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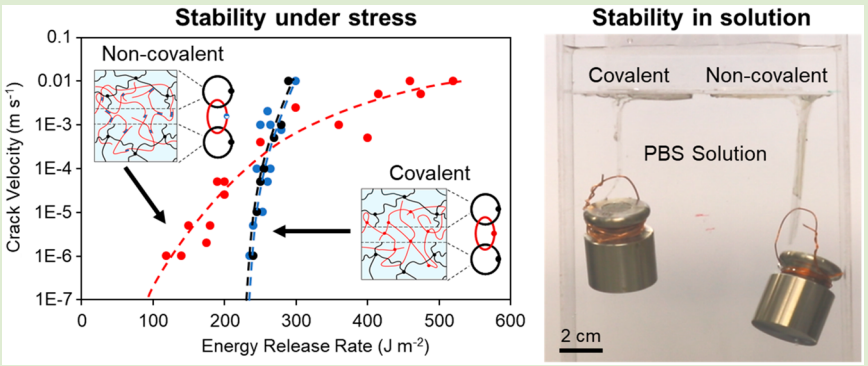
# Covalent Topological Adhesion

Jason Steck, Jiawei Yang, and Zhigang Suo*

John A. Paulson School of Engineering and Applied Science, Kavli Institute for Nanobio Science and Technology, Harvard University, Cambridge, Massachusetts 02138, United States

Supporting Information




**ABSTRACT:** Tough adhesion between wet materials (i.e., synthetic hydrogels and biological tissues) is undergoing intense development, but methods reported so far either require functional groups from the wet materials, involve toxic chemicals, or result in unstable adhesion. Here, we present a method to achieve biocompatible, covalent adhesion, without requiring any functional groups from the wet materials. We use two hydrogels as model adherends that have covalent polymer networks, but have no functional groups for adhesion. We use an aqueous solution of biopolymers and bioconjugate agents as a model adhesive. When the solution is spread at the interface of the hydrogels, the biopolymers diffuse into both hydrogels and cross-link into a covalent network in situ, in topological entanglement with the two polymer networks of the hydrogels. We characterize the chemistry and mechanics of the covalent topological adhesion. In a physiological fluid, the covalent topological adhesion is stable, but a noncovalent topological adhesion separates. Covalent topological adhesion presents immediate opportunities to advance the art of adhesion in diverse and complex environments.



Adhesion between hydrogels and various materials is essential to many existing and emerging applications, including hydrogel ionotronics,[1,2] bioelectronics,[3] tissue adhesives,[4,5] wound closure,[6,7] and drug delivery.[8,9] Hydrogels are used in these applications because of their unique combination of properties, such as biocompatibility, high stretchability, tunable stiffness, molecular permeability, and ionic conductivity. However, the abundance of water in hydrogels has long made it difficult to adhere hydrogels to most materials, including themselves. Tough hydrogel adhesion has seen transformative advances recently.[10] Existing methods either restrict to specific functional groups,[5,11] require chemical modification,[12−14] or use cytotoxic glues.[15] Recently developed topological adhesion overcomes these issues by forming a stitching polymer network in situ, in topological entanglement with the polymer networks of two preformed materials (Figure 1a).[16] Topological adhesion requires no functional groups from either material, achieves tough adhesion, and retains softness. Topological adhesion demonstrated so far forms the stitching network using noncovalent interactions, such as hydrogen bonds[16] and polyelectrolyte complexes,[17] which are vulnerable to dissociation in environments with ions or pH variation. Furthermore, many noncovalent interactions show pronounced rate-dependent behavior, which can spontaneously dissociate under sustained load, and lose adhesion.[16,18−21] Developing a method of tough and stretchable adhesion with biocompatibility, chemical generality, and long-term stability remains a challenge.

