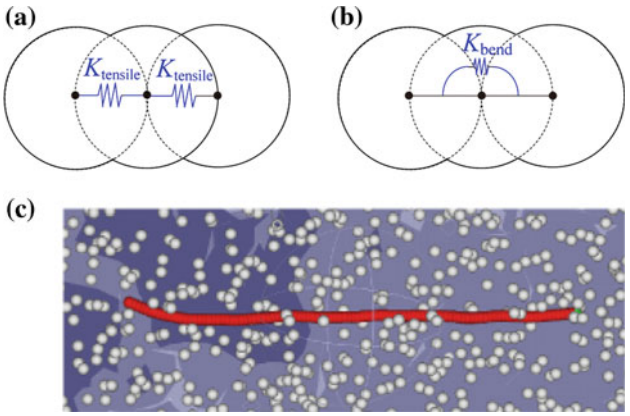

Fig. 7 Serial spring models and simulation based on the BD model. **a** Linear spring bonding neighbor two particles. $K_{tensile}$ denotes a constant for tensile spring. **b** Bending spring bonding neighboring three particles. K_{bend} denotes a constant for bending spring. **c** Dynamic behavior of filament while deforming due to thermal fluctuation in solvent (as seen through Cellon, provided by VCAD Solutions Co., Ltd.). The *white spheres* represent the free actin monomers in solution

to have bonded. In depolymerization models, the number of particles separating from the filament per unit time is taken to be fixed (Pollard et al. 2000), while in the severing model, the severing of the filament is taken to occur at the same rate between particles (Carlsson 2006). The solvent (water molecule) is expressed as a continuum, whose effects on the solutes (actin molecule and filament) are calculated as random and dissipative forces.

Actin filaments in the cytoskeleton undergo repeated dynamic changes consisting of polymerization, depolymerization, and severing while deforming due to thermal fluctuations in the cell's cytoplasm. Such structural changes play an important role in various cellular activities, such as adaptation of cell shape to the surrounding mechanical environment. For this reason, it is significant to analyze these cytoskeletal structural changes by clarifying cellular structure and functions. Shimada et al. (2009) used a BD model to show the behavior of the actin filament as it deforms due to thermal fluctuation (Fig. 7c).

Furthermore, the BD models are used to investigate remodeling processes of actin dynamics (Inoue et al. 2010), cross-linked network morphology (Kim et al. 2009), binding free energies of structures along the nucleation pathway (Sept and McCammon 2001). Of course, the dissipative particle dynamics (DPD) approach (Hoogerbrugge and Koelman 1992; Espanol and Warren 1995) is useful for examination of mechanical behavior of actin filament in coarse-grained solute/solvent (see references Padding 2009; Ter-Oganessian et al. 2005, as examples for applications to semiflexible polymers). In the future, coarse-grained modeling and simulations taking into account such thermal fluctuations may explain the mechanical and biochemical interactions of actin filaments (Adachi et al. 2010).

4 Continuum level: from actin filaments to networks

4.1 Continuum dynamics approach

Three-dimensional polymer networks formed by actins not only have function as a cytoskeleton supporting intracellular and extracellular forces, but are also related to the generation of forces acting during cellular motion and the transmission of force. The coarse-grained model discussed in Sect. 3 is generally used to analyze the mechanical behavior of actin cytoskeletons at the filament scale, while models based on continuum dynamics are applied in the mechanical analysis of even higher-order structures of the actin cytoskeleton. Consequently, the greater the object of analysis to the cellular scale from molecular scale, the greater will the coarse-grain level extent to the actin filament and actin network scales, as shown in Fig. 1e, f, and g.

Normally, even if the deflection angle and twisting angle of the filaments is large, such states can be taken to be minute deformations locally, and so linear elasticity can be applied to the bending and twisting of filaments. In fact, the typical length of actin filaments is at the micrometers length scale, which is the order of magnitude longer than their diameters (Kojima et al. 1994; Tsuda et al. 1996). In addition, when multiple filaments form networks, the actin filament demonstrates various mechanical behaviors different from those of a monofilament. Section 4 introduces continuum models of the actin cytoskeleton as applied to various mechanical behavior analyses, ranging from analyses of single actin filaments to analyses of network structures.

