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Origami-Inspired Approaches for Biomedical Applications

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Mini-Review

Origami-Inspired Approaches for Biomedical Applications

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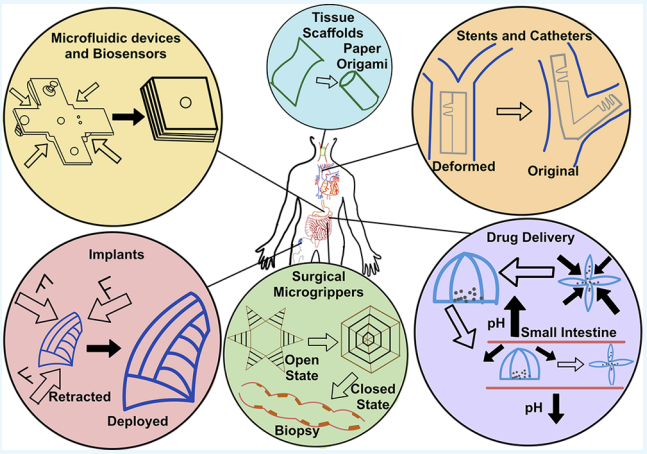
ABSTRACT: Modern day biomedical applications require progressions that combine advanced technology with the conformability of naturally occurring, complex biosystems. These advancements yield conformational interactions between the biomedical devices and the biological organisms' structures. Biomedical applications that adapt origami-inspired approaches have accrued aspired advances. Along with application-specific advantages, the most pertinent advances provided by origami-inspired strategies include voluminous structures with the ability to conform to biosystems, shape-shifting from two-dimensional (2D) to three-dimensional (3D) structures, and biocompatibility. Throughout this paper, the exploration of new studies, primarily within the past decade, with origami-based applications of biomedical devices, including their theories, experimental results, and plans for future testing are reviewed. This mini-review contains examples that aid the advancement of biomedical applications and hold promising future discoveries. The origami-inspired applications discussed within this paper are tissue scaffolds, drug delivery approaches, stents and catheters, implants, microfluidic devices, biosensors, and origami usage in surgery.



1. INTRODUCTION

Origami is defined as the process of folding paper; the meaning of this process is embedded in the roots of the Japanese word, *oru* meaning to fold and *kami* meaning paper.[1] Traditional origami is the simplified process of solely folding paper, with the sequences of folding usually passed down orally, or without trademark. First practiced in Japan in the sixth century, the applications of traditional origami were both recreational and ceremonial/religious, and origami came to be acknowledged as an art form through its expansion of practice.[1] With its fabrication becoming more widespread, modern origami was founded on the basis of additions to folding paper, such as marking, cutting, gluing, and taping, as well as the artistic ability to trademark each sequence of creation. The complexity involved in interactions between various parts of an origami structure adds to its versatility.[2] This induces a practical implementation of such methodologies into environments that require minimized invasiveness, as is seen in many scientific applications. One example of this is the use of origami in the form of a gastrointestinal microsurgery robot. This helps in minimized invasiveness during surgery and ease in production.[3] Such practicality of origami fabrication is also being employed in engineering settings. Other advantages of origami-inspired approaches include fabrication of voluminous structures that can conform to biosystems, compact deployment, shape-shifting capabilities from two-dimensional (2D) to three-dimensional (3D) structures, cost efficiency, reduced complexity and time in manufacturing, reconfigurability, and biocompatibility. Common uses include reconfigurable storage capabilities and simplification of manufacturing processes.[4] Further, the principles of origami are currently being utilized and studied in scientific applications such as medical stents, the deployment of airbags within cars, and the large solar panel arrays of space satellites.[5] With the application of origami to medical stents, the flexible, foldable delivery method enables easier maneuvering through variously shaped canals in the body with the expansion of the final shape occurring in the designated location, yielding minimally invasive procedures.[5] Origami within airbags is used for its contractable state of storage, with the inflated, or 3D expansion, deployed only when activated. NASA is currently working on creating space power plants for energy-use on Earth and with the origami application, the self-assembly of solar-panels in space is attainable, negating the requirement for astronaut assembly.[6] The overall concept to these mathematical and scientific

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applications, is the shape-shifting that can be obtained through origami.[7] There is a wide range of these techniques that are currently being used, and others that are being studied within biomedical applications.

In synthetic biosystems, the assembly methods are predominantly bottom up in which the materials are layered and added in a stepwise process.[8] This mechanism takes from the naturally occurring unity, complexity, and 3D nature of naturally occurring biosystems. To help aid this suboptimality, origami usage within the medical device field yields material uniformity, the aptness to transform from a thin sheet to a voluminous structure, as well as benefits of simple design, low cost of material, and disposability.[3] Mathematical and technological applications, including the structure and kinematics, of origami are known as *origamics* and are used to deduce these biosystems, as well as other biomedical devices. The discovery of six Huzita Axioms and one Hatori Axiom, each of which defines a folding method, maximizes the use of origamics in its applicability.[3] 3D structures can further be exploited via simulating software and 3D printing to yield precise patterns, variability, and customization.[8] *Cell origami*, or 3D cell-laden microstructures, can also be developed in the areas of microsized containers as well as scaffolds for artificial tissues.[5] The two forms of origami, being 2D and 3D, or the process of shape-shifting, are advantageous for insertion, travel, and removal within the body and are achieved by an external signal utilizing chemical, electrical or temperature initiators.[5] The shape-shifting structures can aid minimally invasive procedures and surgeries by reducing the size of the structure to its compact form upon entry and navigation.

