Cooperativity and frustration in protein-mediated parallel actin bundles
Physical Review Letters **103**, 238102 (2009)
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Recommended with a commentary by Thomas R. Powers, Brown University

Many structures in the cell are formed by actin filaments bound together by cross-linker proteins. A ubiquitous motif is the bundle of actin filaments, which are used in the stereocilia of the hair cells in the inner ear [1] as well as the rod-like filopodia that form at the leading edge of a migrating cell [2]. The nature of the cross-linkers is crucial for the structure of the bundles and their biological function. For example, mutations of the espin cross-linker protein found in stereocilia have been linked to deafness [1]. Small-angle x-ray scattering studies have shown that wild-type espin leads to hexagonally-coordinated actin bundles, whereas the mutant leads to nematic ordering [3]. The much lower bending stiffness of the bundles with nematic ordering is thought to reduce the sensory capabilities of the stereocilia.

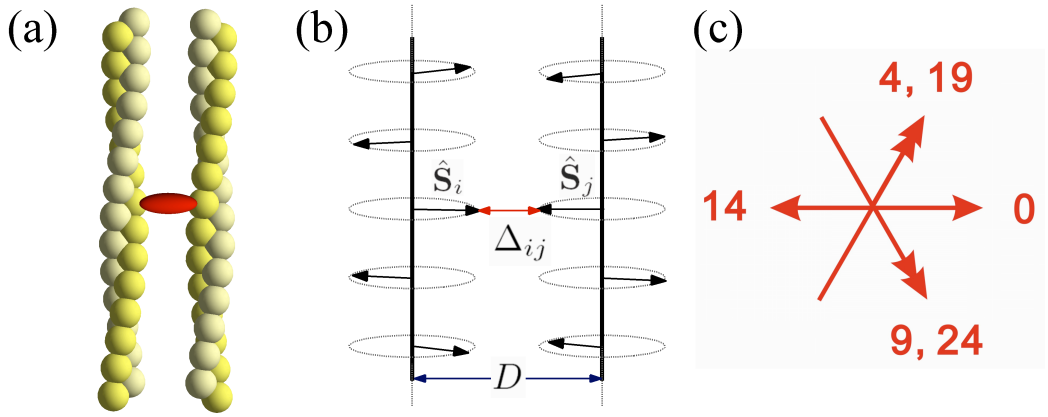

Figure 1: (a) Two actin filaments and a cross-linker. The geometry of each filament is 13/6, in which 13 monomers are found in exactly 6 turns. (b) Model in which the monomers are represented by planar spins $\hat{\mathbf{S}}_i$; the binding sites for the cross-linkers sit at the tips of the spins. The spins wind around in a left-handed manner. The vertical scale has been expanded relative to (a). (c) There are six monomers perfectly aligned with the hexagonal lattice directions in the predicted 28/13 structure. The red numbers label the monomers with cross-linkers. Cross-linkers can bind together neighboring filaments at these sites without stretching. Figure courtesy of Homin Shin, slightly modified from [4].

In a recent paper, Shin *et al.* [4] examine the mechanism of bundle formation by two different cross-linkers, espin and fascin. Fascin is found in filopodia. The authors use small-angle x-ray scattering to determine the bundle structure as a function of linker concentration. The actin filaments in the bundles form a hexagonal lattice. As the concentration of fascin increases, the twist of the filaments in the bundles increases smoothly [5], whereas the actin-espin system has only two states (which can coexist): native twist and over-twist.

To best appreciate these results, we must recall the twist structure of actin filaments. The monomers of actin form a tight left-handed helix, with 13 monomers every 6 turns (Fig. 1a). This structure is denoted as 13/6, and the angle between successive monomers is $-12\pi/13$, with the minus sign signifying left-handed twist. In bundles with high concentrations of either espin or fascin, the actin twist is increased relative to the native state to 13 turns per 28-monomers repeat, for an overtwist of $2\pi(13/28 - 6/13) \approx 1^\circ$.

What property of the linkers is responsible for difference in the nature of the transition from 13/6 to 28/13 with increasing linker concentration? The authors propose that the crucial property is the stiffness of the linkers, and they turn to theory to examine the question. Since the angles between successive monomers in either the 13/6 or 28/13 state are not commensurate with the angles of the hexagonal lattice, there is a competition between linker stretching and filament twisting. The key idea is to suppose that the filaments in the bundle do not twist uniformly but instead have blocks of uniform twist. In this way the number of perfectly aligned monomers (such as the middle monomers in Fig. 1) can be maximized while keeping the twist strain small. By exhaustively searching all composite twist structures up to 40 monomers in length, the authors found that the structure with the highest number of perfectly aligned monomers is a 28/13 structure, composed of two 4-monomer-long blocks of the undertwisted 24/11 structure, and four 5-monomer-long blocks of the overtwisted 30/14 structure. Consider a composite structure made with blocks in the order 455554. The angle between the first monomer of the first block, monomer 0, and the first monomer of the second block, monomer 4, is $-(2\pi)11/6$, or $\pi/3$ (Fig. 1c). Likewise, the 5-monomer blocks lead to a net angle of $-2\pi/3$. Thus, there are 6 sites per 28-monomer repeat with perfect alignment between the monomers and the hexagonal lattice directions. By permuting blocks and rotating filaments by $\pi/3$, all the filaments in the lattice may be linked at the aligned monomers to form a regular structure of cross-linkers.

To determine what fraction of the 6 sites per repeat are occupied as function of the concentration of cross-linkers in solutions, the authors use a simplified single-filament model that captures the essence of the interplay of filament twist and linker stiffness. The model shows that when a linker binds two filaments together at a particular site, it is favorable for other certain nearby sites to bind also. If the linkers are sufficiently stiff, there is a cooperative transition. The theory also predicts that the amount of overtwist is a monotically increasing function of the linker occupancy. Thus, the theory predicts that overtwist will increase smoothly with linker concentration for compliant linkers, and discontinuously for stiff linkers.

The combined experimental and theoretical results of Shin *et al.* give a beautiful picture of the nature of the transition from the native 13/6 state to the 28/13 state in cross-linked actin bundles. As the authors imply, it will be interesting to further investigate the role of the physical properties of the actin-binding proteins on the precision of the biological process of bundle formation in stereocilia and filopodia.

References

[1] M. M. Mogensen, A. Rzadzinska, and K. P. Steel. The deaf mouse mutant whirler suggests a role for whirlin in actin filament dynamics and stereocilia development. *Cell Motil. Cytoskeleton*, 64:496, 2007.

[2] J. Faix and K. Rottner. The making of filopodia. *Curr. Opin. Cell Biol.*, 18:18, 2006.

[3] K. R. Purdy, J. R. Bartles, and G. C. L. Wong. Structural polymorphism of the actin-espin system: a prototypical system of filaments and linkers in stereocilia. *Phys. Rev. Lett.*, 98:058105, 2007.

[4] H. Shin, K. R. Purdy Drew, J. R. Bartles, G. C. L. Wong, and G. M. Grason. Cooperativity and frustration in protein-mediated parallel actin bundles. *Phys. Rev. Lett.*, 103:238102, 2009.

[5] M. M. A. E. Claessens, C. Semmrich, L. Ramos, and A. R. Bausch. Helical twist controls the thickness of F-actin bundles. *Proc. Natl. Acad. Sci. U.S.A.*, 105:8819, 2008.