4.2 Analyses of the dynamics of single actin filaments

This section introduces studies on the analysis of the deformation behavior of a single actin filament. In these studies, the actin filament is treated as an elastic body and its deformation behavior is analyzed by evaluating its vibrational properties. Also considered in these studies are stretching-twisting coupling, which returns the spirally twisted state when spiral filaments are pulled, and bending-twisting coupling, which causes further twisting when filaments are bent. For this reason, attempts have been made to analyze the deformation behavior of actin filaments in order to learn more about such coupling behavior.

Ming et al. (2003a) focused on an analytical method called the substructure synthesis method (SSM; proposed by Hale and Meirovitch 1980) and used it to analyze the vibration of actin filaments, taking large biomolecular complexes as an example. With this method, which is generally used for the analysis of the dynamics of complex flexible structures, the motion of each substructure is represented by a given number of admissible functions of substructures. The weighted residual method is used to connect these substructures and to

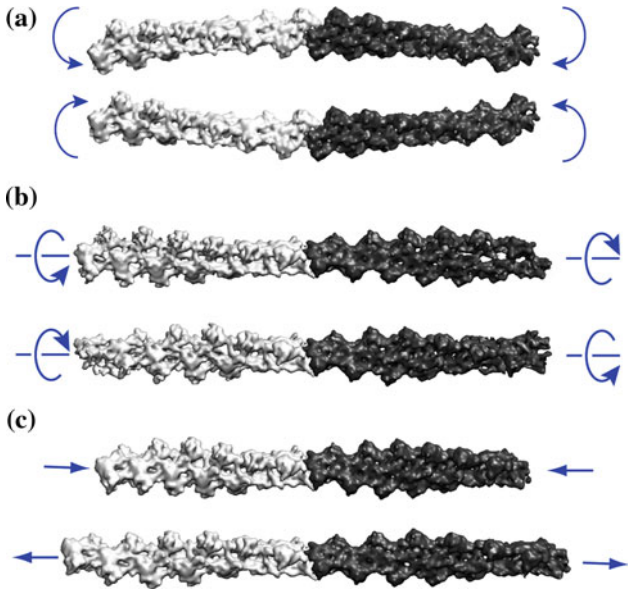

Fig. 8 Low-frequency mode of actin filaments obtained by SSM. **a** Bending, **b** twisting, and **c** stretching/compression deformations. Each actin filament is composed of two 13-subunit repeats, and the two repeats are in different colors. Two opposite end-point structures are shown for each mode. The figure is modified from Ming et al. (2003a) (Copyright 2005 National Academy of Sciences, USA)

analyze the mechanical characteristics of the whole structure. Normally, low-order polynomials are taken as the admissible functions; this enhances the efficiency of analysis of the whole structure and allows the motion of large molecular complexes to be investigated. In the study by Ming et al. (2003a), the single helical repeat F-actin (35.75 nm), consisting of 13 subunits, was treated as one substructure, and the vibrational properties of filaments in which two of these substructures are connected were investigated (Fig. 8). These authors also applied the SSM simulation method to actin filaments whose lengths ranged from two to 2^7 substructures (4.6 μm) (Ming et al. 2003b). Their results showed good agreement with theoretical solutions for long homogeneous elastic rods in the very low-frequency region.

The results of this research demonstrate that microscopic information obtained from atomic level simulations can be applied to the analysis of vibrations at macroscopic scales. Furthermore, the use of SSM was hierarchically also found to support the effective analysis of complex structures with periodic repeats. The normal mode analysis used in this method ignores anharmonicity in molecular motion, but is adequately effective for the analysis of the deformation behavior of large biomolecular complexes such as actin filaments. The characteristics of flexible actin filaments are also studied using general normal mode analysis (Ben-Avraham and Tirion 1995). Normal mode analysis has served as a useful tool for analyzing the flexibility of proteins and efficiently complements MD techniques which can only be applied to the analysis of short time spans (Ben-Avraham and Tirion 1998).

