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Steered molecular dynamics analysis of the role of cofilin in increasing the flexibility of actin filaments

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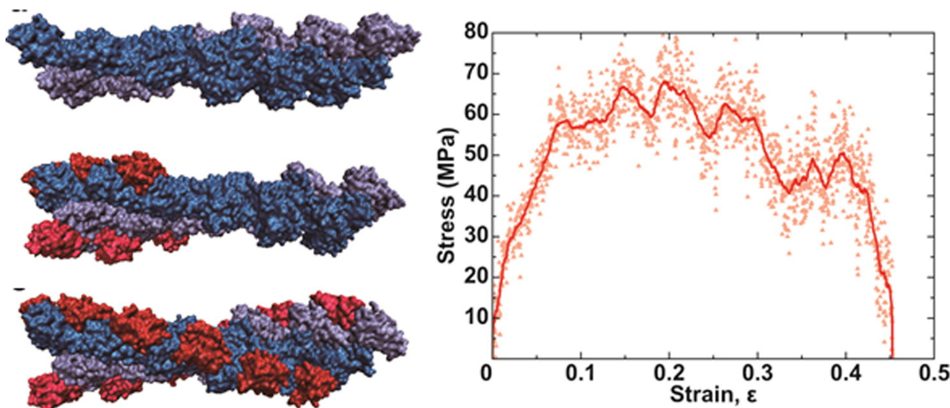
HIGHLIGHTS

- Flexibility of actin filament is increased by cofilin binding.
- Partially decorated cofilin weakens mechanical property of actin filament by increasing discontinuity.
- During extension of actin filament, cofilin endures from early destruction.

GRAPHICAL ABSTRACT



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ABSTRACT

Cofilin is one of the most essential regulatory proteins and participates in the process of disassembling actin filaments. Cofilin induces conformational changes to actin filaments, and both the bending and torsional rigidity of the filament. In this study, we investigate the effects of cofilin on the mechanical properties of actin filaments using computational methods. Three models defined by their number of bound cofilins are constructed using coarse-grained MARTINI force field, and they are then extended with steered molecular dynamics simulation. After obtaining the stress–strain curves of the models, we calculate their Young's moduli and other mechanical properties that have not yet been determined for actin filaments. We analyze the cause of the different behaviors of the three models based on their atomistic geometrical differences. Finally, it is demonstrated that cofilin binding causes changes in the distances, angles, and stabilities of the residues in actin filaments.

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1. Introduction

Cofilin is a regulatory protein that interacts with actin monomers and performs an essential role in both the assembly and disassembly of actin filaments, simultaneously increasing their mobility and dynamics [1–6]. At the initiatory stage, actin filaments are composed of adenosine triphosphate (ATP)–actin monomers forming a double helix structure. However, ATP–actins are changed into adenosine diphosphate (ADP)–actins after hydrolysis, and depolymerized into G-actins. After exchanging ADP into ATP, ATP–actins are consequently rebuilt into actin filaments which may fulfill their functions again [6, 7]. The heterogeneity of ATP-actin and ADP-actin was also one of the

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interests for studies [8]. To prepare ATP-actins to polymerize into actin filament again, the severing stage executed by cofilins should be performed [9,10].

The binding of cofilin results in conformational changes to the actin filament, initiated from conformational change of each subunit and making the actin filament severely unstable [11]. Furthermore, it is known that the density of bound cofilins in filaments critically affects the extent of actin deformation or stability [3,12]. An individual actin filament can show different conformational changes based on the environmental conditions in living cells, and comprehending the effects of cofilin under these conditions is essential.

Since actin was discovered, many studies have analyzed the mechanical properties and structural characteristics of actin filaments induced by cofilin. From a biological point of view, understanding actin filaments provides a physical foundation for describing the mechanical properties of cytoplasm [9]. In mechanics, the interaction between actin and cofilin is an intriguing subject, as the structural changes of actin filaments induced by cofilins directly result in changes to their properties. For example, a cofilactin filament, which is an actin filament with cofilins bound to each actin monomer, is more flexible than a pure actin filament [4,13–15]. Additionally, investigating the role of cofilin in defining filament properties could be important in controlling diseases, because the locomotion of cells, which is facilitated by cofilin, has a strong relationship with the invasion process of tumors, cancers, and viruses [16]. Lastly, the possibility of using actin filaments for biomaterials has recently been highlighted because of its rigid and flexible properties depending on binding of other proteins, which are similar to properties of other biomaterials [17,18].

