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Hierarchical toughening: a step towards matching the complexity of biological materials

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Organ transplants are capable of saving lives and improving the quality of life for people who suffer from illness or have experienced trauma. In order to perform these transplants an organ source is required, usually in the form of a living donor or from a cadaver. Being able to create synthetic organs and tissues is a “holy grail” of the biomaterials field and would allow surgeons significant freedom in the ability to treat patients without supply limitations and the ethical concerns of transplant lists. The reality is that matching the awesome complexity of living organs is extremely difficult and requires significant scientific advancement in wide-ranging fields.

Narrowing our focus towards specific load bearing tissues such as ligaments and tendons, some specific requirements become obvious. These materials must be strong enough to support the significant forces they experience, yet tough enough to prevent failure over a long lifespan. They must also be able to integrate seamlessly with the everchanging active environment of the human body. Requirements of biomaterials can be oversimplified into three categories: mechanical, biocompatibility, and functionality, and it is extremely difficult to develop materials that simultaneously possess all three. Carbon fiber may possess the mechanical strength to act as a ligament replacement, yet independently it is not biocompatible. Poly(dimethylacrylamide) and other simple hydrophilic polymers can be used to form a biocompatible hydrogel yet cannot support the loads experienced by these tissues. Furthermore, methods are still required to enable the active participation of synthetic materials in maintaining health and homeostasis.

To attempt to overcome mechanical limitations, researchers have focused on implementing toughening mechanisms into soft materials. The goal of these toughening mechanisms is to prevent rapid and uncontrolled failure that occurs from ever-present defects that occur during synthesis or fabrication. During brittle failure, a crack will quickly run through the bulk of a material, leaving two mostly pristine fragments. Polymer strands at the crack ruptured while away from the crack the network is unperturbed. Using an automobile as an analogy, this is akin to a car breaking down due to running out of gas—the majority of the

car is in excellent condition, yet it will not run. In tough gels with sufficient toughening mechanisms over many length scales, widespread damage occurs prior to fracture. Before a crack can grow, polymer strands must fracture throughout the entire bulk, even far away from the initial defect. Returning to our analogy, our car has again broken down, but this time the engine froze, the windows blew out, and the wheels fell off. One can imagine the simultaneous occurrence of all of these problems is exceedingly rare, and likewise is the probability of spontaneous failure of a multi-length scale reinforced tough material.

To make robust materials, researchers have developed methods of both molecular and macroscale toughening. One of the first techniques developed is called the double network concept, where a stiff and brittle sacrificial network is synthesized that interpenetrates a stretchable omnipresent polymer network.¹ Upon stretching, the covalent bonds of the sacrificial network break, dissipating energy. Sacrificial bonds have since been extended to weak bonds, such as ionic or hydrogen bonds, with the added benefit of reformability of the sacrificial bonds when stress is released.² The essence of this concept has also been extended to the macroscale, where fabricated fabrics or rigid skeletons can be used to act as sacrificial networks.³⁻⁶ However, in most cases, the aim has been to implement toughening mechanisms at a prechosen length scale: developing a hierarchical toughening mechanism that works from the molecular- to the macro-scale and the length-scales in-between would be revolutionary.

A recently published article entitled “Strong tough hydrogels via the synergy of freeze-casting and salting out” by Ximin He and coworkers has demonstrated that significant strengthening and toughening of soft materials is possible through the fabrication of multi-length-scale, hierarchical, anisotropic structures.⁷ A solution of poly(vinyl alcohol) (PVA) was immersed into an ethanol cooler bath at a controlled rate to form aligned ice crystals, while causing densification of the polymer phase. Subsequent immersion in a salt solution of sodium citrate for an extended period caused phase separation and crystallization to occur within the polymer phase. The resulting structure possesses unique structure over

many length-scales (**Figure 1a**). At the largest length scale, channel structures are observed, similar to the fibrillar structure seen in natural tendon. Within a single fibril, a porous nanostructure is further observed, made up of the flexible polymer network. Through one simple fabrication method, hierarchical, anisotropic poly(vinyl alcohol) (HA-PVA) hydrogels can be formed.