In general, it is not possible to consider bending, twisting, and stretching elastic deformations independently. One theory that can treat all these coupling behaviors is the Cosserat rod theory (Cosserat and Cosserat 1909), in which rotational degree of freedom is added to a one-dimensional elastic rod, thereby realizing a theory free from contradictions even with respect to large deformation behaviors. Various studies on one-dimensional continuums have since been carried out from various perspectives (elastic rod, beam, filament), and applications of the method to DNA and carbon nanotube have been reported since around 2000 (Marko 1997; Hoffman et al. 2003; Smith and Healey 2008; Burton and Gould 2007). As the Cosserat continuum model is appropriate for the behaviors of continuums with microscopic structures, it is expected to play a significant role in the analysis of actin filaments and networks.

Actin filaments with a double-helix structure have a spiral centroid, which is mismatched with respect to the geometrical central axis of the elastic rod representing the filament (Fig. 9). The present authors have proposed a Cosserat continuum model of an actin filament taking into account this mismatch between centroid and central axis (Yamaoka and Adachi 2010a), and the results of these investigations suggest pulling-twisting coupling behavior caused by the deviation of the centroid with respect to the central axis. In the future, this model, which explicitly includes microstructures, may be applied to higher-order cytoskeletal structures such as actin bundling and meshworking (for a general framework of a directed medium, see also Yamaoka and Adachi 2010b).

In the above-introduced articles, the theoretical and simulation models for investigating the deformation behaviors

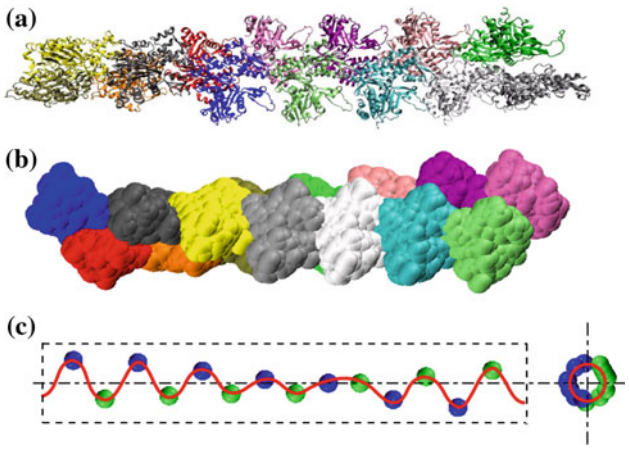

Fig. 9 Illustration of a half pitches of an actin filament consisting of 14 monomers. **a** Ribbon representation. **b** Coarse-grained description. **c** Continuum rod model showing the centroid of the actin filament (*left*) and its projection onto a transverse section (*right*). The figures are modified from Yamaoka and Adachi (2010a) (Copyright 2010 Elsevier)

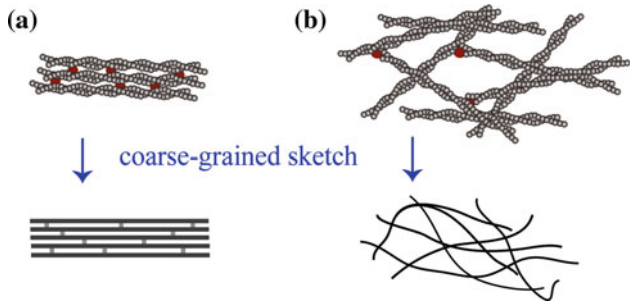

Fig. 10 Corse-grained modelings of actin cytoskeletons. Illustrations of (**a**) an actin bundle and (**b**) an actin network. *Red circles* denote actin-binding proteins such as Arp2/3. The lower figures are their coarse-grained sketches, that is, the actin filaments are viewed as strings without thickness and inner structures

of single actin filament were proposed and discussed. Since these models are based on the continuum dynamics, some new ideas are desired to extend the models to ones for branched and meshworked filaments. Furthermore, it is interesting to examine effects of the solvent and related proteins by using the aforementioned models, that is, the actin filament under various environments.