Existing biomedical devices, including biosensors, tissue scaffolds, and microfluid devices, are promising in application, though each face limitations in their respective advancement. Current tissue scaffolds can analyze properties of a perspective biological organism both on a cellular and subcellular basis. Biosensors can be used to detect various biomarkers for health conditions, forensic applications, or detection of chemicals, as well as testing environment reagents and food and water safety.[9] New approaches aiming at the biomolecular sensing in situ are currently being explored.[8] One limitation encountered by the conventional biomedical devices is their structures are 2D while most biosystems are 3D in structure, resulting in a loss of information. For instance, the origami-based application that could be applied to tissue scaffolds is the shape-shifting from a folded 2D structure to a 3D geometrically complex structure that wraps the cells or biomolecules upon exposure to unique shape-shifting stimuli.[8] Microfluidic devices can mimic the vascular networks within the human body to serve a variety of applications such as to enable drug screening, delivery, or to generate vascularized tissue engineering scaffolds.[8] However, these devices have limitations which include not having cross sections that are directly compatible with the human body. This limitation could be addressed by origami-based solutions in which the curved and folded fluidic networks can help better replicate the human 3D vascular networks.[8] Future origami-based enhancements in biomedical applications show promising advancements including the capability of generating 3D structures, improving biocompatibility, and enabling shape-shifting features.

Within this review, applied modern origami techniques are examined to highlight the key aspects contributing to a promising future within biomedical apparatuses and synthetic biosystems. These key features provided within origami-based applications are shape-shifting, continuity of material, biocompatibility, disposability, and customization. The applications discussed include origami-inspired tissue scaffolds, drug delivery approaches, stents and catheters, implants, microfluidic devices, biosensors, and origami usage in surgery.

2. ORIGAMI-INSPIRED TISSUE SCAFFOLDS

A promising scientific application of origami is its use in the fabrication of 3D scaffolds for tissue engineering and regenerative medicine.[10] Extensive damage to the body often requires a guided and enhanced means of regeneration for tissues. For such means, a widely known approach has been the use of scaffolds, which are supporting template materials that provide a 3D environment for cells in order to facilitate tissue formation.[11] Camci-Unal et al. has generated origami-inspired paper templates in guiding calcium phosphate deposition by osteoblasts for template-guided mineralization.[12] Whatman filter paper (grade 114) with a thickness of 190 μm and an average pore size of 25 μm was used to fabricate the scaffolds in this study. Paper was chosen as the scaffolding material because it is composed of naturally derived cellulose fibers, is biocompatible and flexible, and has the ability to support cell viability and growth in 3D origami-folded structures. The paper scaffolds were sterilized, seeded with osteoblasts in collagen, and cultured for up to 21 days. The deposition of hydroxyapatite by the osteoblasts in the paper scaffolds were then evaluated using analytical methods. For example, calcium and phosphate staining were carried out in addition to high resolution SEM microscopy and elemental analysis to confirm the formation of hydroxyapatite minerals. Additionally, micro-computed tomography (micro-CT) scans were critical in establishing the distribution of mineralized regions within the origami-folded scaffolds.[12] This study has shown the proof of concept of using filter paper to fabricate origami-inspired tissue scaffolds for biomineralization. Due to paper's wide availability, flexibility, low cost, and biocompatibility, this approach could possibly be used in different tissue engineering applications, developing personalized disease platforms such as organ-on-paper models and analytical detection of cellular metabolites.

In another study, origami-based self-folding 3D microstructures were generated using alginate as a sacrificial component in the scaffold fabrication process. Replicating the in vivo functionality of human tissues is generally achieved with the utilization of cocultured cells in 3D microenvironments. He et al. has found cell origami to be advantageous as it can provide highly viable culture conditions in 3D conditions to maximize the area of interaction between different cell types.[13] Patterned microstructures were produced using a monolayer of fibroblasts (NIH 3T3) on alginate-coated microplates and liver hepatocellular cells (HepG2). NIH 3T3 cells were first seeded and cultured on the microplates followed by HepG2 cell seeding on the NIH 3T3 fibroblast-attached microplates for 4 h. The alginate sacrificial layer facilitated the detachment of the cells from the surface of the microplates using the alginate lyase enzyme. Degradation of the alginate layer induced the folding of the patterned NIH 3T3 cell layer around the HepG2 cells to create a dodecahedron, with the NIH 3T3 cells acting as hinges between the microstructures. Confocal microscopy images were acquired to reveal the positions of each cell type during the formation of the 3D microstructures. The viability of the cocultured cells was evaluated by discerning between live and dead cells through viability staining. In addition, the amounts of secreted albumin

