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Poly-albumen: Bio-derived structural polymer from polymerized egg white

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ABSTRACT

Bio-derived materials could play an important role in future sustainable green and health technologies. This work reports the synthesis of a unique egg white-based bio-derived material showing excellent stiffness and ductility by polymerizing it with primary amine-based chemical compounds to form strong covalent bonds. As shown by both experiments and theoretical simulations, the amine-based molecules introduce strong bonds between amine ends and carboxylic ends of albumen amino acids resulting in an elastic modulus of ~4 GPa, a fracture strength of ~2 MPa and a high ductility of 40%. The distributed and interconnected network of interfaces between the hard albumen and the soft amine compounds gives the structure its unique combination of high stiffness and plasticity. A range of in-situ local and bulk mechanical tests as well as molecular dynamics (MD) simulations, reveal a significant interfacial stretching during deformation and a micro-crack diversion leading to an increased in ductility and toughness. The structure also shows a self-stiffening behavior under dynamic loading and a strength-induced aging suggesting adaptive mechanical behavior. This egg white-derived material could also be developed for bio-compatible and bio-medical applications.

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1. Introduction

Designing materials either by inspiration from nature or extraction from natural materials is always a fascinating idea for materials scientists. The two-fold benefit of such materials development is first to build a green earth (with close cycle materials usage, i.e. zero waste) and second to connect scientific development (bioelectronics and biomedical devices) to the living world. The designed bio-inspired materials mostly result in unique architectures with several interesting properties such as self-stiffening, self-healing etc. [1–6]. There has been a large effort in recent past by the bio-material community to design and fabricate artificial materials that are porous [7–9], stiff [10–12], and bio-compatible [13]. In a search for such materials, several ceramic-based [13–15], carbon-based [16–18] and collagen-based [15] composites have been proposed.

The search for completely biodegradable materials is not restricted to structural applications only. With an explosion of implantable electronic devices, there is a need to find implantables that can disappear within the body by resorption [19,20] without causing any problem to the user. Therefore, finding such materials can be useful to the field of implantables with improved health.

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Taking inspiration from nature, this work demonstrates the clever use of biological building blocks [21,22] through the cross-linking chemistry to make a unique, interesting and unexplored bio-polymer material. We used egg white, which consists of protein macromolecule (albumen) and water, as our building block, and 'polymerized' it with bio-compatible molecules to create a poly-albumen (PA) polymer. Egg albumen is crosslinked with primary amine-based molecule like diethylenetriamine (DETA) to build the bio-polymer. A simple physical mixing process followed by natural (sun light) and oven heating is used in this simple process. The mechanical properties of PA are determined using standard macroscopic tensile and compression tests. The results are further verified using in-situ local indentation and AFM modulus mapping, which is further supported by molecular dynamics (MD) simulations. To explore unique mechanical properties of PA, we have measured stiffness as a function of frequency and aging times. Although the individual components used to make PA are bio-compatible and even edible, we have confirmed the bio-integrity of PA using the biological cell viability and cell growth and illustrated the use of PA as circuit board material for implantable electronics.

2. Experimental section

2.1. Synthesis of poly-albumen

To prepare the material, amine-based crosslinker diethylenetriamine (DETA) was added to egg white liquid extracted from chicken eggs. Specifically an increasing amount of crosslinker (5%, 10%, 20%, 40% etc.) was added in egg white (3 ml) to initiate polymerization, mixed thoroughly, degassed in a vacuum oven and cured at 50 °C for an hour. The discussion is mainly focused on the films which was 5% and 10% of cross-linker in egg white.

2.2. Physical characterization

Fourier transform infrared spectroscopy (FTIR) test was conducted on a Nicolet FTIR Infrared Microscope. Thermo-gravimetric analysis (TGA) was done on a Q600 (TA Instruments, USA) equipped with a DTA to study thermal stability of composite. The material was subjected to a temperature ramp test from 30 °C to 100 °C at 10 °C/min. Optical images were taken on a MM Optical machine while high resolution scanning electron microscope (SEM) images were taken on a FEI Quanta 400 ESEM, at scanning electricity of 15–20 kV. Spectroscopy was performed on a Cary 5000 UV–Vis–NIR spectrophotometer (Agilent Technologies, USA) using specialized sample holder to hold the material in the beam path during the measurement. After first test, the material was soaked in water for 5 min, dried with a paper towel and test retaken.