4.3 Studies on actin network dynamics

In early research on cytoskeletal networks, cytoskeletons were modeled with a lattice shape to investigate the stability and mechanical dynamics of the structure (for an example, see Satcher and Dewey 1996). These models then developed into tensegrity models (Ingber 2003), and simulations using these models are still being conducted (Sultan et al. 2004). Meanwhile, cross-linked and bundled actin networks (whose coarse-graining sketching are shown in Fig. 10) exist everywhere in cells, and their elastic characteristics are important in many cellular functions. For this reason, the mechanical behaviors of actin networks have been studied using diverse approaches (MacKintosh et al. 1995; Kroy and Frey 1996; Marko 1997).

Studies on actin networks such as those investigating elastic characteristics have revealed that the mechanical behavior of the actin cytoskeleton differs from that of other polymer gels. Actin filaments exhibit the properties as semiflexible polymers, for example, they form gels at much lower volume fractions than required for flexible polymers and thus, serve as an interesting research topic from the viewpoint of the elastic characteristics of polymers. For this reason, studies are being conducted on the bending motion of filaments in solvents in addition to theoretical research attempting to describe the rheological characteristics of actin filaments.

To date, analytic studies on the behavior of actin filaments in actin solvents have been conducted by Maggs (Isambert and Maggs 1996; Marko 1997) and Morse (1998a,b,c).

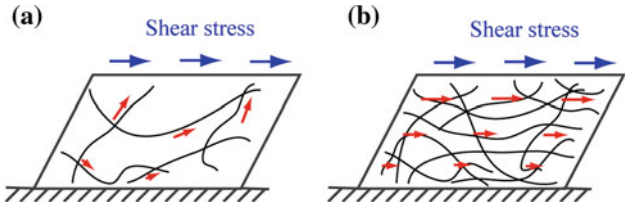

Fig. 11 Elastic behavior of actin networks under shear stress with **a** low and **b** high cross-link density. The *red arrows* at inside of the networks indicate the deformations. The network at low cross-link density is deformed along filaments, while one at high cross-link density is done uniformly

Maggs described the dynamic behavior of semidilute solutions of actin filaments and pointed out some of the rheological regimes present. Morse (1998a,b,c), on the other hand, used a tube model to study the effects of entangling on the linear viscoelasticity of solvents in tightly entangled solutions of semiflexible polymers. He also discussed the statistical mechanics method for investigating the elastic characteristics of polymers in tubes (Morse 2001). As an example, he used an actin filament solvent as an example of a semiflexible polymer, and compared predictions from simulations with measurements of elastic modulus.

MacKintosh et al. (1995) developed a model for cross-linked gels and sterically entangled solutions of semiflexible biopolymers to explain the elastic properties of networks in vitro, and successfully showed that the ease of network deformation depends on the concentration of actin solution. MacKintosh and collaborators also evaluated the elastic properties in actin solution by simulation using 2D models and derives macroscopic mechanical properties (Head et al. 2003; Levine et al. 2004; Das et al. 2007). Their results show good agreement with experiments on nonlinear elastic properties of networks (Liu et al. 2007) and have been utilized to understand experiments on macroscopic properties of networks and gels (Mizuno et al. 2007; Janmey et al. 2007).

Later Gardel et al. (2004) clarified that actin networks demonstrate characteristic elastic behavior reflecting the mechanical properties of individual filaments and categorized the behavior into two types. One type has low actin filament density as well as low cross-link density of the network (Fig. 11a). In this case, the deformation behavior of the whole network reflects the bending behavior of a single filament, and strain is highly inhomogeneous. The other type has high actin filament density as well as high cross-link density of the network (Fig. 11b). In this case, the deformation behavior of the actin network reflects the stretching of thermally induced filament fluctuations and entropic elasticity, and strain is homogeneous.