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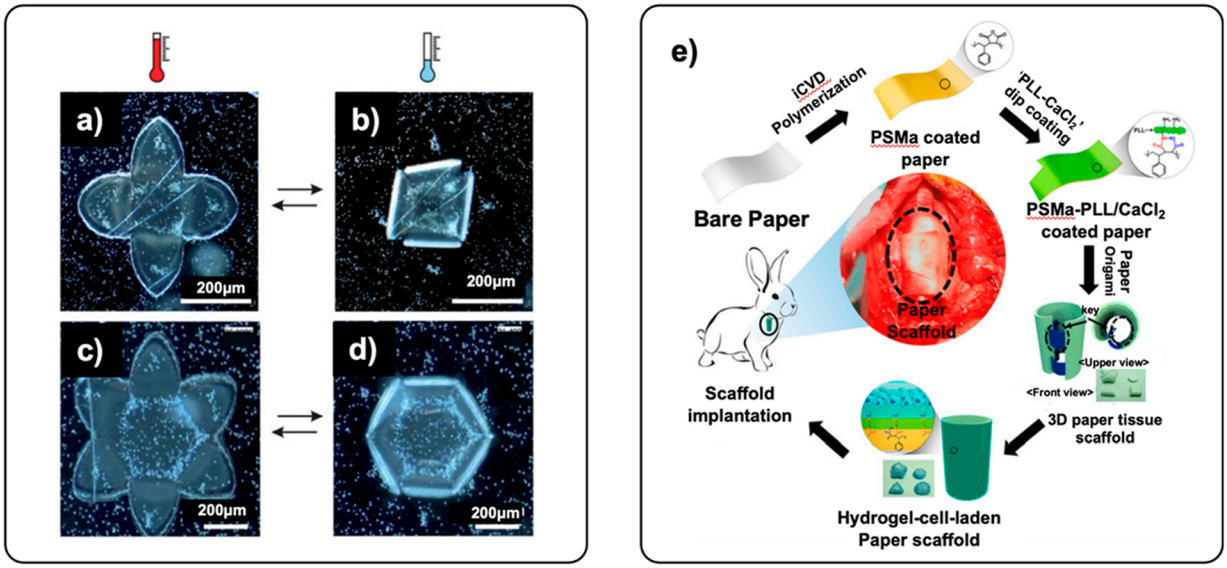

Figure 1. Origami-inspired examples for cellular applications. Thermoresponsive self-folding capsule with reversible structural changes. (a,c) Open configuration at an elevated temperature. (b,d) Full encapsulation at lowered temperatures. Adapted with permission from ref 14. Copyright 2011 Soft Matter. (e) Step-by-step procedure in fabrication of cell-laden paper scaffold for use as an implant (Adapted with permission from ref 15. Copyright 2015 National Academy of Sciences).

from the HepG2 cells were analyzed to assess the functionality of these cells.[13] In all, this research minimized the self-folding process of cells from 3 days to 2 min with high cell viability. The potential to vary microplate shape and design confers versatility to produced microstructures, allowing them to be applicable to regenerative medicine, cell therapy, and drug development.

Design and application of self-folding origami microcapsules using thermoresponsive polymers was utilized for the controlled and reversible capture of yeast cells. Stoychev et al. reported the fabrication of biodegradable thermoresponsive capsules using poly(*N*-isopropylacrylamide) (PNIPAM) and polycaprolactone (PCL).[14] The polymers formed cross-linked four- and six-arm star-shaped bilayers through the use of photolithography. Results showed that the star-shaped bilayers bent after 5−10 s at temperatures below the cloud point of poly(NIPAM-ABP) and formed 3D capsules (Figure 1a−d). Figure 1a−d demonstrates the thermoresponsive capabilities of specifically sized capsules according to temperature changes. This was shown for four-arm and six-arm stars and resembles the functional application being discussed. Further functionality of the bilayers was tested using yeast cells, which were seeded on the polymer bilayer at elevated temperatures and encapsulated by cooling of the polymer bilayer.[14] This study has thus demonstrated thermoresponsive self-folding capsules with an improved performance for reversible encapsulation of cells. Such an origami-inspired folding mechanism shows a promising application in controlling the activity of bacteria and fungi and even shows the ability to assemble into 3D scaffolds capable of being used for cell delivery and tissue engineering.

Further studies in origami-based tissue engineering revealed a capacity for assembling biofunctionalized paper into multiform structured scaffold systems. Kim et al. was able to integrate and manipulate hydrogel-laden paper in creating scaffold systems capable of area-selective cell seeding.[15] The cellulose-based paper contained macroporous structures that facilitated nutrient transport and oxygenation. A polymer film of poly(styrene-*co*-maleic anhydride) (PSMa) was coated on the paper using initiated chemical vapor deposition (iCVD). The PSMa film provided reactive anhydride groups to form a covalent bond with amine functionalities in poly-L-lysine (PLL) for immobilization. The efficacy of the chemically modified paper was tested by fabricating cylindrically shaped scaffolds and coating them with rabbit articular chondrocytes for tracheal reconstruction (Figure 1e). Figure 1e is used to show the sequential process of creating hydrogel and cell-laden paper scaffolds for eventual implementation in the trachea of a rabbit. Successful in vivo functionality was achieved with adequate airtightness and strength in the airway while fully replacing the native trachea with transplanted engineered tissue.[15] This study, as shown, combined origami concepts with the iCVD process in preserving the morphology and robustness of paper scaffolds necessary in trachea tissue engineering. Additional applications of the lock-and-key design of planar sheets in encapsulating chondrocytes for tissue regeneration show the versatility of using origami-based tissue engineering approaches.