Mechanical tests were done on a dynamical mechanical analysis DMA Q800 (TA Instrument, USA). Tests were conducted in a tensile and compression mode at ambient conditions. Controlled force and strain tests were done for compression test while the tensile test was done by ramping the force at 0.5 N/min to the limit of the DMA (18 N). The nanoscale stiffness mapping of both materials was conducted by PeakForce technique on a Multimode 8 AFM (Bruker, USA) with contact mode. Relative quantification method was employed to find the stiffness. The deflection sensitivity was calibrated by a 'Ramp' on a silicon sample surface, and the spring constant of each specific cantilever was calibrated by thermal tuning, with the information of the standard stiffness of the substrate. It should be noted that the deflection sensitivity and spring constant need to be carefully performed before each characterization. The contact-mode cantilever (FESP) with a spring constant about 5 N/m is used for both materials, (Bruker, USA).

Bio-compatibility study was done by mixing polybumen in sterile conditions at room temperature to make a solution. The solution was then used to make a uniform coating on a tissue culture grade 24-well plate. The plate was then soaked with the culture media for 24 h to allow the media to seep through the material and analyze the compatibility of the material in the culture medium for cell growth. The cell growth was done by using metastatic breast cancer cell line MDA-MB-231.

2.3. Computation details

Computational studies were carried out to understand the egg white and amine chemical affinity and the mechanical impact thereof. Pertaining to the exploration of the egg white and amine chemical affinity, Molecular Docking is a computational method that uses scoring functions to determine the preferred binding orientation of one molecule with respect to another to form a stable complex [23]. Such docking simulations are performed to understand the role of cross-linkers in the complex egg white structure and to shed light on the underlying cross-linking mechanism between egg white and the cross-linker. Egg white mainly consists of water (88%) and proteins [24] (11%). Ovalbumin constitutes over half the egg white protein by weight. The structure of Ovalbumin was obtained from the Protein Data Bank with PDB code 1ova [25], rendered using Chimera [26]. Fig. 1a shows a bound configuration of cross-linker molecules with Ovalbumin. To determine the best possible binding sites for cross-linker, AutoLigand [27] is used to locate the high affinity binding sites on the surface of the Ovalbumin protein where the cross-linker binder has the highest binding probability. The basic premise of AutoLigand is that the different elements of a ligand have different binding affinities and AutoLigand mimics this behavior by generating adjoining fill volumes that generates maximum negative free energy change of binding per unit volume [27]. The supplementary video (S1) shows the morphology of various high affinity binding sites. These high affinity binding pockets are then used as search spaces for docking calculations performed with AutoDock Vina [28]. Docking calculations were performed to identify the best binding configurations of cross-linker (flexible ligand) at each high-affinity binding pockets using AutoDock Vina, an open source program for molecular docking. The calculation of the binding affinity of the ligand in the high affinity binding sites are expected, specifically in the case of the highest affinity binding site, to produce a statistic of the amino-acid mostly responsible for the cross-linker/ovalbumin affinity, which was found to be Glutamic Acid.

Based on the previous insight, the first-principles simulations to test the mechanical quality of the interface between two glutamic acid R-groups, a glutamic acid R-group and a cross-linker monomer, are performed using classical molecular dynamics (MD) as numerically implemented in the large-scale atomic/molecular massively parallel simulator (LAMMPS) using the Reax Force Field (ReaxFF) parameterizations for silicon carbide [29], a timestep of 0.25 fs, and the Nosé-Hoover thermostat at room temperature. In a manner similar to the fracture force simulations performed by *Tsafack* et al. [30], investigating the mechanical effect of cross-linker's insertions into ovalbumin proteins can be broken down to understanding the mixture's interfacial bond strength and stability. The setups in Fig. 2I–II are constructed under the assumptions made in Fig. 2c–e whereby two abutting glutamic acids can either vertically connect their amine and carboxyl groups through peptide bonding (Fig. 2b), or horizontally connect the carboxyl ends of their R-groups through condensation (Fig. 2c). Both processes involve the creation of a water molecule with H coming from the amine end of the top amino acid or the H from the hydroxyl end of one R-group, reacting with OH coming from the carboxyl end of the