As the surrounding conditions yield different mechanical properties of these filaments, an exact understanding of the polymerization processes and mechanical properties of diverse models should be obtained. Numerous experiments and simulations have been conducted to determine the mechanical properties of actin and cofilactin filaments. However, experiments exhibit some limitations in analyzing proteins. Although Huxley et al. determined that the Young's modulus of actin filaments is 2500 MPa using a small angle scattering system assembled on a high-flux multipole wiggler beamline, only one reflection shot could be taken because of camera limitations, and the number of experiments that could be conducted was limited by the time required for each trial [19]. Similarly, Gittes et al. calculated the mean flexural rigidity as $7.3 \times 10^{-26}\ \mathrm{N \cdot m^2}$ by analyzing the thermally driven fluctuation in the shape of the filaments, which was the most accurate measuring technique at that time. However, in this method, the resolution of the microscope and video apparatus is limited, and the nonzero depth, torsion, and convective currents that occurred in the experimental chamber during the experiment caused errors [20]. In the optical trapping technique performed by Yasuda et al., the beads, which had a radius of 0.44 μm, could cause errors, and this technique cannot be applied when determining the properties of nanosize materials, which are much smaller than microsize materials [21]. Of particular concern was the fact that these types of errors may result in huge differences in the magnitudes of target values, necessitating the continual invention and application of new analysis techniques to determine the exact mechanical properties of proteins and characterize their mechanical behaviors regarding nanoscale phenomena. Moreover, the properties related to the flexibility of proteins, such as their ductility, resilience, and toughness, are typically difficult to obtain by using traditional experimental techniques.

To eliminate some causes of errors when analyzing proteins on a small scale, molecular dynamics (MD) stands out as an alternative method for determining the protein's dynamics and elucidating the details of molecular motions [22–24]. Computational simulation methods can provide complementary insights into the molecular mechanisms, which may be difficult to explain using traditional experimental methods [25]. In particular, steered molecular dynamics (SMD) allows us to explore biological processes and explain their underlying physical meaning. The concept of pulling proteins began with atomic force microscopy (AFM) unfolding experiments [26]. SMD simulations were originally applied to study the unfolding behaviors, mechanical properties, and energy landscapes of proteins using various models [23,27–32]. Currently, SMD simulation techniques are being used to analyze the dynamics and conformational changes of proteins, including actin filaments [24,33–38]. SMD simulations explain the unfolding mechanism on an atomic level, which can be only minimally observed with current experimental methods, and supplement the experimental results, such as AFM, laser optical tweezers, and bio-membrane force probe experiments [38,39]. In addition, simulation approaches to the analysis of protein dynamics and behaviors are gaining recognition as bridges between experiments and physical phenomena, as recent advances in computer hardware and software have dramatically reduced the calculation time and increased the accuracy of the results [40].

However, the more computer technology develops, the more profound studies become. All atom MD simulation methods may show some weaknesses when treating large structures and require long calculation times because they must repeat numerous individual calculations [41–43]. Especially, actin is a large structure forming a filament and interacts with various molecules. Various coarse-grained methods have been developed to analyze actin filament [44–49]. These disadvantages led to the creation of coarse-grained (CG) models. MARTINI, a force field for the construction of CG structures, provides suitable CG models [50,51]. MARTINI maps all-atom structure with generally four to one mapping. It has been applied in studies of membrane lipids, carbohydrates, biological molecules, such as ion channels and liposomes, and even proteins, increasing the time scale from two to three orders of magnitude [52,53].

In this study, tensile tests are performed using three models—an actin filament, a fully decorated cofilactin filament, and a half-decorated cofilactin filament—by applying SMD simulations to find effect of cofilin binding to actin filament as material. After equilibrating the three models, they were extended in the longitudinal direction, and the obtained stress–strain curves were analyzed to calculate the Young's modulus and other mechanical properties of the filaments, such as their ductility, toughness, and resilience, which have been difficult to estimate using traditional methods. To make good use of the advantages of these atomic simulations, we scrutinized the underlying grounds inducing the discrepancies in the mechanical properties of the three models by examining the displacements, dihedral angles, and number of hydrogen bonds of the residues, simultaneously validating previous results.

We found that the binding of cofilin causes actin filaments to be more flexible and reduces their Young's modulus. In particular, the Young's modulus of the partially bound cofilactin filament is surprisingly lower than that of the bare and fully cofilin-decorated filament segments, meaning that the partial binding of cofilins can efficiently destabilize the actin filaments. Therefore, not only were the roles of cofilin in inducing the increased pliancy and instability in actin filaments confidently verified, but the influence of partial cofilin-decoration was also successfully observed.

2. Materials and method

In this study, we used cofilactin filament structures based on cryoelectron microscopy data, which correspond to a protein data bank (PDB) ID of 3J0S [54]. This structure has a resolution of 9 Å in low resolution, but it is fit with a high-resolution structure [54]. Additionally, we adopted this structure as fully decorated cofilactin and constructed pure actin in previous studies [55,56]. 3J0S is a twisted double strand with a length of a half pitch and a fully cofilin-decorated cofilactin filament, which has 12 actin monomers and 12 cofilin monomers (model 12C), as shown in Fig. 1c. To analyze the influence of cofilin binding on the mechanical behavior and properties of actin filaments, we modified 3J0S to prepare two additional types of actin filaments: a

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