Patterned paper as a template for the delivery of reactants in the fabrication of planar materials

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This account reviews the use of templates, fabricated by patterning paper, for the delivery of aqueous solutions of reactants (predominantly, ions) in the preparation of structured, thin materials (*e.g.*, films of ionotropic hydrogels). In these methods, a patterned sheet of paper transfers an aqueous solution of reagent to a second phase—either solid or liquid—brought into contact with the template; this process can form solid structures with thicknesses that are typically ≤1.5 mm. The shape of the template and the pattern of a hydrophobic barrier on the paper control the shape of the product, in its plane, by restricting the delivery of the reagent in two dimensions. The concentration of the reagents, and the duration that the template remains in contact with the second phase, control growth in the third dimension (*i.e.*, thickness). The method is especially useful in fabricating shaped films of ionotropic hydrogels (*e.g.*, calcium alginate) by controlling the delivery of solutions of multivalent cations to solutions of anionic polymers. The templates can also be used to direct reactions that generate patterns of solid precipitates within sheets of paper. This review examines applications of the method for: (i) patterning bacteria in two dimensions within a hydrogel film, (ii) manipulating hydrogel films and sheets of paper magnetically, and (iii) generating dynamic 3-D structures (*e.g.*, a cylinder of rising bubbles of O_2) from sheets of paper with 2-D patterns of a catalyst (*e.g.*, Pd^0) immersed in appropriate reagents (*e.g.*, 1% H_2O_2 in water).

Introduction

This account reviews the use of paper as a template for the delivery of solutions of reactants in the fabrication of thin materials such as films of ionotropic hydrogels or sheets of paper with shaped deposits of precipitates. In these methods, a patterned sheet of paper transfers a reagent (in an aqueous solution) to a second phase brought into contact with the template to form solid structures with thicknesses that are typically 1.5 mm or less. The shape of the template and the pattern of a hydrophobic barrier on the paper control the features of the product by restricting the delivery of the reagent in two dimensions, while the concentration of the reagent and the duration that the template remains in contact with the second phase—which we call the acquisition phase—control growth in the third dimension (*i.e.*, thickness). In this account, we review the general

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method and discuss how it can be modified for specific applications. We examine the utility of delivery templates of paper, include an analysis of their benefits and limitations relative to alternatives, and highlight challenges to the improvement of the method.

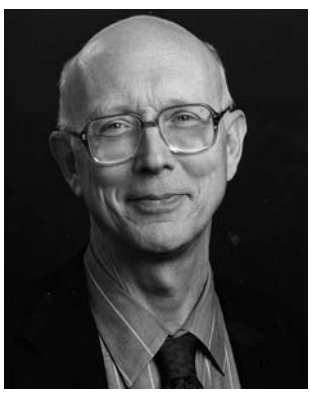
A "delivery template" is a patterned material (here, paper) that both stores a reagent or substance and delivers it, in a predetermined pattern, to a second medium. In materials science, specific examples of methods that employ delivery templates in the fabrication of patterned materials include: (i) the use of PDMS stamps inked with alkyl thiolates to pattern self-assembled monolayers (SAMs) on surfaces of metals,[1,2] (ii) the use of molded agarose stamps inked with bacteria or human osteoblasts to pattern cells on hydrophilic surfaces,[3,4] (iii) the use of hydrogel stamps in wet stamping (WETS) to introduce aqueous reagents to a hydrogel substrate, where precipitation reactions occur in patterns to produce devices such as microlens arrays,[5,6] and (iv) the use of masters functionalized with single-stranded DNA to generate microarrays of complementary strands on a reactive surface.[7,8]