Huisman and coauthors reported a three-dimensional simulation for cross-linked F-actin networks subjected to large

deformations (Huisman et al. 2007). They demonstrated that 3D network behavior not only depends on actin concentration and cross-link density but also on network architecture such as the connectivity and the filament length. Palmer and Boyce (2008) constructed a detailed three-dimensional micromechanical modeling and investigated stress-strain behavior of the network. In addition, a three-dimensional model of actin gels was proposed based on the Brownian dynamics and the effects of various system parameters on the growth and morphology of the cross-linked network (Kim et al. 2009).

These models suggest important concepts for understanding the dynamics of networks in which actin filaments are linked by such bridges in cells. Research on actin networks dynamics is thus actively being pursued by various research groups (see Stricker et al. 2010 and references therein). In the future, it is expected to construct a model of intracellular actin networks and investigate cooperative dynamics of networks in cell migration.

5 Summary

This review has focused on the multiscale behaviors/structures of the actin cytoskeleton in relation to the expression of cellular functions, and has introduced the mathematical analyses and simulation methods applied in related studies. The individual approaches employed at the different scales of the actin cytoskeleton are important for understanding the functions that are expressed at each scale. Studies aiming to elucidate cellular functions on the basis of the interactions of mechanical and biochemical factors in the dynamics of the actin cytoskeleton as a mechanical structure will thus become increasingly important (Okeyo et al. 2010). Some of the functions of the actin cytoskeleton are also expressed over different temporal and spatial scales, and the development of new methods that can link the different concepts applied for the different scales is awaited with interest.

Also required are simulation methods taking into account the dynamic behavior of the various elements that form not only the actin cytoskeleton but also other structures within cells, which will enable the simulation of cellular functions created by the interactions of mechanical and biochemical factors at the molecular level. Such research on the simulation of cellular dynamics demonstrates the significance of taking into account intracellular substances and mechanical fields in order to understand various cellular functions. Thus, it is also important that discrete and continuum dynamics ranging from functional expression at the molecular level to macroscopic functional expression at the whole cell level are applied to multiscale research.

Acknowledgments This work was partly supported by a Grant-in-Aid for Scientific Research (#20001007) and by Research and Development of the next-Generation Integrated Simulation of Living Matter, a part of the Development and Use of the Next-Generation Supercomputer Project of the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

Adachi T et al (2010) Approach behavior of binding proteins toward actin filament: Brownian dynamics simulation. Trans Japan Soc Mech Eng A Sol Mech Mater Eng 76:1119–1127 (in Japanese)

Alder BJ, Wainwright TE (1957) Phase transition for a hard sphere system. J Chem Phys 27:1208–1209

Ayton GS et al (2007) Multiscale modeling of biomolecular systems: in serial and in parallel. Curr Opin Struct Biol 17:192–198

Bathe M (2008) A finite element framework for computation of protein normal modes and mechanical response. Proteins 70:1595–1609

ben-Avraham D, Tirion MM (1995) Dynamic and elastic properties of F-actin: a normal-mode analysis. Biophys J 68:1231–1245

ben-Avraham D, Tirion MM (1998) Normal modes analyses of macromolecules. Physica A 249:415–423

Bossis G et al (1982) Brownian dynamics and the fluctuation dissipation theorem. Mol Phys 45:191–196

Burton DA, Gould T (2007) Dynamical model of Cosserat nanotubes. J Phys 62:23–33

Carlsson AE (2006) Stimulation of actin polymerization by filament severing. Biophys J 90:413–422

Cascella M et al (2008) Topologically based multipolar reconstruction of electrostatic interactions in multiscale simulations of proteins. J Chem Theory Comput 4:1378–1385

