Mechanics and dynamics of biopolymer networks

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Summary

In this thesis, we presented a study on the collective mechanical and dynamical behavior of biopolymer networks. The largest part of this work is dedicated to the development of theoretical models for these systems, although we have also included some experimental studies and an extensive discussion of the comparison between our theoretical predictions and experimental results. This work was part of a fruitful collaboration with various members of the lab of Dave Weitz at Harvard University.

My work is directly inspired by the cytoskeleton of living eukariotic cells. One of the major structural components of the cytoskeleton is actin, which forms several micrometers long filaments that are cross-linked into a network structure. The mechanical properties of the cytoskeleton are tightly controlled by a large number of actin binding proteins that enable diverse cellular behavior such as division, locomotion, and shape changes. Nucleating and capping proteins regulate the polymerization of monomeric actin into filamentous actin (F-actin). Crosslinking proteins bind the actin filaments together to form elastic gels and bundle structures, whereas motor protein assemblies control tension within these networks by internally straining the actin filaments. Even though the important molecular components are known, relatively little is understood of how this large ensemble of proteins collectively contributes to the mechanical response of the cytoskeleton. One approach to investigate the origins of the mechanical response of the complex and composite structure of the cytoskeleton has been to study reconstituted *in vitro* F-actin networks in the presence of purified binding proteins. These reconstituted networks form simplified modulus of the cytoskeleton and allow for a precise control of its biochemical composition, which enables a systematic investigation of its properties. Both on the theoretical and the experimental level, this thesis follows this approach to study biopolymer networks.

In chapter 2, we investigated the dynamics of semiflexible polymer networks with transient cross-links. The intrinsic dynamics of physiological actin cross-linkers may have important implications for the constantly remodeling internal networks of cells. Recent experiments on F-actin networks with transient linkers provide evidence of a complex viscoelastic behavior. We developed a microscopic model for the long time network relaxation governed by cross-link dynamics. This cross-link governed dynamics (CGD) model describes the structural relaxation that results from many independent cross-linker unbinding and rebinding events. We showed that this model provides a good quantitative description of the complex stress relaxation in these networks. Finally we discussed the effects of large stresses on the dynamic mechanical response of these networks. We observe that the unbinding rate of the linkers is dramatically reduced in networks that are subjected to a constant stress; this reflects a stabilization of the cross-linker-actin bond under an applied load. On the macroscopic scale, the applied stress enhances the solid-like nature of the gel.

In chapters 3 and 4, we investigated the nonlinear elasticity of stiff polymer networks with flexible cross-linkers. We quantitatively showed that the nonlinear elastic response of actin gels cross-linked with the physiological linker filamin can be accounted for by the highly flexible nature of the filamin cross-links. To describe these systems we developed a self-consistent mean field theory for the macroscopic nonlinear elasticity of these networks. The networks are modeled as a collection of randomly oriented rods connected by flexible linkers to a surrounding elastic continuum, which is required to self-consistently represent the behavior of the network. Using this model, we also showed that the dominating failure mode of these networks is due to the rupture of actin-filamin bonds.

In chapter 5, we examined various rheological protocols for the measurement of the nonlinear response of biopolymer gels. Using both strain ramp and differential prestress protocols, we investigated the nonlinear response of a variety of systems ranging from extracellular fibrin gels to intracellular F-actin solutions and F-actin cross-linked with permanent and physiological transient linkers. In particular, we designed a new experimental protocol to investigate how both the linear and nonlinear mechanical response changes as the system creeps and deforms plastically under a large applied shear stress. In this protocol the differential response is determined under steady shear stresses of varying magnitude alternated with periods without load. The total strain and differential response are monitored continuously. We found that the nonlinear response measured with the prestress protocol is remarkably insensitive to creep. This demonstrates that the nonlinear mechanical response of these biopolymer networks is robust, even when the network is flowing. By developing a simple, yet general phenomenological model that includes the nonlinear elasticity of the network as well as network flow on long timescales, we provided further insight into this behavior.

In chapter 6, we investigated the elasticity of random fiber networks. Fibrous networks, such as those that form the cellular cytoskeleton or the extracellular matrix, exhibit rigidity at remarkably low connectivity—well bellow the Maxwell central force isostatic point. This rigidity is due to additional constraints provided by the fibers' resistance to bending. We studied disordered fibrous networks with variable coordination number, both above and below the central-force isostatic point. This point controls a broad crossover from stretching- to bending-dominated elasticity. We showed that this crossover exhibits an anomalous power-law dependence of the shear modulus on both stretching and bending rigidities. At the central-force isostatic point—well above the rigidity threshold—we find divergent strain fluctuations together with an associated divergent correlation length, implying a breakdown of continuum elasticity. Thus, in this simple mechanical system we observe a remarkably rich demonstration of zero-temperature critical phenomena.

In chapter 7, we studied the effects of motor generated stresses on stiff polymer

networks. Reconstituted *active* F-actin networks with motor proteins form a good model system for the study of cellular mechanics. The motor proteins generate forces that drive the network far from equilibrium and strongly affect the network mechanics. To elucidate the basic principles of the effects of force-generating motors on the mechanics of networks with the architecture of biopolymer networks with binary cross-links, we developed a lattice-based approach to design networks with a connectivity of 4 or less. We showed how heterogeneous internal stresses generated by motors can lead to stiffening in such networks that are governed by filament bending modes. The motors are modeled as force dipoles that cause muscle-like contractions. These contractions "pull out" the floppy bending modes in the system, which results in a dramatic stiffening of the networks' mechanical response.

In chapter 8, we investigated the origins of the elasticity of intermediate filament (IF) networks. Intermediate filament networks in the cytoplasm and nucleus are crucial for the mechanical integrity of metazoan cells. While filamentous actin and microtubules have been extensively studied, much less is known about IFs. In particular, the mechanism of cross-linking in these networks and the origins of their mechanical properties are not understood. In close collaboration with the experimental group of D. Weitz, we have shown that divalent ions can mediate a cross-linking interaction between the negatively charged tail domains of intermediate filaments. We used an affine model for the nonlinear elastic response of these systems, which includes both the entropic stiffening and the enthalpic stretching of the individual filaments, as well as geometric affects that arise in networks under large shear deformations. This model enabled us to extract microscopic parameters from the measured macroscopic rheological behavior, including the cross-linking lengthscale of the network as well as the Young's modulus and persistence length of the filaments.