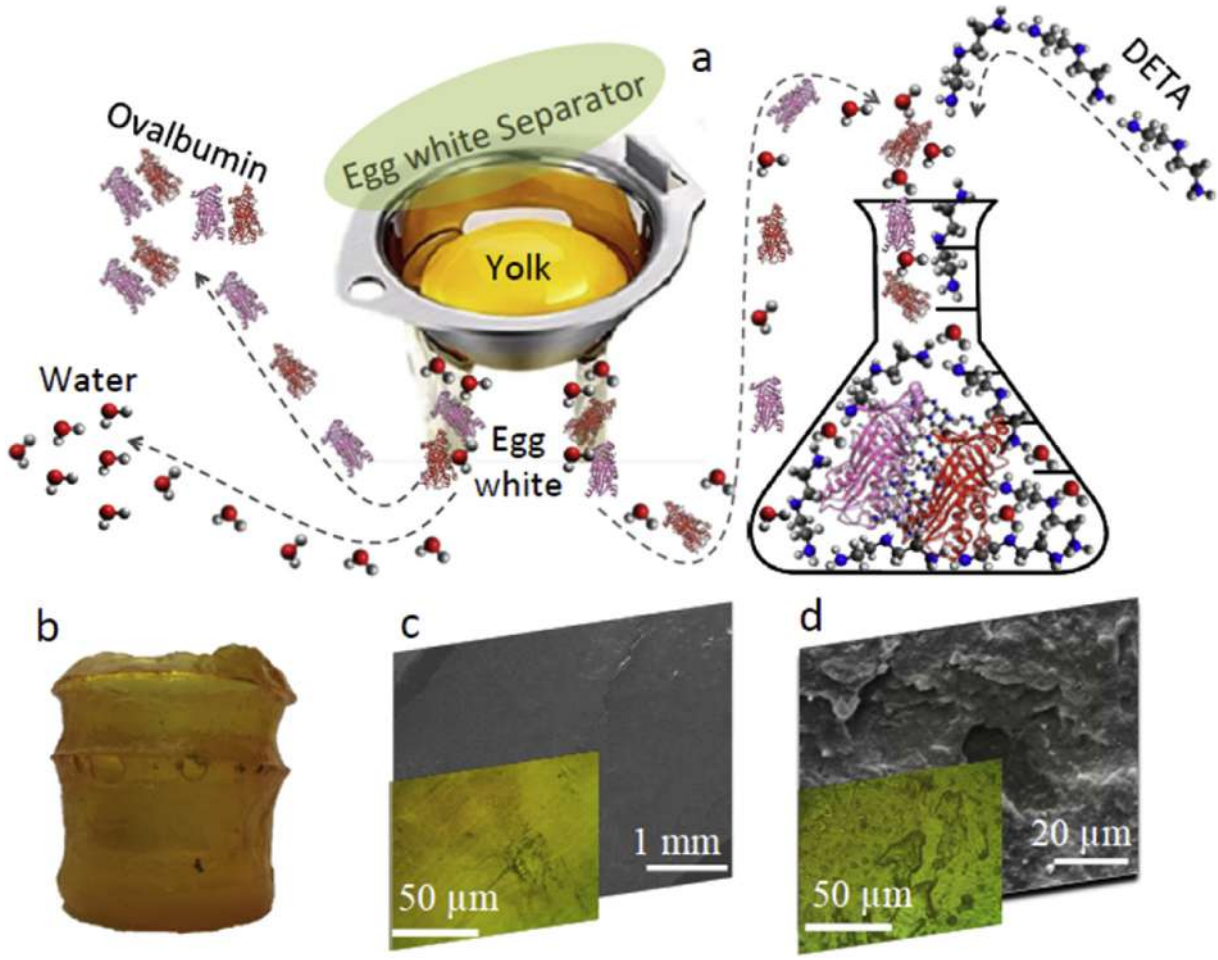

Fig. 1. Morphology of poly-albumen. (a) Egg white is extracted from an avian egg and a cross-linker added to polymerize it resulting in a flexible and tough material. (b) Large-scale (cm) polymerized structure (c) Optical and SEM images of the crystalized pristine egg white characterized by smooth surfaces with visible cracks on the surface. (d) Optical images of polybumen showing homogeneous ridges spread all over the sample forming sheets like cramps. Layered structured of polybumen as seen on the SEM.

bottom amino acid or the carboxyl end of the other R-group, as the case may be. In addition, to be a very common way biological cells link monomers together, the aforementioned process legitimates a comparable linking mechanism between cross-linker amine ends and glutamic acid R-groups' carboxyl ends (Fig. 2c).

In configurations I and II from Fig. 2I–II, two identical chains of five interconnected glutamic acids are linked through their R-groups (configuration I) and through one amine monomer (configuration II). Each chain is held in place by two handles located at the carboxyl end of the top glutamic acid and at the amine end of the bottom glutamic acid leaving both the rest of the chain and the linking intermediary materials free to interact, equilibrate and move. A first equilibration process on the whole structure (NVT), except for the handles, takes place for 25 ps. The subsequent equilibration process (NVT) eventuates with a series of consecutive 1 ps cycles in which the handles in the right chain move down by 0.05 Å while the rest of the structure reacts accordingly. The interfacial bond lengths, indicated in the respective configurations in Fig. 2c–e as β, are monitored as the moving chain travels an increasing distance δ. The interfacial bond length is expected to remain reliably stable and to gradually increase before complete rupture, see supplemental videos for visual rendering. The difference between the equilibrium bond length and the bond length at rupture, Y, qualitatively describes the stiffness of the interface whereas $t = X/v$, the time it takes to get to the end of the bond stretching process from the beginning thereof (X being the difference between δ at the rupture and δ at the end of the equilibrium bond length, v being the speed of the moving chain) qualitatively describes the ductility of the interface. Interfacial parameters, Y and t, can hence give a qualitative insight into the mechanical behavior of the mixtures.