3. ORIGAMI-INSPIRED DRUG DELIVERY APPROACHES

The use of origami in drug delivery approaches has seen great strides through a study that implemented an oral delivery device based on self-folding hydrogels. He et al. produced a self-folding miniature device capable of demonstrating improved mucoadhesion, targeted unidirectional delivery, and drug protection through the mucosal epithelium[16] (Figure 2a−b). Figure 2 exhibits the functionality of the device over time in a controlled setting. Results from the figure showed an enhanced capability for folding and mucoadhesion. This indicates future efficacy for drug delivery applications. The device was fabricated with soft-lithography using three functional layers with one being a drug-loaded mucoadhesive layer at the top. The pH-sensitive, swelling middle layer was made of polymethacrylic acid (PMAA) that was cross-linked using tri-ethylene glycol dimethacrylate (TEGDMA). The nonswelling bottom layer was made using hydroxyethyl

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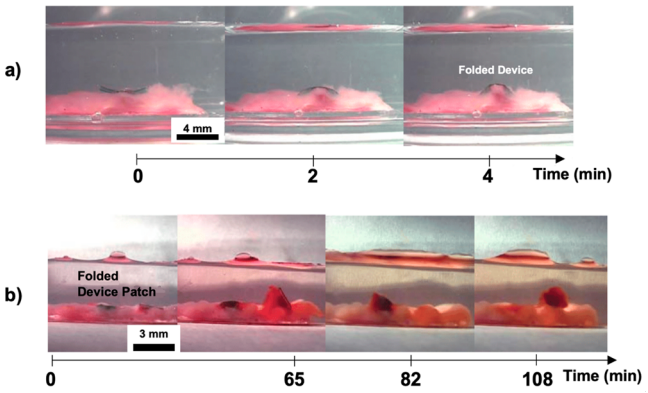

Figure 2. Use of a self-folding miniature device to display dynamic functionality on mucosal tissue. (a) Testing for folding behavior and the time it takes for effective folding. (b) Mucoadhesive behavior of the device over time when placed in a buffer of pH 6.5 and a temperature of 25 °C (Adapted with permission from ref 16. Copyright 2005 Elsevier).

methacrylate (HEMA) cross-linked with diethylene glycol dimethacrylate (DEGDMA) and acted as a diffusion barrier preventing the leakage of the drug. The mucoadhesive drug was chemically tethered to the bilayered hydrogel. A significant amount of swelling took place when the pH-sensitive PMAA was exposed to the bodily fluids that facilitated the folding and curling of the device upon adhesion to the mucosal epithelium. Efficacy tests were carried out using two model drugs, AO8 and BSA, on a porcine small intestine.[16] Results showed that the miniature hydrogel devices yielded 3D folded structures capable of unidirectional delivery and demonstrated promising outcomes for oral administration of protein-based drugs.

Another study reported a drug delivery approach based on origami folding using bilayer hydrogels to generate tunable microcapsules. Shim et al. utilized photolithography to fabricate hydrogel bilayers, which induced in situ encapsulation of a model small molecule upon swelling.[17] Poly(2-hydroxyethyl methacrylate-*co*-acrylic acid) (p(HEMA-*co*-AA)) was used as the active layer capable of swelling and driving conformation changes while poly(2-hydroxyethyl methacrylate) (p(HEMA)) was used as a passive layer for inhibiting the degree of swelling. Flower- and snowman-shaped microstructures were tested with fluorescently labeled dextran as a model encapsulant to find that a pH of 9 induced a highly swollen and closed compartment while a pH of 4 restored a planar conformation to release the contents of the microparticles. This study, as shown, integrated tunable microcapsules reliant on anisotropic volume expansion for reversible conformational changes in the bilayer.[17] Results were found to be promising for application of such microcapsules in drug delivery, 3D cell encapsulation, tissue scaffolding, and soft robotics applications.

4. ORIGAMI-INSPIRED STENTS AND CATHETERS

The principles of origami have been used to fabricate stents and catheters for biomedical uses. In a study by Taylor et al. exploring the medical use of origami structures, the application of catheters for atrial fibrillation (AF) heart rhythm disorder was investigated for its aid in both diagnosis and treatment.[18] With the expansion of electrophysiology (EP) therapy for arrhythmia, a safe and specialized mapping catheter is needed to create accurate spatial voltage distribution, collected at various locations throughout the chambers of the heart, to locate and treat the source of abnormal tissue.[18] In this study, the novel expandable catheter was a circular sheet of polycaprolactone, with copper plating applied near the edge of the sheet to form imaging coils, folded into an origami pattern. The material of construction was flexible enough to enter the body's vasculature as well as leave in the expanded form and it is stiff enough to expand and conform upon arrival inside the heart chamber. The catheter's ability to conform to the human body and pass through the aortic arch was optimized using mathematical models to compare the height, expanded area, and stowed area to the expanded diameter as well as the number of folds in the structure. The MRI compatibility of the resulting 3D structure was tested and confirmed. This novel origami-based catheter, used for diagnosing and treating arrhythmia, proved promising with the capability to be incorporated with tuned and matched imaging coils, yielding the catheter MRI compatible.