The mechanical properties of HA-PVA are excellent. From the stress-strain curve of HA-PVA formed from 5wt% PVA, we see these materials have both high failure stress of around 12 MPa, and a failure strain of over 30 (**Figure 1b**). The combination of both high failure stress and strain means the toughness, or the energy required to fracture the material, is extremely high, $\sim 200 \text{ MJ m}^{-3}$. These materials are also fatigue resistant, demonstrating no

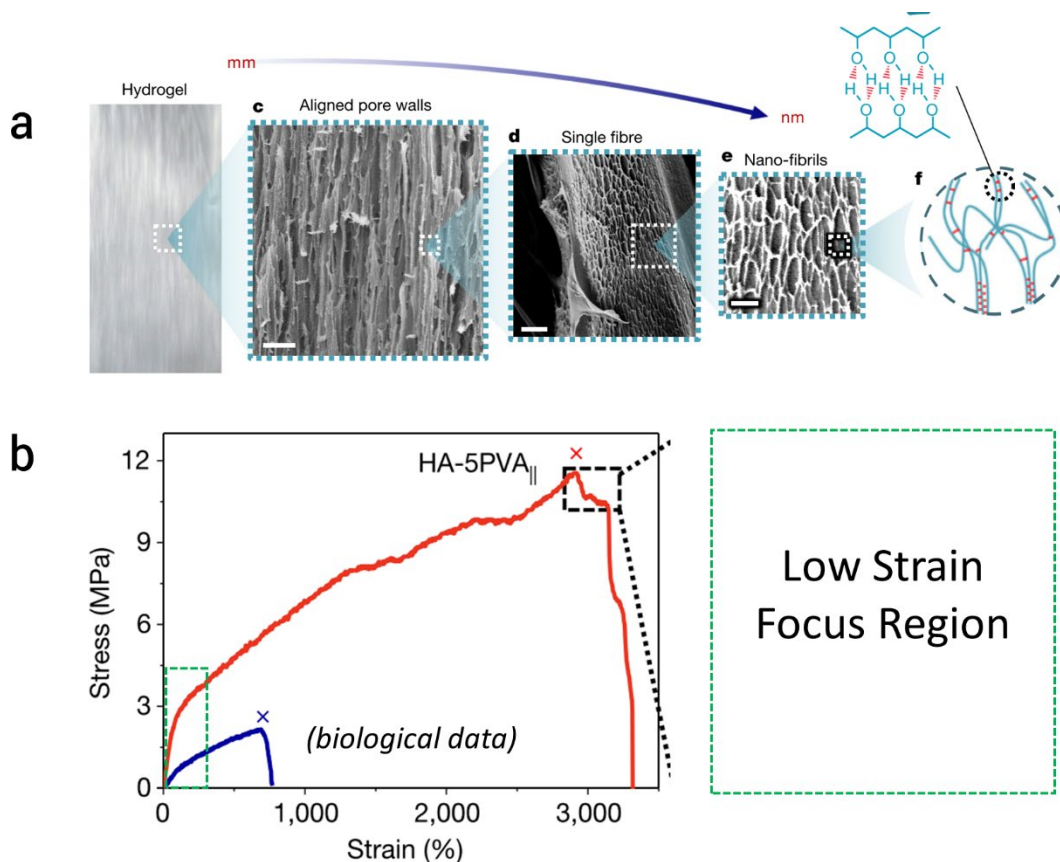


Figure 1. Physical and mechanical properties of hierarchical, anisotropic poly(vinyl alcohol) hydrogels. a) images of the structure of these gels at varying length-scale. b) Mechanical response of an HA-5PVA gel, compared to biological tissues.

crack propagation over 30,000 cycles, even with a high applied load (energy release rate: 10 kJ m^{-2}). The properties shown here make them extremely suitable for biomaterials, as they match or exceed the mechanical properties of many important biotissues (**Figure 1b focus region**).

The resulting hierarchical design possesses toughening mechanisms over many length-scales. On the molecular level, hydrogen bonds can break and reform, either in their home location, or at a new position after deformation. The nano-fibrils are capable of deforming, but due to their differing individual lengths, will break over large areas, dissipating energy. On the largest scale, the fibers that were formed by ice templating can support and distribute load over large areas, further making use of the aforementioned dissipation mechanisms, similar to fiber-reinforced composites.⁸ Importantly, the fabrication process introduced here results in a direct connection between the molecular- and macro-scale. The combination of these toughening mechanisms results in the incredible synergistic toughening observed in these materials.

The hydrogels developed here demonstrate an important step towards the fabrication of robust biomaterials. However, some challenges still exist in the fabrication of synthetic tissues and organs regarding their *in vivo* suitability. All tissues, from bone to fat, play a role and are actively connected to the living organism. Now that we have at our disposal a method to match the incredible complexity of natural structures, we need to consider their involvement and function within active systems. Can they be incorporated into the active circulatory system and metabolism of the human body? Furthermore, can we tune their mechanical response so that they more closely match specific tissues? For example, many tissues exhibit a specific “J-shaped” character that allows for some initial stretch before hardening occurs.⁹ The further modification of these robust, tough gels to match specific functions is an important next step.

While there are still many challenges yet to be overcome, the breakthroughs demonstrated by He and coworkers mark an important step towards the fabrication of synthetic biotissues that will improve life for everyone.

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