Motivation

Delivery templates of patterned paper enable the fabrication of millimetre-thick films of ionotropic hydrogels in a variety of shapes and compositions. Ionotropic hydrogels are hydrated matrices of ionic polymers cross-linked by multivalent ions of the opposite charge. The most common examples are of anionic polysaccharides, such as alginic acid (AA) and ι-carrageenan (ι-CG), cross-linked by multivalent cations, such as Ca^{2+} and Fe^{3+}.[9–11] These types of polymers are used in drug delivery,[12–14] for encapsulation of cells,[15–17] as sorbents for toxic metals,[18] in wound dressings,[12,19] as radioactive implants for the treatment of tumors,[20,21] and in *haute cuisine*.[22,23] The production of ionotropic hydrogels in millimetre-sized shapes other than spheres is challenging, because it is difficult to introduce the solution of cross-linking cations without disturbing the shape of the solution of un-cross-linked polymer, and gellation typically occurs on contact. Methods for the production of non-spherical 3-D structures of these hydrogels on the millimetre scale include injecting slow-gelling mixtures (*e.g.*, $CaCO_3$ and AA) into shaped molds[17,24] or printing threads of these mixtures with a robot.[25] Hydrogel molds can be used to produce shaped microparticles and membranes of ionotropic hydrogels by controlling the release of cross-linking agent to the solution of un-cross-linked polymer.[26] Non-spherical structures of alginate have been used in wound dressings[12,19] and as cellular scaffolds for seeding chondrocytes in tissue engineering.[24,25]

We have described methods for the production of films of ionotropic hydrogels in simple shapes (*e.g.*, discs and squares), topologically complex shapes (*e.g.*, interlocking rings and Möbius strips), and heterogeneous (gel-in-gel) patterns.[27,28] These methods employ templates of patterned paper to control the delivery of cross-linking ions to the un-cross-linked polymer in two dimensions, with millimetre precision (a dimension set by diffusion, not by the dimensions of the template). The procedure is simple, rapid, and feasible in any laboratory—templates can be constructed by hand or with an unmodified color printer. In many cases, there are no alternative methods for fabrication of these structures.

We have also adapted these templates to serve as stamps for patterning solid precipitates within the pores of sheets of paper.[29] We, the Pelton Group at McMaster University, and others are developing patterned paper as a platform for low-cost diagnostic assays, and the ability to pattern materials within paper could be used to introduce function to these paper-based devices.[30–33] Enzymes or transition metals precipitated within paper can be used to catalyze chemical reactions, and insoluble paramagnetic materials patterned in paper allow for manipulation of the paper with magnets.



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Description of the method

We use paper templates to deliver the ions that form ionotropic hydrogel films or solids precipitated within porous sheets of paper. A hydrophobic barrier—usually adhesive tape, a sheet of plastic, or a layer of printed toner—patterns the transfer of a reagent present in a solution adsorbed on the paper to an acquisition phase (*e.g.*, a solution of un-cross-linked polymer or second sheet of paper) where a reaction occurs to produce a product (*e.g.*, a hydrogel or an inorganic precipitate). The template is usually removed to leave a free-standing final product. Fig. 1 illustrates the method for the production of a film of an ionotropic hydrogel by the delivery of a multivalent cation (Fe^{3+}) to a solution of an anionic polymer (2% sodium alginate).

Use of paper

Paper is useful as a template because it is generally: (i) thin and flexible—most types of paper will not fracture when folded or bent; (ii) porous—the pores readily absorb aqueous solutions of reagents and allow the flow of liquids through the material; (iii) smooth on the ~100 μm scale—a non-textured surface ensures conformal contact with other surfaces and a smooth finish to the products; (iv) commercially available—paper is sold in a variety of shapes and sizes, and many types are inexpensive; (v) convenient—numerous machines (*e.g.*, printers, cutters, copiers) and products (*e.g.*, glue, tape, laminating sheets) exist specifically to