In another study, the application of origami structures in catheter-based diagnosis and treatment for atrial fibrillation (AF) was explored with the intent of optimizing intracardiac magnetic resonance imaging (ICMRI).[19] Radiofrequency ablation (RFA) therapy, a form of minimally invasive electrophysiology therapy, locates the abnormal tissues and ablates those tissues rendering them electrically inactive. This technique was accomplished in the study of Taylor et al. by embedding RFA electrodes through microfabricating and laser-cutting square copper circuits directly into the tips of a square polycaprolactone sheet, which was then folded into an isoflasher origami structure.[19] The benefits of the catheter consist of optimized conformation to the vessel in both the stowed and expanded forms, multiple imaging coils which enable parallel imaging to be performed, and the low-cost and disposable design. Preliminary ex vivo studies have shown promising results yielding high contrast image quality and faster imaging, which improved the efficiency in intraoperative monitoring of AF. In addition to cardiac catheters, origami-based deployable devices could also be used in applications in which expansion, deployment, or shape-shifting is required.

Similarly, other studies have shown promising applications of kirigami, which is a variation of origami that adds cutting of the folded paper structure. Kim et al. created bifurcated stents using kirigami structures made of polyurethane-based shape memory polymers (SMPs).[20] Here, a new 4D-printing strategy was utilized to yield customizable cylindrical stents in Figure 3a–f. This figure shows a blood vessel (a), the 3D printed bifurcated stent (b, c), in both its original and deformed shapes (d), designed based off its conformation to a 3D replicated blood vessel. The figure shows the deployment process, both theoretically (e) and experimentally (f), of inserting the deformed stent, with its side branch within the main branch, and the shifting to its original shape when reaching the branching point of the blood vessel. 4D-printing of SMPs included the ability of the material's shape to be time-transient in morphology, responding to an initiating source of temperature. Once molded into a customizable negative replica of a blood vessel, the SMPs were heated above the glass transition temperature (T_g) where they can be easily molded and simultaneously cooled below T_g, resulting in the desired shape. Because the pathways of the blood vessels undergo compression, the stiffness of the stent, as a factor of both repeated pattern and thickness of the structure, needs to be controlled for the deployed target site. Kirigami-inspired

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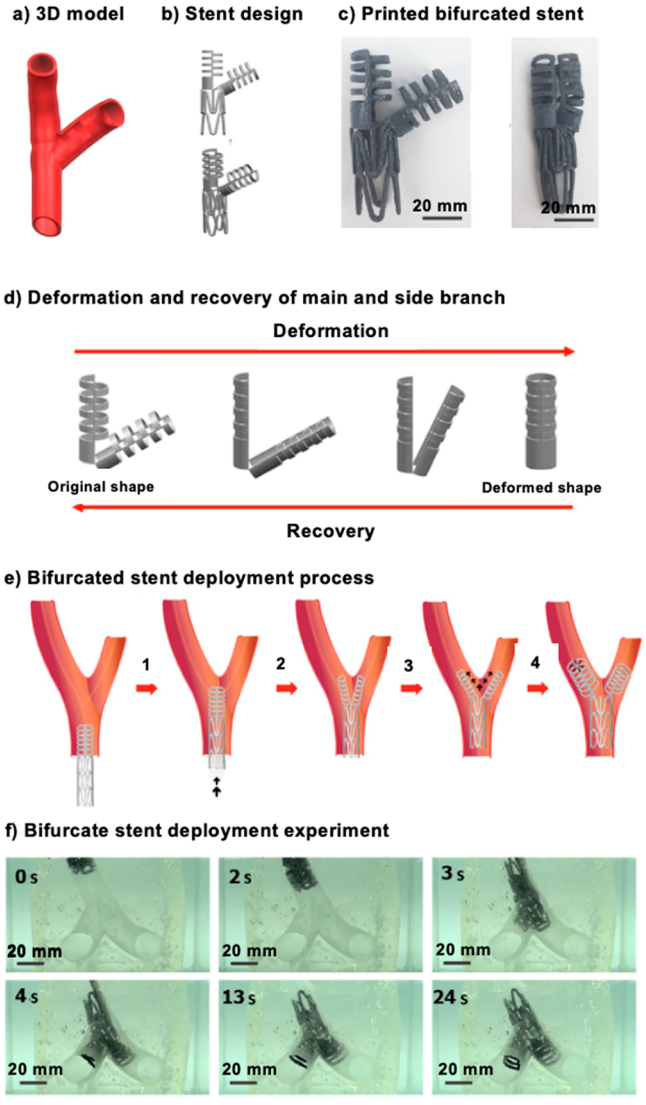

Figure 3. 3D printed stent for a blood vessel. Stents are largely based on a kirigami design. (a) Model blood vessel. (b) Corresponding stent design. (c) Printed stent with adaptable configurations. The length and width of the stent are 80 and 50 mm, respectively. (d) Stages of transformation from deployed to compact shape. (e) Procedure for deployment of stent. (f) Mock experiment exhibiting the stent's adaptability once inserted into its desired environment (Adapted with permission from ref 20. Copyright 2018 The Authors).

structures provided the flexibility to conveniently modulate the stiffness of the bifurcated stents. This study proved an attainable solution to the hindrance and obstruction of conventional stents in bifurcating vessels, by noninvasively inserting a thin structure that converts to a bifurcating volumetric shape via external stimuli.