Chen LF et al (2002) Molecular modeling of averaged rigor crossbridges from tomograms of insect flight muscle. J Struct Biol 138: 92–104

Chu JW, Voth GA (2005) Allostery of actin filaments: molecular dynamics simulations and coarse-grained analysis. Proc Natl Acad Sci USA 102:13111–13116

Chu JW, Voth GA (2006) Coarse-grained modeling of the actin filament derived from atomistic-scale simulations. Biophys J 90:1572–1582

Cosserat E, Cosserat F (1909) Théorie des corps deformable. Hermann et Fils, Paris

Dalhaimer P, Pollard TD (2008) Nucleotide-mediated conformational changes of monomeric actin and Arp3 studied by molecular dynamics simulations. J Mol Biol 376:166–183

Das M et al (2007) Effective medium theory of semiflexible filamentous networks. Phys Rev Lett 99:038101

Deriu MA et al (2011) Biomechanics of actin filaments: a computational multi-level study. J Biomech 44:630–636

Espanol P, Warren P (1995) Statistical mechanics of dissipative particle dynamics. Europhys Lett 30:191–196

Gardel ML et al (2004) Elastic behavior of cross-linked and bundled actin networks. Science 304:1301–1305

Geiger B, Bershadsky A (2001) Assembly and mechanosensory function of focal contacts. Curr Opin Cell Biol 13:584–592

Gittes F et al (1993) Flexural rigidity of microtubules and actin filaments measured from thermal fluctuations in shape. J Cell Biol 120:923–934

Goldberg MB (2001) Actin-based motility of intracellular microbial pathogens. Microbiol Mol Biol Rev 65:595–626

Graceffa P, Dominguez R (2003) Crystal structure of monomeric actin in the ATP state—structural basis of nucleotide-dependent actin dynamics. J Biol Chem 278:34172–34180

Hale AL, Meirovitch L (1980) A general substructure synthesis method for the dynamic simulation of complex structures. J Sound Vib 69:309–326

