Computational Investigation of Dynamic Properties of Actin Networks with Crosslinking Proteins

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Detailed Terms
INTRODUCTION

Due to the increasing recognition of the role that force plays in biological processes, a new field, mechanobiology, has recently emerged. One aspect of this is the need to gain a physical understanding of the viscoelastic properties of the cytoskeleton. Numerous studies, both in living cells and in reconstituted actin gels, have been conducted, but important questions still remain. Of these an important issue revolves around the role played by actin crosslinking proteins (ACPs), and whether they undergo unfolding or unbinding under stress. This issue is complicated by the fact that single molecule studies show that both events occur within a similar range of forces, on the order of 20-100 pN.

We have taken the approach that greater insight can be gained by the use of a geometrically-realistic three-dimensional (3D) computational model that accurately portrays the elastic properties of the actin filaments and crosslinking proteins, that allows for unbinding and unfolding kinetics of ACPs, and that is thermally active. We have recently published some aspects of this model and extend it here to examine issues related to crosslink dynamics.

METHODS

An actin network bearing a close resemblance to reconstituted actin gels was generated using a parallelized Brownian dynamics code in which mechanics of F-actin and ACPs are governed by extensional and bending stiffness with thermal fluctuation [see 1T. Kim et al., 2009 for details]. The ACPs consisting of two unfoldable arms reversibly crosslink actin filaments at nearly right angles. Also, the ACPs can unbind from actin or unfold, characterized by Bell’s equation, however with different values of sensitivity to force and a zero-force rate coefficient. In the simulation, the ACP arm exhibits a sawtooth force-extension curve while it remains bound to actin, which captures multiple unfolding events of sub-domains. Unbinding can occur on either of two arms, and once unbound, the free end of the ACP is capable of rebinding to the same or another filament. Shear stress and viscoelastic moduli of actin networks are measured via bulk rheology where the top face of the simulation box, on which tips of F-acts are clamped, is sinusoidally oscillated or uniformly displaced while holding the bottom face [2T. Kim et al, 2009].

Strain-stiffening behavior

Shear stress acting on the actin network and the frequency of unbinding and unfolding events are measured, responding to applied linear shear strain with various rates.

Stress relaxation

The actin network is first sheared at 50% with neither unbinding nor unfolding of ACPs, and then shear stress is probed after allowing both events. In addition, viscoelastic
moduli of network samples extracted from a stress relaxation process at a certain time are measured in the absence of unbinding or unfolding.

RESULTS AND DISCUSSIONS

Strain-stiffening behavior

With large shear strain rates ($\geq 1.4 \text{ s}^{-1}$), unfolding events are predominant compared to unbinding, and shear stress steadily increases, albeit with slower rates compared to the case when ACP unfolding or unbinding is not permitted (Fig. 1). By contrast, small shear strain rates corresponding to physiological values result in the collapse of shear stress with frequent sudden drops up to levels observed in experiments, $\sim 10 \text{ Pa}$, indicating that the low level of shear stress in reality is attributable to the unbinding process, not unfolding. Also, it is found that ACPs unbinding with larger forces have a tendency to rebind to different filaments after experiencing significant displacements from their original unbinding locations.

Stress relaxation

It is observed that shear stress significantly reduces to physiological levels only as a result of unbinding, not by unfolding. Also, the inclusion of re-binding creates a configuration capable of resisting low stress so that stress does not converge to zero level quickly. As the network experiences more stress relaxation, $G'$ tends to decrease and exhibits an increased frequency dependence, closer to the power law behaviors observed in vivo (Fig. 2).

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REFERENCES