Here we report a method of covalent topological adhesion between two wet materials (Figure 1b). In general, adhering two wet materials requires each material to have a preformed polymer network. If either material contains monomers or uncross-linked polymers, when the two materials are placed in contact, they will diffuse and form an interpenetrating network. Here we focus on a common and particularly challenging case: the two wet materials have covalent polymer networks, but have no functional groups for adhesion. Therefore, they adhere weakly by themselves. We spread a thin layer of an aqueous solution of biopolymers and bioconjugate agents on the surface of one wet material, and place another wet material on top. Subsequently, two kinetic processes concur: the biopolymers and bioconjugate agents diffuse into the wet materials, while

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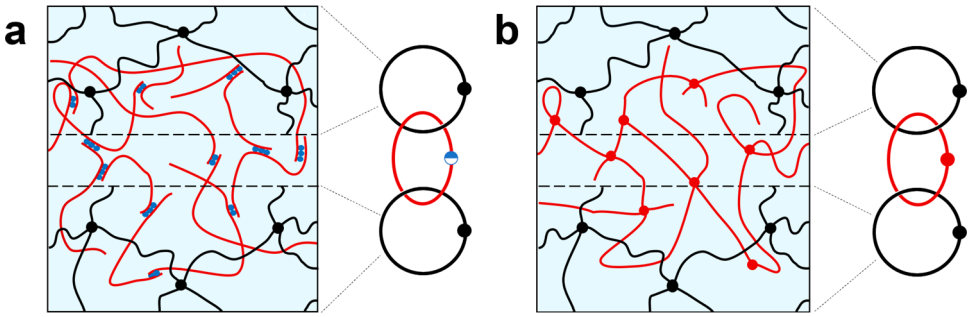


**Figure 1.** Topological adhesion of wet materials. Each of the two wet materials has a polymer network (black) of covalent cross-links, but the two networks have no functional groups to interlink. A species of stitching polymers (red) diffuse into the two wet materials, form a thin layer of network in situ, in topological entanglement with the polymer networks of the two wet materials. (a) In noncovalent topological adhesion, the stitching polymers form a network of noncovalent cross-links. (b) In covalent topological adhesion, the stitching polymers form a network of covalent cross-links. In the diagrams of the two topologies, we represent a polymer network by a circle, a covalent cross-link by a filled dot, and a noncovalent cross-link by a half-filled dot.