Hayakawa K et al (2008) Actin stress fibers transmit and focus force to activate mechanosensitive channels. J Cell Sci 121:496–503
Head DA et al (2003) Distinct regimes of elastic response and deformation modes of cross-linked cytoskeletal and semiflexible polymer networks. Phys Rev E 68:061907
Hoffman KA et al (2003) Link, twist, energy and the stability of DNA minicircles. Biopolymers 70:145–157
Holmes KC et al (1990) Atomic model of the actin filament. Nature 347:44–49
Hoogerbrugge PJ, Koelman JMVA (1992) Simulating microscopic hydrodynamic phenomena with dissipative particle dynamics. Europhys Lett 19:155–160
Huisman EM et al (2007) Three-dimensional cross-linked F-actin networks: relation between network architecture and mechanical behavior. Phys Rev Lett 99:298193
Ingber DE (2003) Tensegrity I. Cell structure and hierarchical systems biology. J Cell Sci 116:157–173
Inoue Y et al (2010) Simulations of dynamics of actin filaments by remodeling them in shear flows. Comput Biol Med 40:876–882
Inoue Y, Adachi T (2011) Coarse-grained Brownian rachet model of membrane protrusion on cellular scale. Biomech Model Mechanobiol. doi:10.1007/s10237-010-0250-6
Isambert H, Maggs AC (1996) Dynamics and Rheology of actin solutions. Macromol 29:1036–1040
Isambert H et al (1995) Flexibility of actin-filaments derived from thermal fluctuations. J Biol Chem 270:11437–11444
Isralewitz B, Gao M, Schulten K (2001) Steered molecular dynamics and mechanical functions of proteins. Curr Opin Struct Biol 11:224–230
Janmey PJ et al (2007) Negative normal stress in semiflexible biopolymer gels. Nat Mater 6:48–51
Kim T et al (2009) Computational analysis of a cross-linked actin like networks. Exp Mech 49:91–104
Kojima H et al (1994) Direct measurement of stiffness of single actin filaments with and without tropomyosin by in vitro nanomanipulation. Proc Natl Acad Sci USA 91:12962–12966
Kroy K, Frey E (1996) Force-extension relation and plateau modulus for wormlike chains. Phys Rev Lett 77:306–309
Lauffenburger DA, Horwitz AF (1996) Cell migration: a physically integrated molecular process. Cell 84:359–369
Lee J et al (1994) Traction forces generated by locomoting keratocytes. J Cell Biol 127:1957–1964
Levine AJ et al (2004) The deformations field in semiflexible networks. J Phys Condens Matter 16:S2079–S2088
Liu J et al (2007) Visualizing the strain field in semiflexible polymer networks: strain fluctuations and nonlinear Rheology of F-actin gels. Phys Rev Lett 98:198304
Lu H et al (1998) Unfolding of titin immunoglobulin domains by steered molecular dynamics simulation. Biophys J 75:662–671
Lyman et al (2008) Systematic multiscale parameterization of heterogeneous elastic network models of proteins. Biophys J 95:4183–4192
MacKintosh FC et al (1995) Elasticity of semiflexible biopolymer networks. Phys Rev Lett 75:4425–4428
Maggs AC (1997) Two plateau moduli for actin gels. Phys Rev E 55:7396–7400
Marko JF (1997) Stretching must twist DNA. Europhys Lett 38: 183–188
Matsushita S et al (2010a) Evaluation of extensional and torsional stiffness of single actin filaments by molecular dynamics analysis. J Biomech 43:3162–3167
Matsushita S et al (2010b) Quantitative evaluation of mechanical behaviors of actin filament under different mechanical conditions. In: Proceeding of the 6th world congress of biomechanics
McCammon JA et al (1977) Dynamics of folded proteins. Nature 267:585–590
Ming D et al (2003a) Substructure synthesis method for simulating large molecular complexes. Proc Natl Acad Sci USA 100:104–109
Ming D et al (2003b) Simulation of F-actin filaments of several microns. Biophys J 85:27–35
Mitchison TJ, Cramer LP (1996) Actin-based cell motility and cell locomotion. Cell 84:371–379
Mizuno D et al (2007) Nonequilibrium mechanics of active cytoskeletal networks. Science 315:370–373
Mogilner A, Oster G (1996) Cell motility driven by actin polymerization. Biophys J 71:3030–3045
Morse DC (1998a) Viscoelasticity of concentrated isotropic solutions of semiflexible polymers. 1. Model and stress tensor. Macromolecules 31:7030–7043
Morse DC (1998b) Viscoelasticity of concentrated isotropic solutions of semiflexible polymers. 2. Linear response. Macromolecules 31:7044–7067
Morse DC (1998c) Viscoelasticity of tightly entangled solutions of semiflexible polymers. Phys Rev E 58:R1237–R1240
Morse DC et al (2001) Tube diameter in tightly entangled solutions of semiflexible polymers. Phys Rev E 63:031502
Narita A, Maeda Y (2007) Molecular determination by electron microscopy of the actin filament end structure. J Mol Biol 365:480–501
Nemethova M et al (2008) Bundling the actin cytoskeleton: filopodia contribute to the construction of contractile bundles in the lamella. J Cell Biol 180:1233–1244
Oda T et al (2009) The nature of the globular-to fibrous-actin transition. Nature 457:441–445
Okeyo KO et al (2010) Mechanical regulation of actin network dynamics in migrating cells. J Biomech Sci Eng 5:186–207
Otterbein LR et al (2001) The crystal structure of uncomplexed actin in the ADP state. Science 293:708–711
Padding JT et al (2009) Efficient simulation of noncrossing fibers and chains in a hydrodynamic solvent. J Chem Phys 130:144903
Palmer JS, Boyce MC (2008) Constitutive modeling of the stress-strain behavior of F-actin filament networks. Acta Biomater 4:597–612
Park et al (2006) Atomistic simulation approach to a continuum description of self-assembled β-sheet filaments. Biophys J 90:2510–2524
Pfaendtner J et al (2009) Nucleotide-dependent conformational states of actin. Proc Natl Acad Sci USA 106:12723–12728
Pollard TD et al (2000) Molecular mechanisms controlling actin filament dynamics in nonmuscle cells. Annu Rev Biophys Biomol Struct 29:545–576
Pollard TD, Berro J (2009) Mathematical models and simulations of cellular processes based on actin filaments. J Biol Chem 284: 5433–5437
Pollard TD, Borisy GG (2003) Cellular motility driven by assembly and disassembly of actin filaments. Cell 112:453–465
Pollard TD, Cooper JA (1986) Actin and actin-binding proteins. A critical evaluation of mechanisms and functions. Ann Rev Biochem 55:987–1035
Prochniewiez E et al (2009) Cofilin increases the torsional flexibility and dynamics of actin filaments. J Mol Biol 353:990–1000
Riveline D et al (2001) Focal contacts as mechanosensors: externally applied local mechanical force induces growth of focal contacts by an mDia1-dependent and ROCK-independent mechanism. J Cell Biol 153:1175–1185
Satcher RL Jr, Dewey CF Jr (1996) Theoretical estimates of mechanical properties of the endothelial cell cytoskeleton. Biophys J 71: 109–118
Schmidt A, Hall MN (1998) Signaling to the actin cytoskeleton. Annu Rev Cell Dev Biol 14:305–338
Sept D, McCammon JA (2001) Thermodynamics and kinetics of actin filament mucleation. Biophys J 81:667–674