5. ORIGAMI-INSPIRED IMPLANTS

The challenge of creating and integrating portable implants with varying deploying and retracting behaviors has been thoroughly analyzed in a study dedicated to applying such implant criteria for in vivo functionality.[21] Bobbert et al. fabricated a deployable meta-implant capable of maintaining an under-sized compact mode that facilitates minimal intrusiveness. The origami-inspired structure changed shape upon application of an external force (Figure 4a–b). Figure 4a–b presents the use of deployable meta-implants in a controlled setting using a bottle and in a theoretical application as a bone implant. In both settings, an applied force changes the starting conformation to either retract or expand according to external stressors. This allows for the implant to be properly fitted to suit its physical environment. Bistable structures were employed for their ability to combine into complex multistable structures with more than two stable equilibria. The bistable elements were used to obtain radially and axially deployable structures along with auxetic structures. Poly(lactic acid) (PLA) was used as a biocompatible polymer and as the main material in 3D printing because of its biodegradability and its placement as a template for cell growth. Testing for the functionality of these meta-biomaterials utilized compression and tension tests.[21] Portable implants used in this study merged parameters of bistable elements in creating structures with diversified forces needed in deployment and retraction processes. Results from these 3D structures show potential applications in minimally invasive surgeries and in use as bone implants.

Another study reinforced origami patterns for deployable orthopedic implants made of aluminum and titanium. Inspired by Russian dolls, Bobbert et al. presented multilayered deployable implants that increase in size using silicon balloons and cube structures of varying sizes.[22] Successful deployment of implants was characterized by the smallest cube deploying until contact with a larger cube, yielding further expansion. Bistability was induced in the flat components of the deployable cubes by using kirigami cut patterns made by laser cutting. A control group of implants made from polylactic acid (PLA) was used for efficacy comparisons with origami-based designs. The origami-based 3D constructs consisted of aluminum sheets that were laser cut and designed with complex surface patterns whereas titanium sheets were used to display the application of designed micropatterns while maintaining folding capabilities. Scaling factors of 30%, 40%, and 50% were used for aluminum layers to replicate the Russian doll principle by placing smaller cubes inside of the larger ones. Origami-based implants achieved dimensions approximately two-times larger once deployed.[22] The results of this study showed that porous aluminum meta-implants fabricated by using origami and kirigami are promising for minimally invasive surgeries and to avoid stress shielding in orthopedic implants.

6. USE OF ORIGAMI IN SURGICAL MICROGRIPPERS

The ability to integrate stimuli-responsive untethered grippers can be outlined for its diverse actuation mechanisms and navigation procedures. Ghosh et al. has broadened the subject of untethered soft grippers for drug delivery and robotic surgery.[23] Among actuation mechanisms, magnetic actuators are found to maximize feasibility for untethered applications. Overall locomotion of grippers is also found to be most versatile and attainable using magnetic fields. This can be achieved by implanting magnetic particles onto the body of the grippers.[23] Other external stimuli such as thermal actuation, pH, light, or ionic strength can also be utilized in origami-inspired grippers through the use of composites of polymers and hydrogels.

Moreover, untethered origami-inspired microgrippers can be actuated via thermal or chemical means to pick up and retrieve substrates or to perform biopsies. Leong et al. designed metal microgrippers that were inspired by the digits of arthropods to

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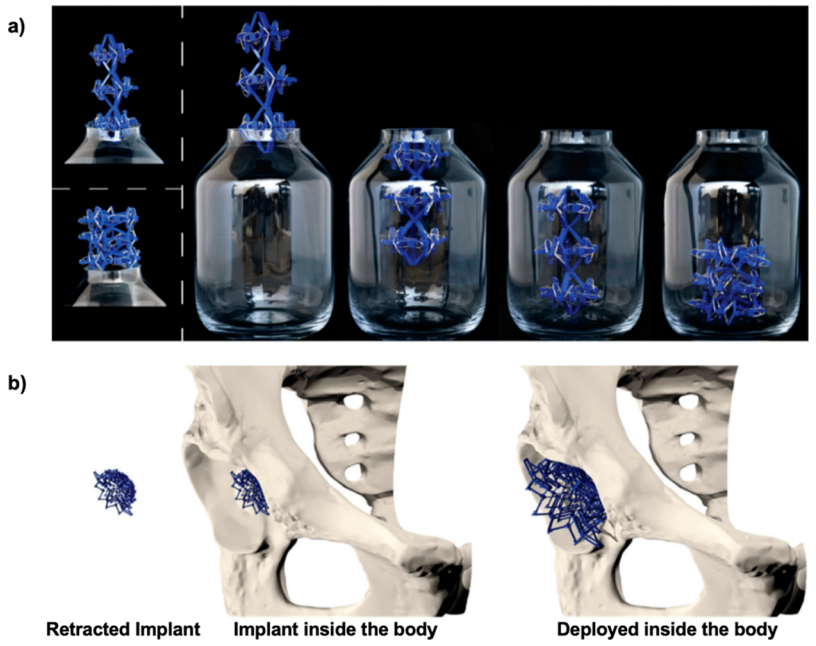

Figure 4. Deployable meta-implant with varying abilities to deploy and retract based on applied force. (a) Deployable and retractable functionality of the implant in a controlled setting using a bottle for minimized intrusiveness. (b) Use of the implant inside the body with both configurations being used (Adapted with permission from ref 21. Copyright 2018 Royal Society of Chemistry).

achieve conformations as small as 190 μm.[24] Remote thermal actuation of microgrippers was achieved in temperatures close to 40 °C while biologically benign reagents were used in the actuation process. The capture and retrieval of live L929 fibroblast cells were accomplished using thermal and biochemical actuation. An in vitro biopsy was performed on a bovine bladder via thermal actuation after which the sample was retrieved using a magnet.[24] The study showed an in vivo functionality of metal, tetherless microgrippers for maximized maneuverability in surgical settings.