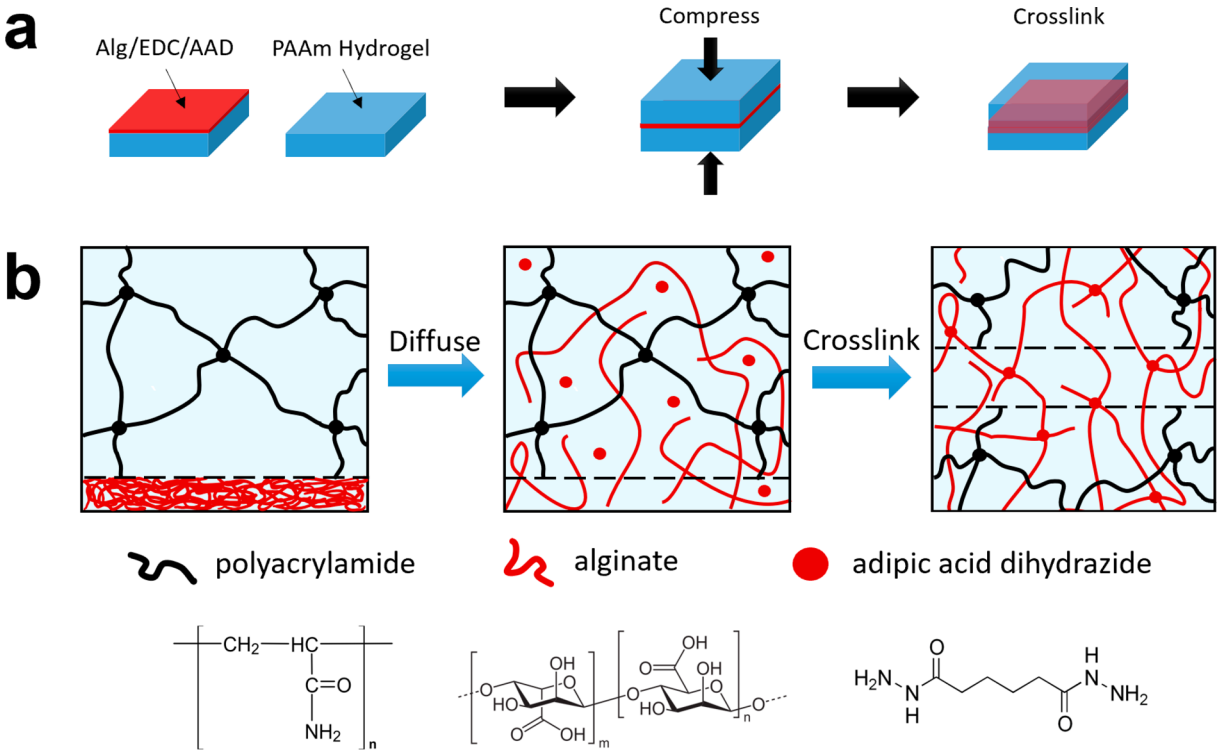


**Figure 2.** Covalent topological adhesion of two polyacrylamide hydrogels. (a) An aqueous solution of alginate, coupling agents NHS and EDC, and bioconjugate agent AAD, is spread at the interface of two PAAm hydrogels, which are subsequently compressed for a certain amount of time. (b) During compression, all ingredients diffuse into both PAAm hydrogels, and AAD forms covalent cross-links between alginate chains in the presence of EDC and NHS. The alginate network is in topological entanglement with both PAAm networks.

the bioconjugate agents cross-link the biopolymers into a covalent network in situ, in topological entanglement with the polymer networks of the two wet materials. We note (i) the topological entanglement does not require any functional group from either adherend, so that our approach is chemically general; (ii) separation of adhered wet materials requires at least one of either the stitching network or one of the two pre-existing networks to rupture, so that the adhesion is tough; (iii) the stitching network is covalently cross-linked, so that the adhesion is stable in most environments.

We demonstrate the principle of covalent topological adhesion using polyacrylamide (PAAm) hydrogels as model wet materials that have covalent polymer networks, but have no functional groups for adhesion. We use alginate (Alg) as a model biopolymer, and adipic acid dihydrazide (AAD) as a bioconjugate agent for alginate, in the presence of coupling agents *N*-hydroxysuccinimide (NHS) and 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDC). EDC couples an amine group on an AAD molecule and a carboxylic acid group on Alg to form a peptide bond,[22] while NHS stabilizes the amine-reactive intermediate of EDC, thereby increasing the cross-linking reaction efficiency. It is known that AAD, EDC, and NHS are biocompatible and the EDC chemistry is commonly used in tissue engineering.[23,24] We choose alginate as a model stitching polymer because alginate can also be cross-linked by calcium ions, so that we can compare the covalent and noncovalent topological adhesion.



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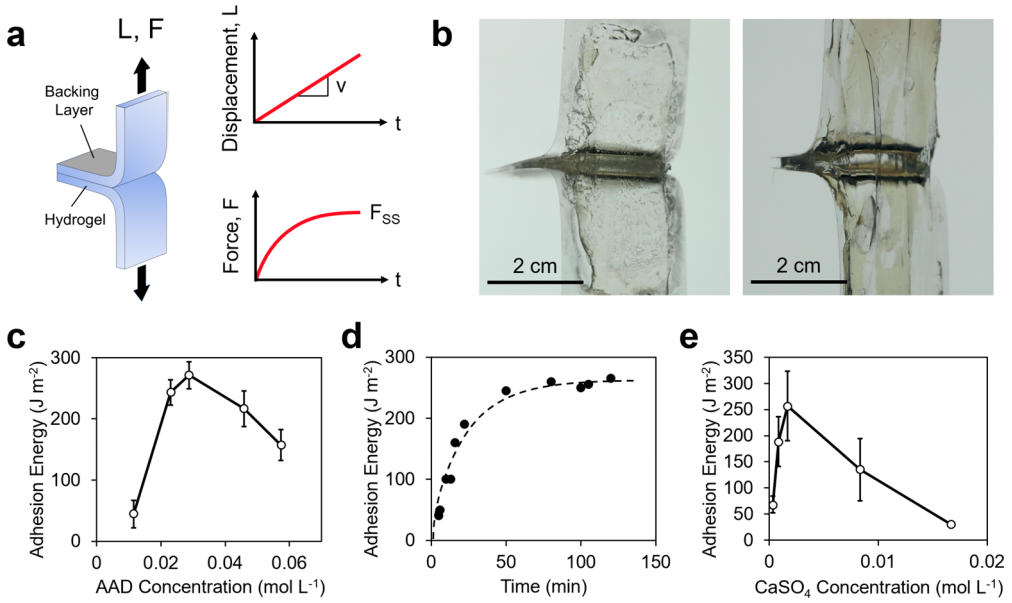