3. Results and discussion

Albumin from egg white was extracted from chicken eggs and the 'polymerization' or cross-linking initiated by primary amine-based molecules. A desired amount of amine-based molecule was added to egg white albumin and cross-linked at 50 °C for an hour resulting in a three-dimensional structure of PA. A relatively low concentration of amine (≤5%) tends to result in thin films while a higher concentration (>5%) leads to the formation of foam-like structures (Fig. S1, Supporting information). The crosslinking occurs mainly due to amine functional groups on the DETA as shown by NMR and FTIR spectra showing the formation of amide binds from crosslinked albumen (Fig. S2, Supporting information). A large-scale (cm) size model of a 'cup' is fabricated as shown in Fig. 1b. In understanding the morphological characteristics of PA, samples were imaged under optical and high resolution scanning electron microscope (SEM). Pristine egg white shows very smooth surfaces with cracks due to the mechanical strains generated

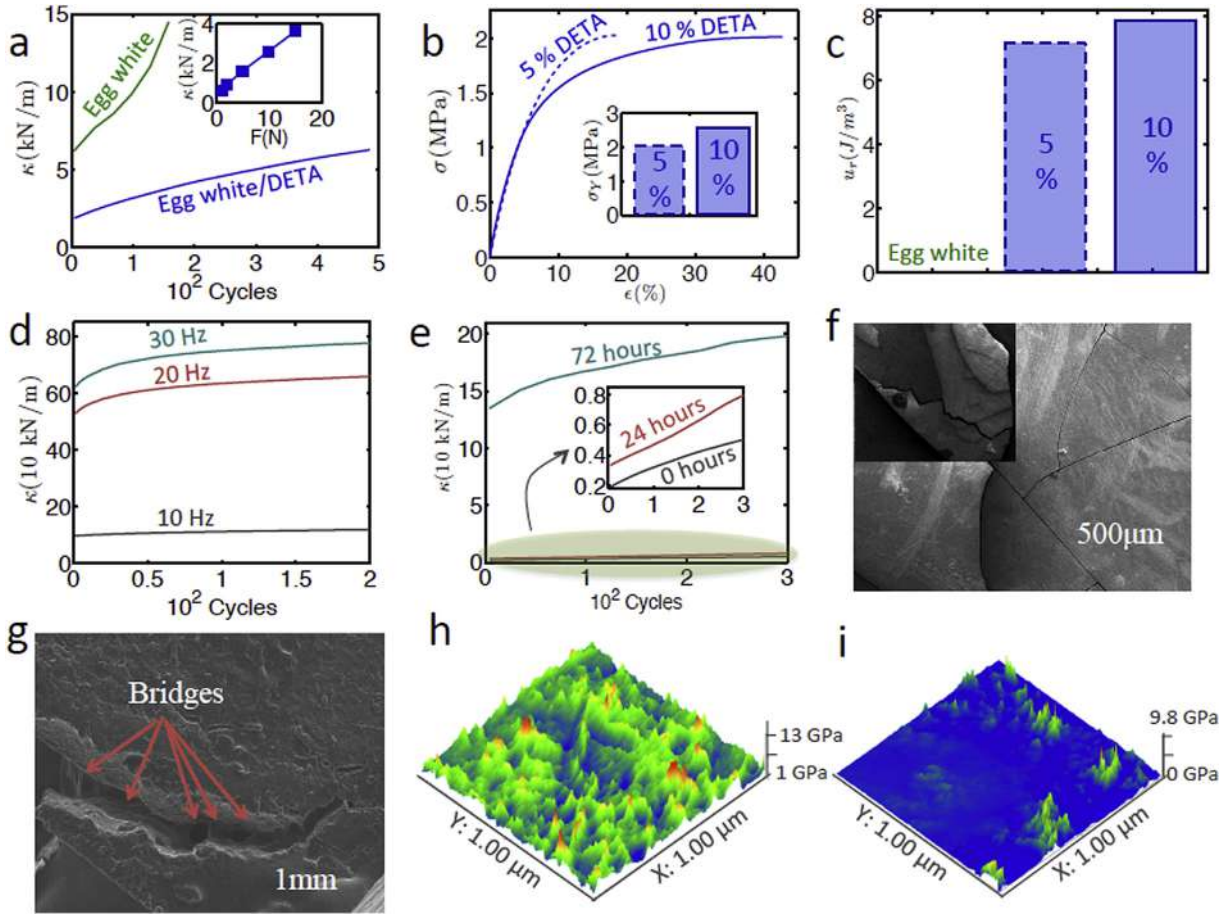

Fig. 2. Mechanical behavior. (a) High compressive stiffness of egg white that breaks within few loading cycles unlike polybumen which sustain many loading cycles without showing any deformation. (b) High toughness and strength of poly-albumen. (c) Quantified toughness in tension mode for egg white, poly-albumen (5%) and poly-albumen (10%). (d) Stiffness increases with increase in frequency. (e) High stiffness with aging. (f) SEM surfaces of pristine egg white showing cracks propagating in all directions. (g) Bridge like network connecting the individual cross-linked sheets preventing brittle failure in poly-albumen. (h) AFM modulus mapping of pristine egg white. (i) Inhomogeneous high modulus distribution regions connected by low modulus areas which provide the elasticity observed in poly-albumen.

