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Influence of semiflexible structural features of actin cytoskeleton on cell stiffness based on actin microstructural modeling

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ABSTRACT

A new actin cytoskeleton microstructural model based on the semiflexible polymer nature of the actin filament is proposed. The relationship between the stretching force and the mechanical properties of cells was examined. Experiments on deforming hematopoietic cells with distinct primitiveness from normal and leukemic sources were conducted via optical tweezer manipulation at single-cell level. The modeling results were demonstrated to be in good agreement with the experimental data. We characterized how the structural properties of the actin cytoskeleton, such as prestress, density of cross-links, and actin concentration, affect the mechanical behavior of cells based on the proposed model. Increasing prestress, actin concentration, and density of cross-links reduced cell deformation, and the cell also exhibited strain stiffening behavior with an increase in the stretching force. Compared with existing models, the proposed model exhibits a distinct feature in probing the influence of semiflexible polymer nature of the actin filament on cell mechanical behavior.

1. Introduction

Cells are the basic unit of all living organisms. A number of studies have indicated that mechanical properties (e.g., cell stiffness) of cells have close correlation with the functions of cells, such as cell division, differentiation, migration, and apoptosis (Bausch and Kroy, 2006; Chowdhury et al., 2010; Kim et al., 2009; Li and Gundersen, 2008; Nagayama et al., 2001; Shen et al., 2008; Tan et al., 2012; Wong and Tang, 2011). The actin cytoskeleton plays a central role in cell stiffness by inhibiting actin polymerization (Lam et al., 2007; Titushkin and Cho, 2007). This function is demonstrated by the following phenomena: stiffness of acute promyelocytic leukemia cells decreased during the process of ATRA-induced differentiation regulated via the actin cytoskeleton (Lautenschläger et al., 2009); Stiffness of human ovarian cancer cells showed the power law in inverse correlation with metastatic potential of cells, which was regulated via remodeling of the actin cytoskeleton of cancer cells (Swaminathan et al., 2011); and the actin cytoskeleton remodeling mechanism played a direct role in drug resistance of cancer cells (Fu and Roufogalis, 2007; Sharma et al., 2011).

Numerous computational models have been developed to simulate the response of cells or subcellular components, ranging from continuum to discrete microstructural descriptions (Vaziri and Gopinath, 2008; Lim et al., 2006). Cells were usually assumed to consist of continuum materials, in which the smallest length scale is larger than the dimensions of microstructural components, in continuum models (Li, 2009). Many mechanical models of the cell based on the cell continuum membrane theory were developed (Dao et al., 2003; Tan et al., 2008, 2010a, 2010b). The alternative discrete microstructural approaches, such as the cell-foam, the cable network (Vaziri and Gopinath, 2008), the tensegrity (Ingber, 1993), and the three-dimensional random cytoskeleton network (Ujihara et al., 2010; Zeng et al., 2012) models, focused on the importance of the cytoskeleton on cell biomechanics.

Despite the progress in cell mechanical modeling, the central influence of the actin cytoskeleton on the mechanical properties of cells has not been sufficiently investigated. The actin cytoskeleton was assumed to be equivalent to the Hookean spring in some models (Ingber, 1993; Ujihara et al., 2010; Zeng et al., 2012). The actin filaments exhibit material properties of semiflexible nature, and the mechanical behaviors of the actin filaments were confirmed to be influenced by actin concentration, density of cross-links, and osmotic stress through the studies of the rheology of the F-actin network (Ciano et al., 2002; Claessens et al., 2006; Gardel et al., 2004; Shin et al., 2004). There is still insufficient information on how the mechanical properties of cells correspond to the alteration in the mechanical behavior of the actin cytoskeleton. The worm-like chain (WLC) model (Discher et al., 1998; Li et al., 2005) was used to reflect the force–extension response of the actin filament. However, the Marko–Siggia WLC approach

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used in the models developed by Discher et al. (1998) and Li et al. (2005) present the flexible polymer and do not capture the semiflexible mechanical response of the actin filament (Palmer et al., 2010). Palmer and Boyce (2008) developed the MacKintosh-derived WLC model to reflect the semiflexible nature of the actin filament.

In this paper, we develop an actin cytoskeleton microstructural model to characterize the mechanical properties of cells via optical tweezers manipulation at single-cell level. The proposed model is represented by the three-dimensional random actin cytoskeleton network formed by the Delaunay triangulation method. Considering the highly weighted influence of the actin filament, we neglect the effect of microtubules and intermediate filaments in our modeling. The actin filaments and actin-binding proteins (ABPs) are used as the basic elements of the actin cytoskeleton network. The MacKintosh-derived WLC model is used to reflect the mechanical properties of the actin semiflexible polymer. ABPs are represented by the linear Hookean springs.