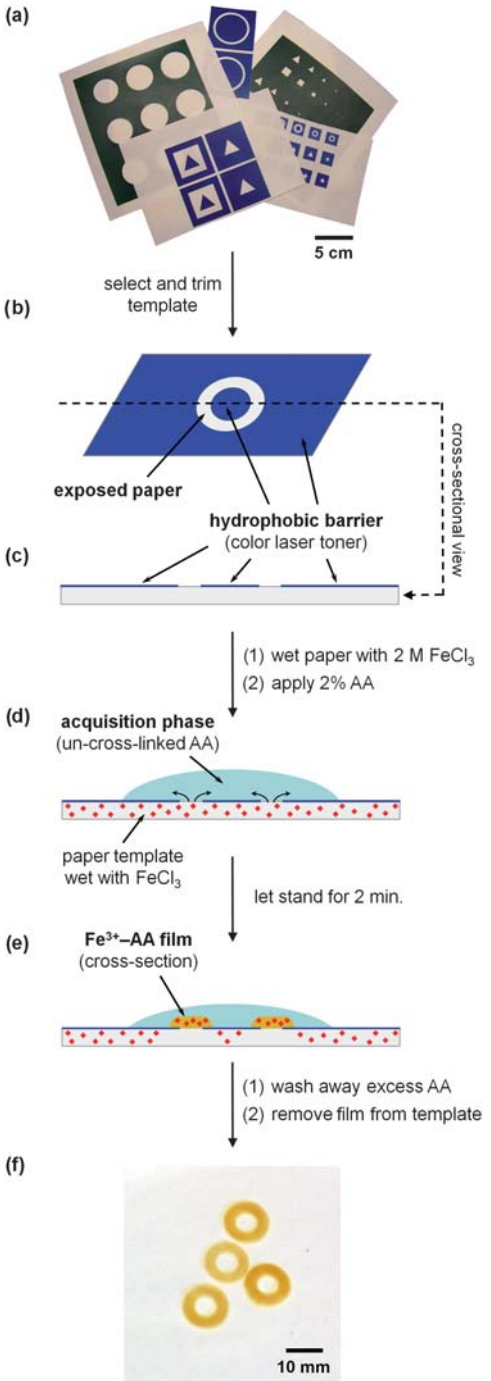

Fig. 1 Schematic diagram outlining the use of templates of patterned paper in the fabrication of rings of Fe^{3+}–AA. (a) An assortment of templates produced with a Xerox Phaser printer by depositing layers of hydrophobic toner on Whatman No. 1 chromatography paper. (b) Oblique view of a paper template designed for the production of a film of an ionotropic hydrogel in the shape of a ring. (c) Cross-sectional view of the same template—the toner serves as a barrier to restrict the area that the multivalent ions can diffuse off of the template. (d) The cross-linking reagents (Fe^{3+} ions) diffuse out of the template and into the acquisition phase (2% AA) applied to the template. (e) Within three minutes, a film of cross-linked hydrogel forms on the exposed regions of the template. (f) Photograph of four ringed films of Fe^{3+}–AA produced by this template. The thickness of the films is ~0.8 mm.

modify paper.[34] For the methods described in these experiments, we obtained the best results when Whatman-brand No. 1 chromatography paper was used to construct the templates. The properties of this type of paper that were especially advantageous were: (i) its sufficient mechanical strength when wet such that it resisted fragmenting and tearing, (ii) its relatively high capacity for aqueous solutions—11 μL cm^{-2},[28] (iii) its lack of additives—*e.g.*, whitening or strengthening agents—that could react with the aqueous solutions of reagents or interfere with the wicking of these solutions through the paper, and (iv) its availability in 20 × 20 cm sheets that were compatible with standard office printers. Other types of commercial papers we examined—including bond paper, copier paper, and membranes of cellulose acetate or nitrocellulose—proved less reliable or unsatisfactory for the methods. These types of paper had lower capacities for aqueous solutions than the chromatography paper, and the solutions wicked across these papers with much slower velocities. The cellulose acetate and nitrocellulose membranes could not be patterned with desktop printers due to their irregular sizes.

Patterning hydrophobic barriers onto paper

In the design of templates, the hydrophobic layer should be: (i) easy to pattern into shapes; (ii) easy to apply to the paper; (iii) thin, to ensure conformal contact with the acquisition phase; and (iv) completely impermeable to aqueous solutions. Convenient barriers include a layer of toner applied with a standard color laser printer, or wax that is applied with a solid-ink printer and melted into the paper with heat.[35,36] Any standard graphics design program (*e.g.*, Microsoft PowerPoint) can be used to draw the pattern. In order to form a completely impermeable barrier of wax or toner, the design is printed two or three times on the same sheet and heated to seal any cracks or holes. The hydrophobic barrier can also be applied by hand. Adhesive tape (*e.g.*, Scotch-brand transparent duct tape) is especially useful to block the back (unpatterned) side of the paper to prevent loss of the reagent from the underside of the template. Another effective barrier is a patterned sheet of transparency film with shaped holes cut through it by a blade or laser. The patterned sheet functions as a mask, where the holes allow passage of the aqueous reagent. Epoxy patterned photolithographically,[31,37] or wax printed on and melted into sheets of paper,[35,38] can restrict the absorption of aqueous solutions by the paper to shaped regions. These areas can be used to template the fabrication of structures with matching shapes.