Shimada Y et al (2009) Coarse-grained modeling and simulation of actin filament behavior based on Brownian dynamics method. Mol Cell Biomech 6:161–173

Smith ML, Healey TJ (2008) Predicting the onset of DNA supercoiling using a non-linear hemitropic elastic rod. Int J Non-Linear Mech 43:1020–1028

Stricker J et al (2010) Mechanics of the F-actin cytoskeleton. J Biomech 43:9–14

Suda H, Saito M (1994) Molecular-dynamics simulations for actin monomers in solution. J Theor Biol 171:347–349

Sultan C et al (2004) A computational tensegrity model predicts dynamic rheological behaviors in living cells. Ann Biomed Eng 32:520–530

Ter-Oganessian N et al (2005) Active microrheology of networks composed of semiflexible polymers: computer simulation of magnetic tweezers. Phys Rev E 72:041510

Theriot JA, Mitchson TJ (1991) Actin microfilament dynamics in locomoting cells. Nature 352:126–131

Tsuda Y et al (1996) Torsional rigidity of single actin filaments and actin-actin bond breaking force under torsion measured directly by in vitro micromanipulation. Proc Natl Acad Sci USA 93:12937–12942

Vogel V, Sheetz M (2006) Local force and geometry sensing regulate cell functions. Nat Rev Mol Cell Biol 7:265–275

Wang N et al (2001) Mechanical behavior in living cells consistent with the tensegrity model. Proc Natl Acad Sci USA 98:7765–7770

Winder SJ, Ayscough KR (2005) Actin-binding proteins. J Cell Sci 118:651–654

Wriggers W, Schulten K (1997) Stability and dynamics of G-actin: back-door water diffusion and behavior of a subdomain 3/4 loop. Biophys J 73:624–639

Wriggers W, Schulten K (1999) Investigating a back door mechanism of actin phosphate release by steered molecular dynamics. Proteins 35:262–273

Yamaoka H, Adachi T (2010a) Coupling between axial stretch and bending/twisting deformation of actin filaments caused by a mismatched centroid from the center axis. Int J Mech Sci 52:329–333

Yamaoka H, Adachi T (2010b) Continuum dynamics on a vector bundle for a directed medium. J Phys A Math Theor 43:325209

Zigmond SH (1993) Recent quantitative studies of actin filament turnover during cell locomotion. Cell Motil Cytoskelet 25:309–316