during the drying process (Fig. 1c). On the other hand, cross-linked egg white exhibits a rough surface in contrast. The SEM images reveal rough PA surface and a sheet-like morphology (Fig. 1d). Higher amine concentration allows the sheet-like structures to transform to highly cross-linked foam-like morphology. PA also shows good thermal stability as seen from thermo-gravimetric analysis. (Fig. S3, Supporting information).

The mechanical properties of the PA material were assessed and compared with those of pristine dried egg white. The egg white is typical of brittle materials exhibiting high stiffness under cyclic load. Despite its initial high stiffness, egg white breaks up in less than 200 cycles (Fig. 2a). PA has low stiffness in initial loading cycles through the stiffness exhibits considerable increase and even surpasses that of pristine egg white at high loading cycles (>3000, inset Fig. 2a). In addition, PA shows a tendency of self-stiffening behavior which continues as the number of cycles increases. The strength of PA was measured in a tensile mode using dynamic mechanical analysis in the tension mode. As shown in Fig. 2b, PA tensile strength is increased multifold by 5%, 10% addition of amine (inset Fig. 2b) unlike pristine egg white which breaks at a pre-load force of 0.01 N. In conventional materials, achieving simultaneous increase in strength and toughness has remained elusive but here it is shown that amine groups can induce both strength and toughness concurrently (Fig. 2c). Frequency-dependent tests show that the PA material behaves like a viscoelastic material where stiffness increases with frequency [31]. There is an order of magnitude increase in stiffness from samples tested at 1 Hz and 10 Hz (Fig. 2d).

PA shows a linear increase in stiffness with time (Fig. 2e). The stiffness almost doubled in 24 h and increased to more than 40-fold after aging for three days (inset Fig. 2e). For the vast majority of synthetic materials, this is unexpected behavior but biological materials do indeed exhibit such traits of increasing strength with time, for example bones in mammals [32]. The stiffness-aging behavior may be explained by the nature of the cross-linking that takes place in egg white. It is suggested that the majority of reactive groups on large-sized protein molecules is not initially exposed to amine groups all at once but progressively. Furthermore under ambient conditions PA loses its hydrogen bonds slowly. From a macroscopic level, SEM and modulus mapping using atomic force microscopy (AFM) can be crucial in understanding the materials' failure mechanism. These two techniques are used here to show the brittle nature of pristine albumin (Fig. 2f) as opposed to PA that shows bridge-like connections that prevent crack propagation (Fig. 2g). To understand the crack resistance and high ductility in the materials, high resolution scanning electron microscope images were taken on the fractured samples. Egg white films developed cracks immediately after drying. These cracks are typical of brittle materials as shown on Fig. 2f. Once the cracks initiate in egg white albumin, they propagate in all directions (Video 1, Supporting information). Unlike egg white, cross-linked films in PA seems to

prevent the catastrophic crack growth as exhibited by the ductile failure of the cross-linked films (Fig. S4 and Video 2, Supporting information). The cross-linked multilayer films are important to prevent crack propagation and absorb much of the fracture energy generated in the material. To further explain PA's high toughness, three-dimensional mapping of the modulus on AFM shows homogeneous distribution of high moduli ranging from 1 to 13 GPa for egg white (Fig. 2h). PA on the other hand, is characterized by a non-homogeneous distribution of the moduli which ranges from 0 to 9.8 GPa (Fig. 2i). In between these high moduli, smooth surfaces separating the moduli are observed. The distribution in modulus in the cross-linked sample connected by smooth or low modulus areas is responsible for the high toughness inherent in the PA where they act like glue to link or interconnect high-modulus regions. To better understand the chemical nature of PA's and relation to high toughness so far macroscopically observed, docking simulations meant to analyze the chemical affinity between egg white albumin and amine as well as molecular dynamics simulations designed to understand the mechanical impact of such an affinity, are carried out.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.mtchem.2018.04.001

Indeed, through the docking of amine groups on the ovalbumin surface (see Fig. 1a for an artistic visualization), it is observed that among the five highest affinity binding sites (colored pockets laying on the gray ovalbumin surface in Fig. 3b), the affinity, measured in terms of binding energy in kcal/mol and visible on top of the colored bars indicating each site, is maximum in Site # 5 (binding energy 3.6 kcal/mol). In fact, even though both Alanine and Glutamic Acid are the most abundant amino acids in the five highest affinity binding sites, in the highest one (Site # 5), the amino-acid most abundant (~3%) within 1.5 Å of amine monomers is Glutamic Acid. This result is to be expected on account of the glutamic acid R-group's end (−COOH) being more reactive and more polar than Alanine's saturated hydrocarbon R-group ($-CH_3$).