The proposed model exhibits the following unique features. First, the developed model highlights the influence of the semiflexible nature of the actin cytoskeleton on the mechanical properties of cells. Many microstructural models merely simplified the actin filament as the Hookean springs, and few of these models considered the influence of the semiflexible properties of

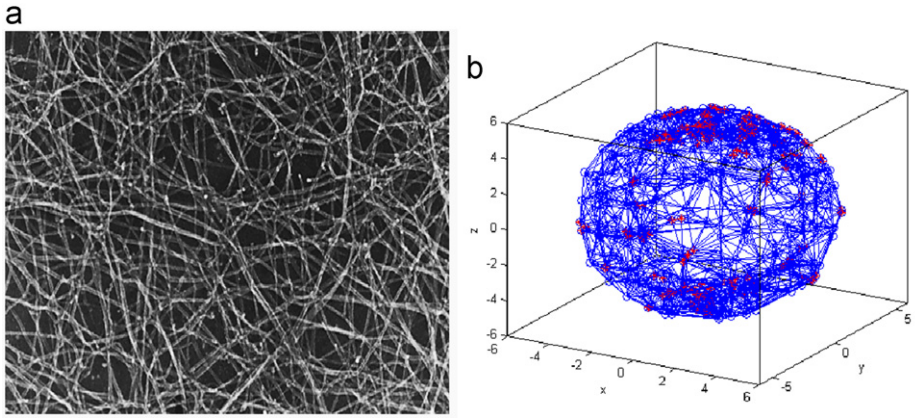

Fig. 1. Actin cytoskeleton structure (a) Electron micrograph image of the actin cytoskeleton adapted from Niederman et al. (1983); (b) schematic of the random actin cytoskeleton network, with actin filaments shown in blue and actin-binding protein in red. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

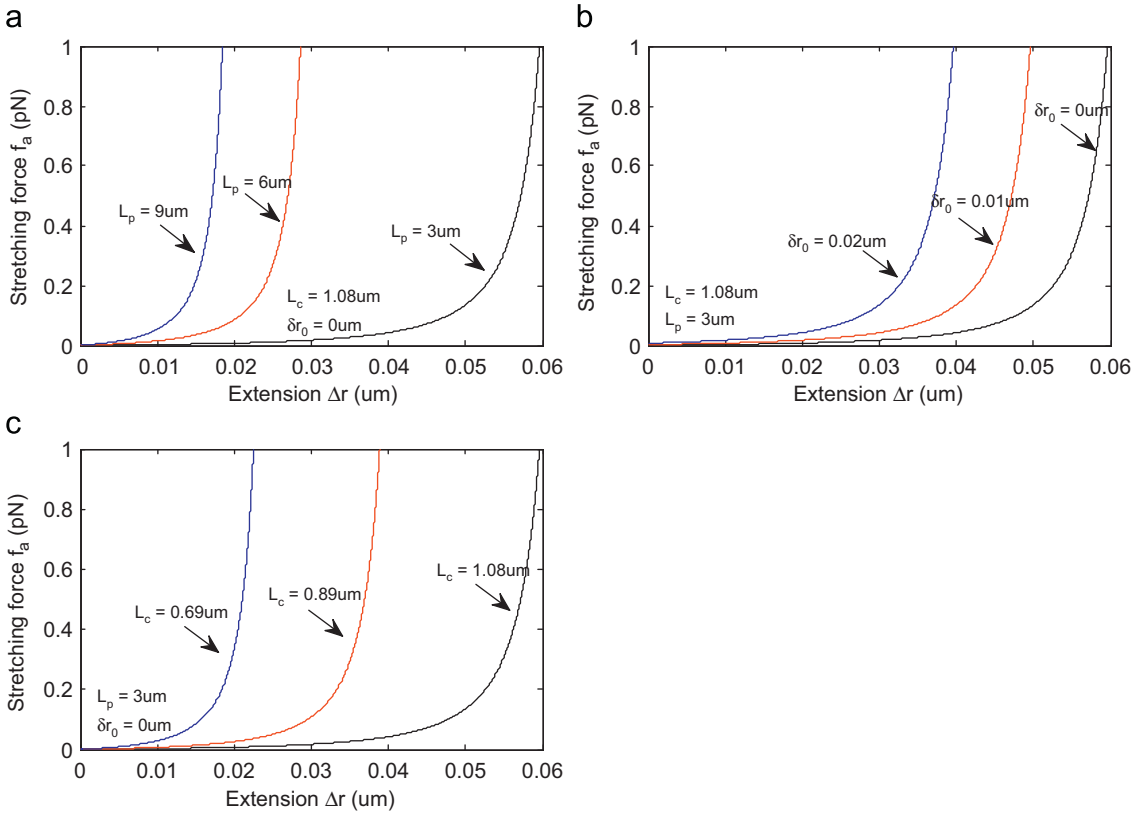

Fig. 2. The influence of the structural parameters of the actin filament on its force–extension behavior: the persistence length effect in (a), the prestress effect in (b) and the contour length effect in (c).