Physical manipulation of the paper

Another method to control delivery of the aqueous solution is to pattern the paper physically by cutting holes through it, or cutting it into shapes. When the pattern need not be precise, the cutting can be done by hand with scissors or a paper cutter. A laser cutter or knife plotter can pattern sheets of paper for higher resolution and more complex designs.[39,40] The templates can also be constructed by bending or folding sheets of paper into desired shapes, including complex shapes such as bowls, rings, interlocking rings, and Möbius strips. Paper manipulated into these shapes will template the production of structures with matching shapes.

Loading reagents onto the templates

Reagents can be loaded onto the templates with a pipette. The solution spreads uniformly into the paper by capillary wicking. (For aqueous solutions, Whatman No. 1 chromatography paper will absorb ~11 μL cm^{-2}.[28]) Alternately, the solution can be introduced to the sheets of paper before the template has been constructed. Once dried with a heat gun, the sheets of paper can then be assembled into the final template and rehydrated when used.[27]

Delivery

During the delivery step, the reagent diffuses into the acquisition phase and forms structures with shapes that roughly match the pattern of exposed paper. Growth of the structures can be terminated by removing the template from contact with the acquisition phase, or by washing off the unreacted acquisition material.

Structures fabricated by the templated delivery method

Shaped homogeneous films of ionotropic hydrogels

Shaped structures of ionotropic hydrogels—especially *soft* hydrogels—are difficult to construct. The method we describe makes it straightforward to fabricate millimetre-thick films of ionotropic hydrogels, in a variety of shapes, without the need for molds or programmed printing devices. The easiest films to produce are 2-D shapes (*e.g.*, discs or squares) of a single ionotropic hydrogel (*e.g.*, Ca^{2+}–AA). This application of the method requires only one sheet of paper and one hydrophobic barrier.[28]

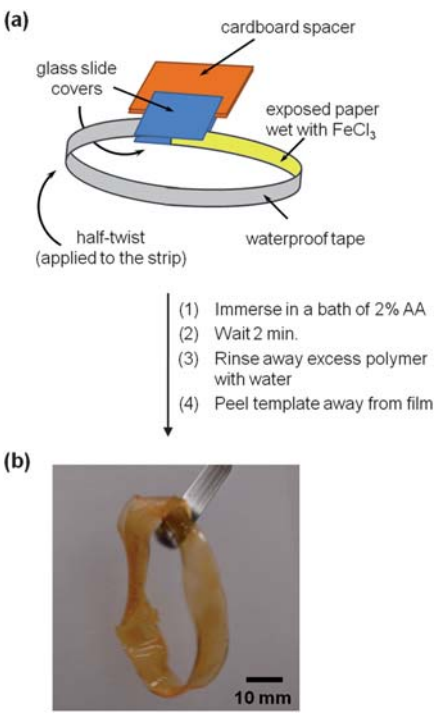

Fig. 2 The template (a) and procedure used to produce a film of Fe^{3+}–AA in the shape of a Möbius strip (b).

The procedure can be altered to produce more complex shapes by manipulating the topography of the paper. To produce shapes such as rings or interlocking rings, a piece of paper is twisted or bent into corresponding 3-D shapes.[28] For these complex shapes, the wet templates are completely immersed in a bath of the uncross-linked polymer. This protocol may require the back side of the template to be sealed (for example, with waterproof tape) to restrict diffusion of the cross-linking ions into the acquisition phase to one side of the paper. The templates can also be modified with handles that allow the paper to be positioned into topologically complex shapes (for example, a Möbius strip, Fig. 2).

