MICROMECHANICS OF CYTOSKELETAL ACTIN NETWORKS

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INTRODUCTION

The Cytoskeleton

Living cells have the ability to sense mechanical forces and convert them into a biological reponse. Examples are many sensory functions (including touch, hearing and gravity sensation), tissue growth and healing, bone remodeling, but also fundamental processes like cell growth, cell differentiation and cell death involve specialized mechanotransduction mechanisms. At the same time, genetic programs orchestrate complex cellular processes such as mitosis and cell motility, involving the generation of mechanical forces. The key cellular component that is responsible for the sensing, transmission and generation of mechanical forces is the cytoskeleton.

The cytoskeleton consists of three types of polymer fibers (see Fig. 1), made from different proteins and with different diameters: actin microfilaments (7nm), intermediate filaments (8-12nm) and microtubules (24nm). The structural form in which actin microfilaments appear is mediated by cross-links with actin-binding proteins. Near the cell cortex, actin filaments are usually either forming bundles or a three-dimensional network. Intermediate filaments and microtubules are centrally organized and their organization in the cell is often colinear, spanning the distance between nucleus and cell membrane. The three types of polymer fibers do not deform independently, but are usually interpenetrated and form contacts by entanglements or cross-binding proteins.

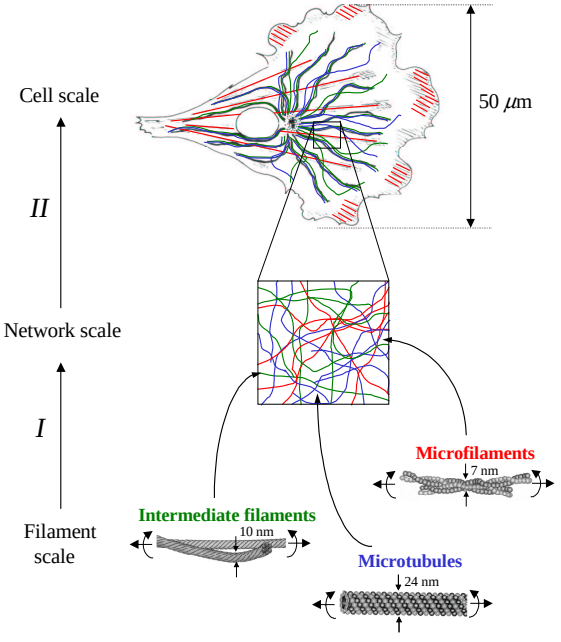

Fig. 1 Multiscale modelling approach to the cytoskeleton in cells.

A Multiscale Approach

We propose to model the cytoskeletal mechanics by using a multiscale modeling methodology (see Fig. 1). Three size scales are identified: (*i*) the scale of individual cytoskeletal filaments, (*ii*) the scale of a network of filaments and (*iii*) the scale of the cell. The goal is to bridge all size scales involved, from the scale of individual filaments all the way up to the cell scale. The focus of the current paper is on the scale transition of the filament scale to the network scale, directing our attention exlusively to the actin filament network.

ACTIN NETWORK MODELING

Single Actin Filament

The starting point in the multiscale approach outlined above is the response of a single F-actin filament. An actin chain is a semiflexible polymer which is often described by the so-called worm-like chain model (see e.g. [1]). This means that the chain is regarded as a very slender beam which is curved due to thermal undulations. The main mode of deformation is bending. Axial extension in the worm-like chain model is caused solely by stretching out the curvature, Fig. 2. Hence, the axial response is governed by the so-called persistance length $\ell = \kappa / k_B T$, where κ is the bending stiffness, T is temperature and k_B is the Boltzmann constant. It will be intruiging for a mechanics person that, even

though this type of chain stretching is akin to buckling but with a different sign, statistical physics treaments (see e.g. [2]) lead to the axial stiffness being proportional to κ^{-2} instead of κ. This is caused by the fact that the amplitude of the thermal undulations scales with $k_B T = \kappa / \ell$.

Although the worm-like chain model has been commonly accepted as the model for actin [1], this paper addresses some overseen features in order to assess its robustness for application in the multiscale framework. The model assumes that the undulations remain unchanged over the timescale of the applied deformation; what if the two timescales are similar? In particular, this is an issue under compression: how does the stretching-of-thermal-undulations (stiffness κ^{-2}) transform into buckling (stiffness κ)? This requires that the three-dimensionality of the undulations is taken into consideration as well as the coupling between bending, extension and torsion, all of which have been ignored so far.

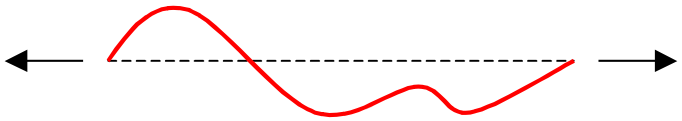

Fig. 2. Axial response of a flexible chain is controlled by the stretching of the thermal undulations.

Actin Network

We use the response of single actin filaments, as discussed in the previous section, to construct initially isotropic three-dimensional networks of actin microfilaments. We use the finite element method to explicitly model the actin network, featuring a tunable density of cross-links (mediated by actin-binding proteins). This enables us to explore the dependence of the overall stress-strain behavior on (*i*) the three-dimensional network architecture, (*ii*) the strength of the network cross-links/entanglements and (*iii*) the actin filament poperties. The effect of different actin-binding proteins (e.g. fascin, filamin, Arp 2/3, alpha-actinin) can be studied through their mechanical behaviour and characteristic cross-binding influence on network morphology (see e.g. [3]). Special emphasis will be put on the structural alterations that occur in the networks during straining. The results will be compared to experimental measurements and observations, and to existing theoretical models based on idealized representations of biopolymer networks, including reptation models, extended for semiflexible polymer networks (e.g. [2,4]), and a cubic unit cell model, representing an orthogonal, cross-linked network [5]. A key difference between the current approach and statistical mechanics approaches is that the three-dimensional network architecture is explicitly accounted for, featuring a direct mechanical coupling between cross-bindings/entanglements to the overall deformation behaviour.

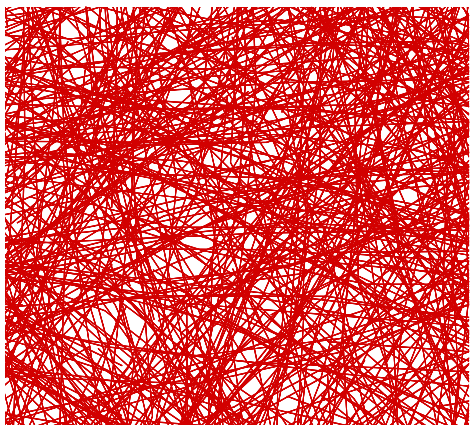

Fig. 3 Actin network model, constructed using the finite element method, enabling large scale simulations.

References

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