Additional forms of in vivo functionality using tetherless, appendage-like microgrippers were experimentally and statistically shown to enhance surgical biopsy procedures. Gultepe et al. implemented untethered endoscopic microgrippers at submillimeter scale for tissue sampling and diagnostic purposes (Figure 5a–c).[25] Figure 5a–c presents the structure and relative size of the microgrippers for reference. The retrieval of the collected tissue showed a sampling success of 45% and 95% for 300 and 1500 grippers, respectively, as opposed to the previously calculated 8% success using conventional biopsy methods. A further application by the same research group made use of origami-inspired ferromagnetic microgrippers to perform an in vivo biopsy of porcine bile for genetic diagnostics and cytologic analysis[25] (Figure 5d–f). Figure 5d–f expands upon the presentation of microgrippers to show wide-scale application, delivery, and retrieval of microgrippers in a colon. The figure especially highlights the ease in applying a large amount of microgrippers for an effective biopsy. These examples provide a promising outlook for the use of origami-inspired microgrippers in humans as a means of enhancing biopsy methodologies.

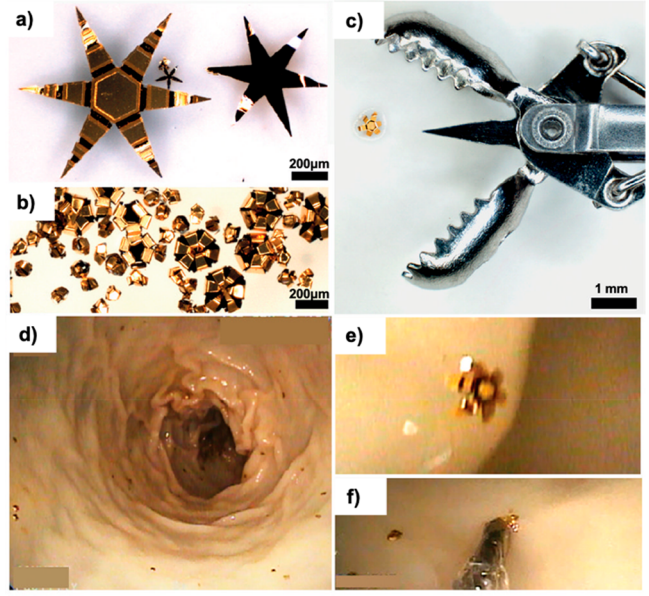

Figure 5. Microgrippers used for tissue sampling and diagnosis. (a) Open configuration. (b) Closed configuration. (c) Microgripper size, which is proportionally smaller than currently used biopsy forceps. (d, e) Images of microgrippers on a colon surface. (f) Use of a magnetic catheter for extraction of a microgripper (Adapted with permission from ref 25. Copyright 2013 AGA Institute. Published by Elsevier Inc).

7. ORIGAMI-INSPIRED MICROFLUIDIC DEVICES AND BIOSENSORS

The methodology involved in origami has been used in significantly mitigating the multipronged approach to fabricating microfluidic devices. Liu et al. outlined this in a study that used origami-based paper analytical devices (oPADs) that can be patterned with multiple reservoirs, channels, and a frame for folding (Figure 6a–d).[26] Figure 6a–d shows the multiple specificities of the paper used for the microfluidic device. Important characteristics of the paper include reservoirs and corner shapes specific for clamping. The aluminum house in which the device was assembled and placed is also shown. The

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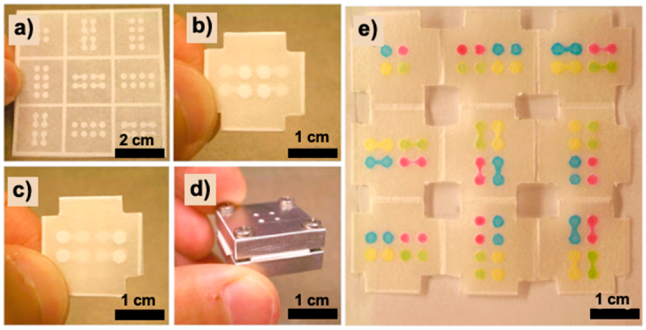

Figure 6. Individual components involved in a 3D paper-based microfluidic device. (a) Chromatography paper fitted with reservoirs, channels, and a frame for folding. (b, c) Top layer and bottom layer with inner reservoirs and edges made for clamping. (d) Aluminum housing used for supporting the microfluidic device with holes for sample solution addition. (e) Unfolded paper microfluidic device showing results of varied samples (Adapted with permission from ref 26. Copyright 2011 American Chemical Society).

device was fabricated using a single sheet of paper that was patterned by photolithography, assembled by manual folding, and had minimized assembly time and costs. The paper itself was 100 μm thick while having channels that were 900 μm wide and reservoirs 2.5 mm in diameter. Subsequent efficacy of these devices was tested by placing different solutions of varying colors on the oPADs to observe the effect of capillary action within each device (Figure 6e).[26] Figure 6e highlights the efficacy of the microfluidic device by allowing solutions to flow through assigned channels and reservoirs without mixing. The results were shown on a nine-layer paper. Layers of the device facilitated parallel colorimetric analysis of multiple analytes including glucose and bovine serum albumin. Similarly, Gharaghani et al. employed 3D thin-layer chromatography (TLC) microfluidic paper-based analytic devices (μPADs) as a means of separating and quantifying two azo dyes for food coloring, Tartrazine (E102) and Indigo carmine (E132).[27] The origami-folded paper devices were inexpensive, portable, and easily disposable. The μPADs, which contained 23 layers of paper, separated the two dyes across the width of the paper. The samples were specifically placed onto hydrophilic regions of the device before folding to minimize differences in band broadening and increase the separation efficiency. The colorimetric results were scanned using a low-cost desktop scanner. Digital image analysis was accordingly used for the analysis and quantification of the separated spots after unfolding of the device.[27] The manipulation of origami in creating microfluidic devices, as such, proves to be an efficient strategy for detection and separation of analytes.