**Figure 3.** Adhesion energy as a function of several variables. (a) T-peel test. Peel velocity is prescribed, and the force as a function of time is measured. $F_{ss}$ is the peel force at the steady state. (b) Photos of the peel test. Left: adhesive peel. Right: cohesive peel. (c) Adhesion energy as a function of AAD concentration. (d) Adhesion energy as a function of time after contact. (e) Adhesion energy as a function of $CaSO_4$ concentration.

Following the procedure described in our previous study, we prepare an aqueous solution by mixing alginate, AAD, EDC and NHS, spread on the surface of one piece of PAAm hydrogel, with thickness about 500 $\mu$m, and then immediately press the other PAAm hydrogel on top, with a compressive strain of ~5.5% (Figure 2a). The alginate chains, AAD, EDC, and NHS at the interface diffuse into both hydrogels simultaneously. The alginate chains are covalently cross-linked by AAD in the presence of EDC and NHS, and form a covalent network in situ, in topological entanglement with both PAAm networks. The topological adhesion forms by two concurrent kinetic processes: diffusion and reaction. Since the diffusion of small molecules can be orders of magnitude faster than that of alginate chains, tough adhesion requires careful balance of kinetics. Compared to diffusion, the reaction cannot be too fast so that the alginate network forms outside the hydrogels, and also cannot be too slow so that AAD, EDC, and NHS diffuse away into both hydrogels and cannot cross-link alginate chains. In our system, the two kinetic processes are concurrent. As the aqueous solution of alginate, AAD, EDC, and NHS is spread at the interface, small molecules AAD, EDC, and NHS diffuse orders of magnitude faster than that of long-chain alginate. This can be seen from the Rouse model $D = kT/(N\eta b)$, where $kT$ is the temperature in the unit of energy, $\eta$ is the viscosity of water, $b$ is the size of the repeating unit of the long-chain polymer, and $N$ is the number of the repeating units, which is typically around 1000 for long-chain polymers and 1 for small molecules. Within the window of reaction time, some amount of AAD, EDC, and NHS have already diffused away from the alginate chains, while the remaining amount should still be able to cross-link alginate chains into a network. An insufficient amount fails to form a network, and an excessive amount leads to a brittle network. Both cause weak adhesion. The optimal balance is provided such that the amount is just right to form a network that can achieve highest adhesion energy. As will be shown later, tough adhesion is achieved in an optimal concentration of AAD.

To study the chemistry and mechanics of covalent topological adhesion, we measure the adhesion energy as a function of several variables using a T-peel test (Figure 3a). The loading machine applies a constant velocity between the two arms, and records the force. Once in steady-state peel, the crack advances at a velocity equal to one-half of the machine velocity, and the adhesion energy is equal to two times the force divided by the width of the sample. We measure adhesion energy 24 h after contact to ensure equilibrium state, since the bioconjugation reaction reaches equilibrium in ~2 h.[5] When adhesion energy is below ~200 J m$^{-2}$, the sample peels along the interface, and the peeled surfaces are smooth (Figure 3b). Otherwise, the sample peels by cohesive failure of PAAm, and the peeled surfaces are coarse. The adhesion energy attains a maximum of ~270 J m$^{-2}$ at an intermediate AAD concentration of 0.0287 M (Figure 3c). When AAD concentration is too low, the alginate network is loosely cross-linked and, thus, readily ruptures. When AAD concentration is too high, the alginate network is densely cross-linked, thereby inhibiting the diffusion of alginate and suppressing the topological entanglement. To test this hypothesis, we vary AAD concentration and measure the gelation time of alginate solution (Figure S1, Supporting Information). Indeed, reaction kinetics do not change with AAD concentration, suggesting that the loss of adhesion energy is due to diffusion and cross-linking density of alginate chains. We study the kinetics of adhesion by measuring adhesion energy as a function of time after contact (Figure 3d). The optimal AAD concentration is used. The adhesion energy rapidly increases in the first 20 min and plateaus after ~2 h. Note that adhesion energy already reaches about 100 J m$^{-2}$ in the first 10 min, which is sufficient in most applications. Importantly, when the adhesion energy reaches plateau value, the adhesion is so tough that the sample peels inside a hydrogel, rather than on the interface.