Heterogeneous films of ionotropic hydrogels

In the method above, a single sheet of paper generated a film of a single hydrogel (*e.g.*, Ca^{2+}–AA). To construct a heterogeneous film composed of two or more ionotropic hydrogels (a "gel-in-gel" structure), we stack multiple sheets of paper into a layered template.[27] Holes cut into the sheets expose underlying layers to the surface of the template, and each sheet delivers a different solution of cross-linking ions. The solutions can contain different cations, or simply, different concentrations of the same cation. Hydrophobic barriers (typically, layers of toner) between the sheets of paper prevent the solutions of ions from mixing, and another hydrophobic barrier (typically, a patterned sheet

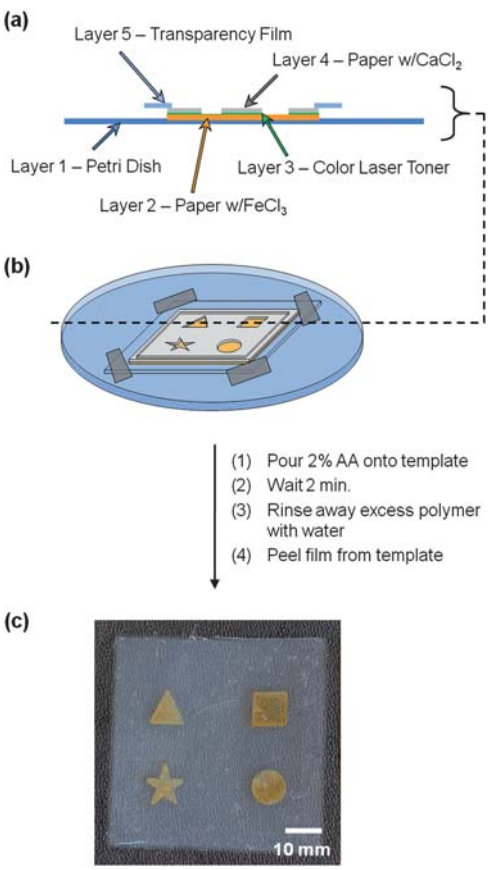

Fig. 3 The template (a, side view; b, oblique view) and procedure used to produce a heterogeneous film (c) of shapes of Fe^{3+}–AA in a field of Ca^{2+}–AA.

of transparency film) affixed to the surface of the template controls the shape of the perimeter of the film. Fig. 3 shows the production of a film with shapes of Fe^{3+}–AA on a field of Ca^{2+}–AA.

Patterning precipitates in paper

In the production of films of ionotropic hydrogels, the acquisition medium that receives reagents from the template is a liquid. The templates can also be used as stamps to deliver reagents to acquisition phases that are absorbent solids. When a template wetted with an aqueous reagent comes into contact with a different, dry sheet that contains a second adsorbed reagent, the solution travels off of the template and into the second sheet, where a reaction can occur. If the reaction results in the formation of a precipitate, the solid will remain trapped in the pores of the paper (Fig. 4).

In all of these methods, the user faces a choice of whether to produce the hydrophobic barrier(s) with: (i) toner deposited by a color laser printer, (ii) wax deposited by a solid-ink printer, or (iii) transparency film patterned by a laser cutter. In the fabrication of films of ionotropic hydrogels, templates made with laser toner, transparency film, or wax *that is not melted into the paper* give similar results. (Templates made with reflowed wax have slightly rougher edges—upon melting the wax into the paper, the resolution of the printed image diminishes.[35]) For the templates used as stamps for patterning precipitates in paper, we prefer to use printed wax that is melted into the paper to form a 3-D barrier. For templates made of laser toner, which is isolated to the surface of the paper, the aqueous ink wicks into parts of the paper under the barrier. If the barrier becomes compromised, the stamped pattern will have defects. In the case of templates produced from wax by reflow, the hydrophobic layer extends through the entire top sheet of the stamp and provides a robust barrier to the ink.