Moreover, origami was utilized to fabricate paper-based microfluidic devices for detection of fraudulent addition of melamine to food. Xie et al. utilized origami-inspired folding techniques in creating μPADs that used polydimethylsiloxane (PDMS) coated paper to generate patterns for flow splitting channels and sample analysis zones.[28] Folded printing paper was patterned with PDMS and then a chromatography paper was placed in between the folded layers. This assembly was heated to obtain a homogeneous distribution of the PDMS on the chromatography paper for generation of hydrophobic patterns. Tests for colorimetric detection of melamine in milk using gold nanoparticles (AuNPs) revealed the efficacy of the low-cost μPADs up to 0.1 ppm melamine concentration, which is lower than the safety limit of 1 ppm.

Furthermore, oPADs have been shown to use shorter channels and embedded reservoirs in order to reduce the sample volume consumption. Chou et al. utilized trilayered oPADs to enhance the preconcentration effect by using an additional hydrophilic area in the microfluidic devices.[29] The research group tested the feasibility of the oPADs using fluorescein and fluorescein isothiocyanate-labeled bovine serum albumin (FITC-BSA) samples. The results indicated that it was possible to achieve 100-fold enhancement of sample preconcentration in the origami-folded paper microfluidic devices. This low-cost, rapid, portable, and simple approach is useful for a wide range of bioanalytical applications in paper-based lab-on-a-chip devices such as detection, separation, and quantification of bioanalytes.

8. CONCLUSIONS

Though there have been significant advancements in the field of biomedicine, the technology and the means of conforming applications to complex, 3D biological systems require specialized strategies to accurately integrate compatible biostructures into these technologies. In addition to being a fascinating art, origami can be used to address these scientific needs. Throughout this review, we provided discussions of various studies conducted, including in vivo, with origami-based adaptations of biomedical applications. We included examples for the use of origami in development of tissue scaffolds, drug delivery systems, stents and catheters, surgical implants and grippers, microfluidic devices, and biosensors. Despite the advantages of the use of origami in biomedical research, limitations still exist in employing such newly emerging technology as the full extent and efficacy of such application has yet to be expanded upon. This can be done using various models, such as those seen in this paper, but more in vivo applications have yet to be discovered. A common limitation among several of the devices mentioned has been the biocompatibility and biodegradability in integrating devices made using origami-inspired methods. Control of devices in a functional and practical environment is also a major point of further research in origami-based structures. These limitations are resolvable with the help from biomaterials science and engineering. The origami-based structures have a promising future for practical applications as well as room for further research toward additional uses and optimizations. The strategies that use the principles of origami yield the capacity for assembling biofunctionalized materials into structures capable of multiform, stimuli responsive, self-folding mechanisms. These intricate structures minimize assembly time, cost, and discontinuity of material while optimizing the biocompatibility and shape conformation, which limits invasiveness of delivery and retraction of these devices from the body.

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Author Contributions

G.C.-U. conceived of the study; A.R.A., O.C.G., and G.C.-U. wrote, revised, and edited the manuscript.

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Notes

The authors declare no competing financial interest.

Biographies

Abdor Rahman Ahmed is a current undergraduate sophomore in the Honors College of Rutgers University through the School of Environmental and Biological Sciences. Additionally, Abdor Rahman is a Louis Stokes Alliance for Minority Participation (LSAMP) scholar. His research interests include microbiology, biotechnology, molecular biology, nanotechnology, and origami. Under the guidance of Dr. Gulden Camci-Unal of UMass Lowell, Abdor Rahman has gained valuable insight into the various applications of origami-inspired structures while also learning extensive skills in technical writing.

Olivia C. Gauntlett studies Chemical Engineering with a Biological concentration and minor in Mathematics at the University of Massachusetts Lowell. She works as an undergraduate research assistant under Dr. Gulden Camci-Unal. Since 2019, her role has been focused on assisting in the research of developing bone cements, mammalian cell culture, analytical lab techniques, and origami-based applications for biomedical uses.

Prof. Gulden Camci-Unal's research at the interface of biomaterials, bioengineering, and diagnostics has made important contributions in generation of engineered platforms for cardiovascular and bone tissue engineering, wound healing, and disease detection including bacterial and viral conditions (e.g., detection of the Covid-19 virus in 5 min). Her current research interests include developing (i) next generation functional biomaterials using unconventional approaches for regenerative engineering, (ii) new tools for origami-inspired tissue engineering and organ-on-paper models, (iii) paper-based biomaterials and medical devices, (iv) in vitro disease models for personalized medicine, and (v) low-cost point-of-care diagnostics to solve problems in global health. The ultimate goal of her research is to improve human health and quality of life.

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