A covalent bond is tough and stable, whereas a collection of noncovalent bonds can also be tough, but may not be stable. We test this expectation by making a noncovalent topological adhesion using calcium cross-linked alginate network (Ca-Alg),



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where pure alginate chains diffuse into two $CaSO_4$ containing PAAm hydrogels, cross-link into a network in situ, in topological entanglement with both hydrogel networks. We vary the $CaSO_4$ concentration, and measure adhesion energy 24 h after contact (Figure 3e). The highest adhesion energy achieved is 260 J $m^{-2}$, when $CaSO_4$ concentration was about 0.00167 M, similar to that by covalent topological adhesion.

Next, we compare the stability of the covalent and noncovalent topological adhesion. The adhesion energy is measured as a function of crack velocity, which is half of the machine velocity (Figure 4). Also, included is the fracture

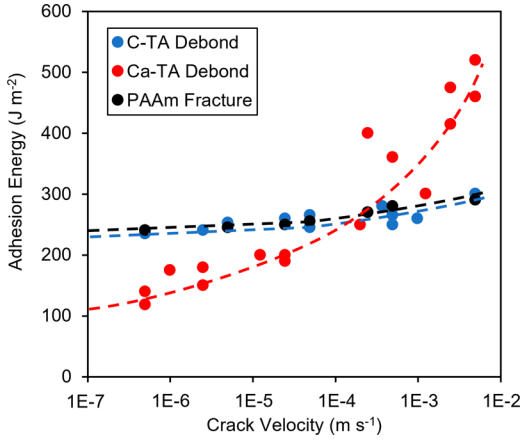


**Figure 4.** Adhesion energy as a function of crack velocity. Two PAAm hydrogels are topohered with either covalent alginate network (C-TA) or $Ca^{2+}$ cross-linked alginate network (Ca-TA). Also plotted is the fracture energy of a homogeneous PAAm hydrogel. Both C-TA debond and PAAm fracture show similar adhesion energy for all crack velocities, approaching ~250 J $m^{-2}$ as the crack velocity approaches zero. For the Ca-TA debond, the adhesion energy increases greatly with crack velocity but approaches ~100 J $m^{-2}$ at lower crack velocities. Each data point represents a single test.

energy of a pristine PAAm hydrogel. The data show that the adhesion energy of the PAAm topohered by covalently cross-linked alginate (C-TA debond) is similar to that of the PAAm fracture at all crack velocities, and both arrive at a constant value of 250 J $m^{-2}$ as the crack velocity approaches zero. This comparison indicates that covalent topological adhesion is peeled by the cohesive fracture of the hydrogel. In contrast, the adhesion energy of the PAAm topohered by ionically cross-linked alginate (Ca-TA debond) varies greatly with the crack velocity. The adhesion energy is 500 J $m^{-2}$ at a crack velocity of 0.005 m $s^{-1}$, but reduces to only ~120 J $m^{-2}$ at a crack velocity of 0.5 $\mu$m $s^{-1}$. By extrapolation, the energy release rate approaches 100 J $m^{-2}$ as the crack velocity approaches zero. The structure of ionic topological adhesion resembles that of a PAAm/Ca-Alg double-network hydrogel.[25,26] If the crack velocity is fast, the ionic bonds in the Ca-Alg network unzip in a large region near the crack tip and dissipate a significant amount of energy. Such dissipated energy amplifies the adhesion energy, which may lead the measured adhesion energy to exceed the fracture energy of the PAAm hydrogel itself. The unzipping of Ca-Alg network can occur even when the sample peels by the cohesive fracture of PAAm, so long as the crack is not too far from the region stitched with the Ca-Alg network. If the crack velocity is slow, the ionic bonds of the Ca-Alg network can dissociate in a thin layer of the interface, which dissipates a small amount of energy. The adhesion energy is low, the sample peels by interfacial fracture, and the PAAm networks remain intact (Figure 3b). Covalent topological adhesion does not show large variation of adhesion energy with crack velocity, which is necessary for applications requiring stable adhesion under prolonged loading.