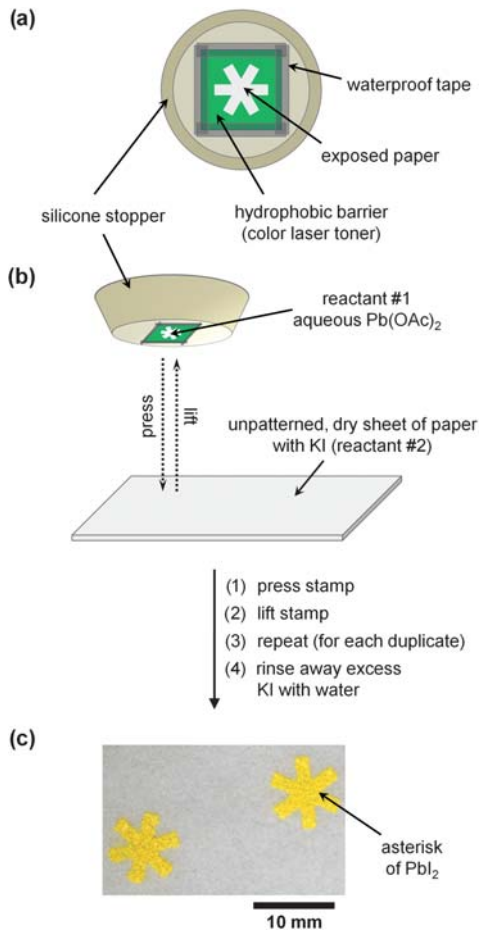

Fig. 4 General method for patterning precipitates of reactions within paper in the context of a specific example—stamping a solution of $Pb(OAc)_2$ into a dry sheet containing KI to form shapes of PbI_2. (a) A bottom view of the stamp (delivery template). (b) Oblique view of the stamping step. (c) Photograph of the product—asterisks of PbI_2 patterned into the pores of a sheet of chromatography paper.

Applications

Thin structures of ionotropic hydrogels are used commercially as wound dressings[12] and in medical research as scaffolds for the implantation of chondrocytes in tissue engineering.[24] Shaped structures of ionotropic hydrogels are also found in *haute cuisine*.[22] Since the method is general and will work for any ionotropic hydrogel, the solutions of ions and polymers can be selected and modified to introduce function to the hydrogel films that they produce. We have demonstrated that pigments (*e.g.*, Pigment Blue 15, a phthalocyanine), sensors (*e.g.*, pH indicators), and sorbents (*e.g.*, activated carbon) can all be incorporated in the ionotropic hydrogels and that these materials retain their function while trapped within the hydrogel matrix.[28,41] When the films are formed from cultures of bacteria (*e.g.*, *E. coli*), the bacteria become immobilized in the film and continue to metabolize substrates while trapped within the hydrogel.[27]

The choice of cross-linking ion can also impart function to the resultant hydrogels. When the ions used to cross-link the polymer are sufficiently paramagnetic (*e.g.*, Gd^{3+} or Ho^{3+}), the hydrogel films respond to gradients in magnetic field. This property allows magnetic manipulation of the films with a simple bar magnet, and paramagnetic films can be separated from diamagnetic films (Fig. 5a).[28,41] The biocompatibility of the hydrogel films can be tuned with the selection of cross-linking metal. For instance, Ni^{2+}–AA, Cu^{2+}–AA, and Al^{3+}–AA are toxic to *E. coli*, while Ca^{2+}–AA and Ba^{2+}–AA are non-toxic.[27]

The ability to form heterogeneous films (gel-in-gel structures) allows the functional materials described above to be patterned in two dimensions.[27] A long strip of Gd^{3+}–AA incorporated within a film of alginate allows the film to be oriented without the need for touching it—the long axis of the magnetic region aligns with the long axis of a bar magnet. For films that are made from cultures of *E. coli* in solutions of sodium alginate, the design of toxic and non-toxic ions used to cross-link the polymer can control both the viability of colonies of the bacteria and the activity of enzymes that are expressed by the bacteria (Fig. 5b).

The ability to pattern solids within the pores of paper allows the introduction of function to paper-based devices and systems.[29] Catalysts (*e.g.*, enzymes precipitated with ammonium sulfate) can be stored on paper for subsequent use. Paramagnetic salts (*e.g.*, $Gd(OH)_3$) trapped within paper allow for pieces of it to be manipulated with simple bar magnets. Designs of insoluble colored pigments can be used as counterfeit deterrents.[42]