Based on the outcome of the docking simulations and the likeliest Glutamic Acid/amine interconnections through condensation (see computational details and Fig. 3c–e), the computer experiment with two five-Glutamic Acid chains connected through R-groups and cross-linker, with the right chain moving downward until the rupture of interconnecting bonds, can shed light on the mechanical effect of cross-linker on the egg white. Indeed, (Fig. 3f shows 1) a sizeable bond stretching difference ($Y_{III} - Y_I \simeq 0.25$ Å) between configuration II and configuration I to the advantage of configuration II, 2) a very different stretching times between

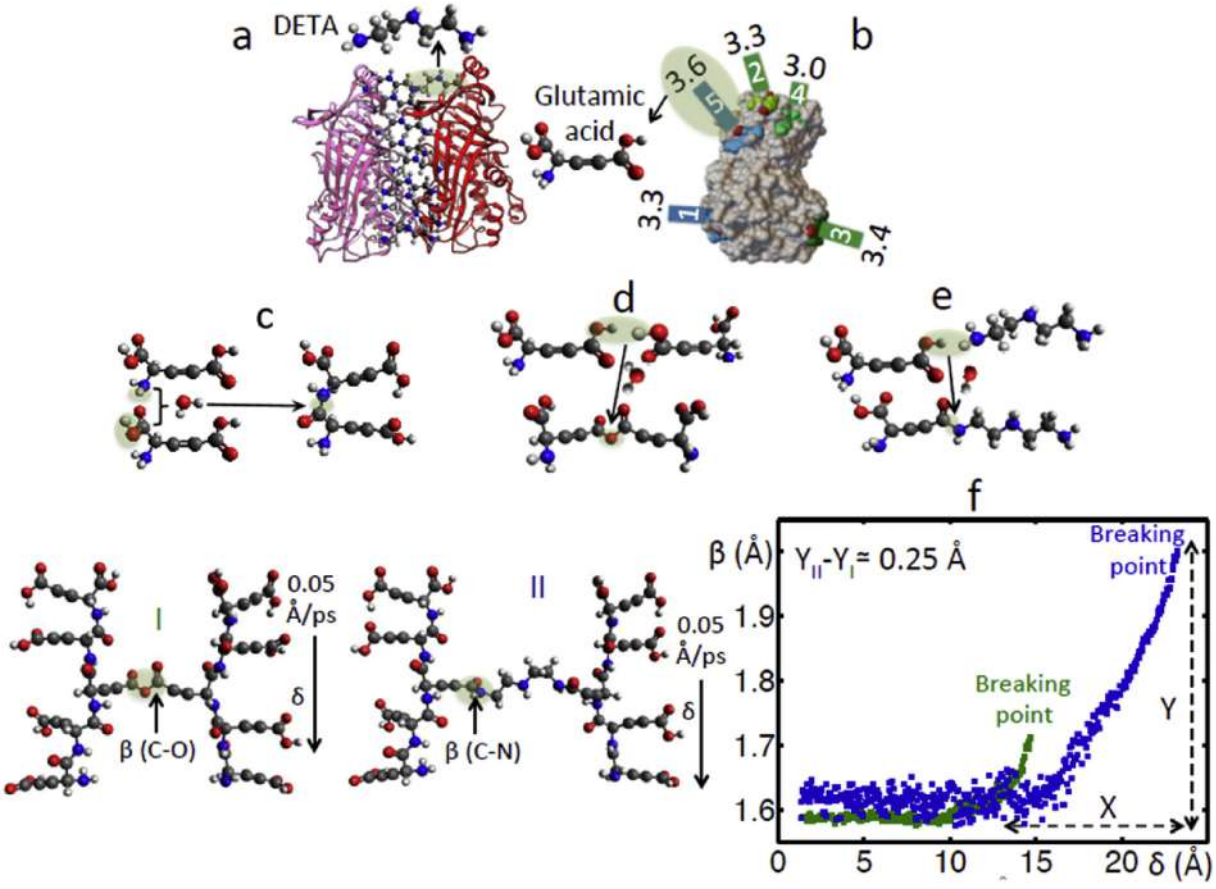

Fig. 3. Artistic visualization of ovalbumin/amine binding. (b) Highest-affinity binding pockets (colored sites) on the gray ovalbumin surface complete with their binding energies indicated on top of the colored bars representing them, the units are kcal/mol. Site # 5 is highlighted to be the highest binding site and the structure of Glutamic Acid is shown as the most abundant amino acid. (c) Glutamic acid/glutamic acid peptide bonding. (d) Glutamic acid R-group/glutamic acid R-group bonding through condensation. (e) Glutamic acid R-group/amine bonding through condensation. Configurations I and II are made up of two identical five glutamic acid chains connected through their R-groups and through cross-linker. The right chain moves downward 0.05 Å/ps while the respective highlighted interfacial bonds, β, are calculated as a function of the distance, δ, and traveled by the right chain until rupture. (f) Through initial/final bond differences, Y, and equilibrium/rupture δ differences, X, show the brittle nature of configuration I, the ductility and stiffening effect of configuration II.

configurations I and II, namely, $t_I \simeq 100$ ps and $t_{II} \simeq 252$ ps. It can then be inferred that, in as much as configuration II provides more stiffness than configuration I and gets to rupture 152 ps later, the interfacial information of configuration II is the main source of stiffness and ductility. Configuration I, because of its much smaller elongation and smaller time-to-rupture with respect to the same parameters in configurations II, does not significantly increase the stiffness nor the ductility of the composite. It can hence be concluded that ovalbumin by itself is likely to be brittle and not sufficiently stiff because it will predominantly be based on the interfacial behavior of configuration I. The addition of amine