To demonstrate potential use in biomedical applications, we show the stability of covalent topological adhesion in phosphate-buffered saline (PBS) solution. Noncovalent topological adhesion is also prepared for control. We attached both C-TA bonded PAAm and Ca-TA bonded PAAm to a rigid acrylic plate and hung a weight of 2 N from each hydrogel. The applied force does not cause debond of either hydrogel. Then, the apparatus is lowered into a bath of 20× PBS. PBS solution can cause ion exchange with Ca-Alg,[27,28] but not with covalently cross-linked alginate. We observe that the C-TA bonded PAAm remains stable, and the crack front does not progress throughout the entirety of the test. In contrast, the Ca-TA bonded PAAm immediately starts to peel at a crack velocity of ~1 mm $s^{-1}$, and after 30 s, it is fully separated (Figure 5; Movie S1, Supporting Information). In this work we have focused on improving the stability of topological adhesion by forming covalent bonds. In our system, it is possible that some factors may limit the lifetime of adhesion. For example, swelling of either the hydrogel or the alginate network weakens their toughness and, thus, reduces the adhesion energy; another factor may be the enzyme attack of alginate to cause degradation. The ideal system for long-term stability would use hydrogels and stitching polymer

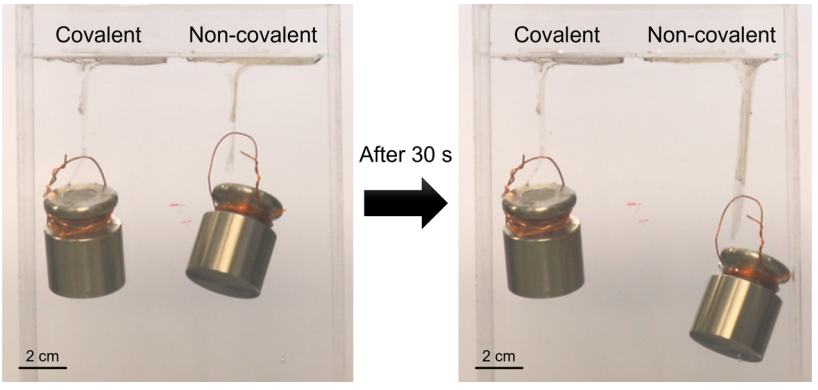


**Figure 5.** Stability of covalent and noncovalent topological adhesion in PBS solution. After 30 s, the covalent topological adhesion does not separate, while the noncovalent topological adhesion separates at a velocity of ~1 mm $s^{-1}$.



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network that are both mechanically and chemically stable in physiological solution. This is a potential topic of future study.

In summary, we have developed a method of covalent topological adhesion for tough adhesion of wet materials that requires no specific functional groups from both wet materials and preserves stable adhesion. The bioconjugation reaction used here is one of many that may be utilized to achieve adhesion with biopolymers.[29] For example, click chemistry is a one-step reaction that allows the joining of specific biomolecules in a mild environment and is bioorthogonal. Covalent topological adhesion using click chemistry can achieve tough and stable adhesion to biological tissues without chemical reaction with the tissues.[30] The stability afforded by covalent topological adhesion enables the use of hydrogel adhesives in environments that were previously inaccessible, such as the gastrointestinal tract, and in applications requiring prolonged stress, such as soft strain sensors and bioelectronics. This stability may motivate the future design of long-term tissue adhesives and sensors. Furthermore, covalent topological adhesion can be further used to develop medical implants and tissue replacements that seamlessly and permanently integrate with the body. It is hoped that the plurality of covalent cross-link chemistries is explored to achieve universal and tailored adhesion between soft materials.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.9b00325.

Material preparation, experimental methods, and additional experimental data (PDF)

Covalent topological adhesion is stable in 20× PBS solution while noncovalent topological adhesion readily debonds (MP4)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: suo@seas.harvard.edu.

### ORCID

Zhigang Suo: 0000-0002-4068-4844


### Notes

The authors declare no competing financial interest.

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