Biophysical *Journal*
New and Notable

Biophysical Society

The Inelastic Hierarchy: Multiscale Biomechanics of Weak Bonds

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Living tissue is a mechanical chameleon. It may behave as a viscous or elastic material, depending on how fast and strong you pull on it. It also responds plastically to permanent loads, as evidenced by the Tutankhamun-style lobe-stretching ear piercings that are currently regaining popularity. To mechanistically explain and quantitatively predict how such impressive versatility and resilience is accomplished by the molecular composition and architecture of living matter is the holy grail of biomechanics. In this issue of *Biophysical Journal*, Kurniawan and coworkers (1) take a major step toward establishing a multiscale hierarchy of weak bonds as one of the main governing principles underlying the unique mechanical performance of biological matter.

As a physiologically important model system, the authors studied fibrin, one of the most resilient naturally-occurring biopolymers, which self-assembles into hierarchical scaffolds consisting of entangled and weakly crosslinked networks of thick fibrin bundles made of much thinner semiflexible fibrin protofibrils. These scaffolds are the essential ingredients of natural blood clots as well as some biomimetic two-component glues employed in plastic surgery. Kurniawan et al. (1) systematically tuned the microstructural parameters of fibrin and used a combination of optical tweezers and fluorescence microscopy to measure, for the first time, the sticky mutual interactions of single fibrin fibers. Thereby, they could identify fiber stickiness as the molecular mechanism making the nonlinear elastic response of deformed and undeformed fibrin networks indistinguishable, although the sample partially breaks and never returns to the original state when deformed. Although one usually expects materials to weaken and possibly yield if internal bonds are broken upon deformation, fibrin's stickiness gives rise to some sort of mechanical homeostasis by constantly forming new bonds between the sticky fibers. It is not a priori self-evident how to strike such a perfect balance between elasticity and plasticity, though. The self-healing effect caused by sticky interactions is, in fact, known to be quite sensitive to the interactions and network architecture. It could easily have an overcompensating effect and lead to cyclic hardening, as, e.g., observed for reconstituted networks of crosslinked actin bundles (2).

By analyzing the rheological response of their fibrin networks to strains ranging from 0.1 to 500% Kurniawan et al. (1) uncover a hierarchy of inelastic yielding. Fibrin scaffolds adapt to moderate strains by network remodeling through the spontaneous formation and failure of transient bonds between the fibers, and they only adapt to larger strains by plastic remodeling of the fibers themselves. The latter mechanism had previously been identified by a comparative study of networks of fibrin and collagen (the major element of extracellular connective tissues and the most abundant protein on earth) (3). This study found strong similarities in the nonlinear mechanical response of both types of networks despite their pronounced structural and functional differences. Both exhibit stress stiffening, inelastic hysteresis, cyclic shakedown, and the Mullins effect. Kurniawan et al. (1) can now show more quantitatively how much of this rheological phenomenology is due to inelastic stretching of individual fibers and how much is due to an inelastic reworking of the network architecture.

The central observation, namely that weak interconnecting bonds within and between fibers allow for structural changes at all scales of self-assembled hierarchical fibrous networks, turns out to be very general. Such inelastic hierarchies were previously suggested to govern fibrous scaffolds of collagen (4) and intermediate filaments (5). Even for some less enigmatic cytoskeletal protein fibers, such as F-actin, and microtubules' structural plasticity (6) and friction-like interactions (7) have recently been shown to govern the mechanical interactions down to the molecular scale. On the other side

Submitted July 28, 2016, and accepted for publication July 28, 2016.

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Editor: Jochen Guck.
http://dx.doi.org/10.1016/j.bpj.2016.07.041

of the hierarchy, quite remarkable similarities have been demonstrated for the inelastic mechanics of transiently crosslinked cytoskeletal networks and living cells and cell aggregates (8–10).

What is common to all of those biomolecular assemblies is their hierarchical fibrous architectures, which are designed to occasionally break during normal everyday performance in response to internally generated or externally applied forces. Using the same general construction principle and tinkering with the details of the architectures, nature can thereby generate widely different materials ranging from ultra-soft slime to fingernails, with stiffness values spanning many orders of magnitude, irrespective of the precise molecular constituents. It is also common to all of these designs that they can adapt their stiffness to the prevailing stresses by viscoelastic stiffening and reversibly yield to imposed strains via inelastic fluidization, viz. the breaking of transient bonds (10). This dual strategy allows them to be elastically sturdy and malleable and adaptive, at the same time. It is widely believed that it might, moreover, play an important role in mechanotransduction, e.g., in triggering cell and tissue remodelling.

The upshot of all this is that biological specificity and function can reside to a large degree in the mesoscale architecture rather than in the potentially less restricted and, therefore often variable or highly redundant, atomic structure. Changes in the mesoscale architecture and ensuing changes in the mechanical properties of biomolecular scaffolds can thus have a severe and immediate physiological impact, e.g., when tumors become metastatic (11).

It would be intriguing if further quantitative studies of the inelastic response of single isolated cytoskeletal or extracellular filaments could directly quantify and compare the strength of their internal and mutual bonding. This could help to put on firmer grounds the notion of an inelastic hierarchy starting with a microstructure of relatively strongly bound elements on small scales giving rise to increasingly soft and malleable mesostructures on larger scales. Further, the universality of this construction principle should be made more explicit in mathematical modeling. So far, a range of models and ad hoc descriptions has been proposed to rationalize and quantify inelastic behavior here and there. But a comparison of the differences and similarities between these parallel approaches is currently missing, not to speak of a unified modeling framework that would allow one to quantitatively relate and compare results obtained with different measurement techniques and experimental protocols.

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