cross-linker to ovalbumin will predominantly be based on the interfacial behaviors of both configuration I and configuration II, and will therefore have a significant increase in ductility and stiffness. The very chemically favorable environment of ovalbumin thus appears to bring out the remarkable stiffening and toughening capabilities of cross-linker, thus confirming on one hand egg white's weak crack resistance ascribed to lack of interconnections (Fig. 2f/a), and on the other hand, PA's high crack resistance ascribed to the presence of bridge-like connections (Fig. 2g/b).

For safe bio-application, a material must conform to desirable properties such as porosity, adhesion, repairable, non-toxicity, affordability and easy-manufacturability. With respect to PA, a discussion of the bio-compatibility, adhesion bond strength in both liquid and air, repairability and as possible electronic board for implantables follows. The bio-compatibility of PA was assessed by evaluation of in-vitro cell cultures by utilizing metastatic breast cancer cell lines MDA-MB-231. The growth of cells in the PA resembled a 3-dimensional cell culture medium rather than growing in 2-dimensional monolayers (Fig. 4a–d). The cell growth observed on the material certainly indicates that PA does not affect the cell proliferation. Fluid uptake was measured by measuring water gain, PA absorbs as much of 0.8% mass of its own weight (Fig. S5, Supporting information). The transparency changes due to moisture can be used as indicator for blood or nutrition flow in bone repair (Fig. S6, Supporting information). If PA is used as a bone replacement scaffold, it could provides an excellent interface for osteoblasts to grow, allowing for bone reconstruction. The shear strength was tested by gluing PA to a chicken bone (Fig. 4e). The shear strength between PA and the bone is very strong in both air and water, sustaining a mass of more than 100 g (Fig. 4f and g). The shear bond was quantified by pulling PA film from the bone in a tensile mode and as shown on Fig. 4h; an ultimate strength of 0.4 MPa and strain to failure of almost 8% was recorded. These values are higher in comparison to other affordable materials used as scaffolds (S7, Supporting information) except expensive silk protein. In addition, PA can easily be repaired after fracture and 'welded'. The fracture strength was re-measured and observed to have a 14% loss only (Fig. 4i–l and Fig. S8, Supporting information). To test the possibility of using PA as a circuit board for implantable