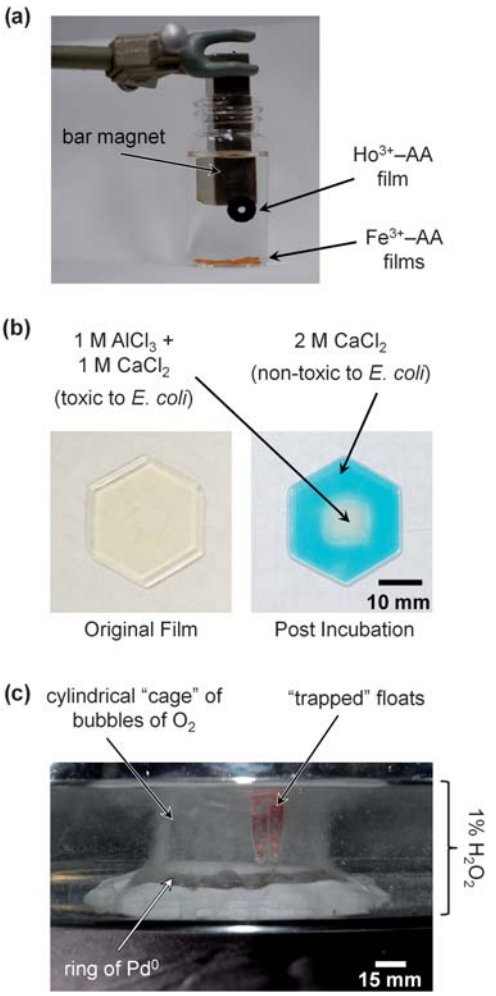

Fig. 5 Applications of templated delivery of reagents to produce materials with function. (a) Films cross-linked with sufficiently paramagnetic cations can be separated from mixtures with a bar magnet. (b) The 2-D design of toxic and non-toxic ions used to cross-link a heterogeneous film of alginate can be used to pattern *E. coli* within the structure. The change in color indicates the presence of viable colonies of the bacterium and arises from the metabolism of 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside (X-gal) into a pigment by β-galactosidase. (c) A 2-D ring of Pd^0 patterned into a sheet of chromatography paper produces a dynamic 3-D cylinder of bubbles of O_2 when immersed in a 1% solution of hydrogen peroxide. The cylinder can be used to encage floating objects.

Two-dimensional patterns of catalysts on paper (*e.g.*, a ring of Pd^0) exposed to appropriate substrates (*e.g.*, H_2O_2) can be used to generate dynamic three-dimensional structures (*e.g.*, a cage of bubbles of O_2, see Fig. 5c).

Outlook: opportunities and challenges

This technique uses paper to fabricate structures that often cannot be fabricated by other methods. The templates are easily constructed, and in many cases, they are also reusable. The technique should be adaptable to high-volume manufacture (*e.g.*, by a roll-to-roll process). A major advantage of this method is its simplicity.

The structures produced by these methods have feature sizes that are limited by two factors: (i) the resolution with which the hydrophobic barrier can be patterned on the templates, and (ii) the loss in resolution that results from the isotropic diffusion of the reagents once free of the templates. The standard office printers we used could reliably deposit wax or toner to produce barriers with features as small as ~1 mm. The templates always produce structures with "rounded" features with respect to the shaped hydrophilic regions of the paper, because the reagents disperse through the acquisition medium isotropically once released from the template. As a result, in the case of the production of hydrogel films, the thickness of the features matches the loss of resolution in the lateral direction. This aspect of the method introduces an inherent limitation—the edge resolution of the film cannot match the dimensions of the template to less than the thickness of the gel. In the case of patterning precipitates within the bulk of sheets of paper, the precipitated features are also rounded (relative to the shaped hydrophilic regions of the stamp) because the stamped ink wicks freely through the substrate layer until the precipitation reaction occurs to generate a solid. Reactions where precipitation occurs quickly display the lowest loss of resolution.

Among other possibilities, future work should examine the uniformity of the composition of the films throughout their *z*-dimension, determine parameters (*i.e.*, ion concentrations and reaction times) for producing films of any desired thickness for a given hydrogel, and investigate the mechanical properties of the materials. A challenge for future improvement is the production of heterogeneous films composed of multiple polymers. While we have developed templates that produce heterogeneous single films composed of one polymer cross-linked by different cations (*e.g.*, distinct regions of Ca^{2+}–AA and Fe^{3+}–AA), an unsolved problem is how to produce a heterogeneous film from multiple solutions of polymer (*e.g.*, distinct regions of Ca^{2+}–AA and Ca^{2+}–CG). Such an advance would be useful for patterning multiple cell types in a single film for biological applications.

Acknowledgements

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