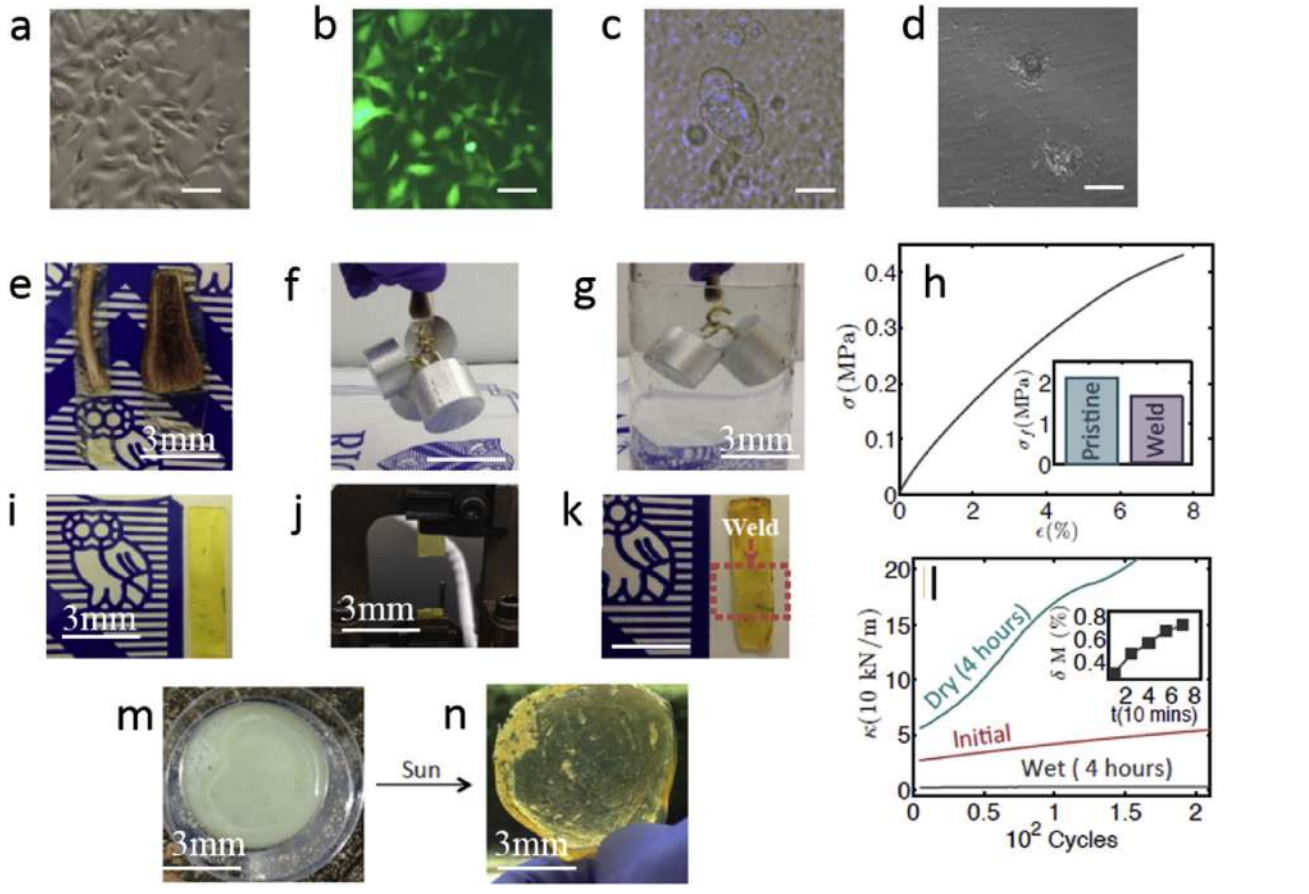

Fig. 4. Unique properties of poly-albumen. (a, b) Show the phase contrast and fluorescent images of the cells in 2D monolayer culture (c) shows the parent cell growth after 3 weeks. The different lobes in the 3D growth of the cells can be clearly seen. (d) Phase contrast images of MDA-MB-231 cells after one week of cell growth (scale bar 20 μm). Highly disorganized growth in 3D culture characteristic of highly metastatic MDA-MB-231. (e) High adhesion of the poly-albumen to avian bones. The bond between the poly-albumen and bones is strong enough to support weight in air (f) and in liquids (g) without any failure. (h) Quantification of the strength of the bond between the bone and poly-albumen. (i) Repairable property of the polybumen. The material is broken (j), 'welded' (k) and only lose less than 14% loss in fracture strength (l). The use of the polymerized egg white as circuit board (m).

electronics, gold patterning was done on a thin film of PA and an LED attached to it as shown in Fig. 4m. The complete biodegradable nature of this material should be advantageous for safety reasons when implanted in bodies. One of the key component for implantable electronics is the ability for them to degrade without causing any harm to the body. This current material can be a positive direction in recyclable and green electronics.

4. Conclusion

It has been shown that primary amine-based molecules form strong interfacial bonds with the egg white albumen resulting in a strong, tough and porous material as demonstrated and explained by experiments and molecular dynamics simulations, respectively. In addition to an adaptable self-stiffening property, the new material shows an increase in stiffness with aging. Also, the new material is non-toxic as revealed by non-detrimental effect on cell growth. This work explored the design of bio-derived materials utilizing readily available cross-linkers to polymerize biological proteins. As shown by experiments and theoretical simulations, this amine-based cross-linker tends to induce the reaction of amino groups on the cross-linker and carboxylic functional groups on the protein amino acids. The non-toxic nature of the material can be used to design 3D scaffolds which can be investigated for their viability as biomedical application such as bone repair. We have also demonstrated that this material can be used as a biodegradable circuit board for implantable electronics. Though nature remains incomparable in its capability to design hybrid materials where contradicting properties like stiffness and ductility are optimized, this work opens the possibility for new design routes for advanced materials with unprecedented properties.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.mtchem.2018.04.001.

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