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Performing Logical Operations with Stimuli-Responsive Building Blocks

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Chemical logic gates can be fabricated by synthesizing molecules that have the ability to detect external stimuli (e.g., temperature or pH) and provide logical outputs. It is, however, challenging to fabricate a system that consists of many logic gates using this method: complex molecules can be difficult to synthesize and these logic gates typically cannot be integrated together. Here, we fabricated different types of logic gates by assembling a combination of different types of stimuli-responsive hydrogels that change their size under the influence of one type of stimulus. Importantly, the preparation of these stimuli-responsive hydrogels is widely reported and technically simple. Through designing the geometry of the systems, we fabricated the YES, NOT, OR, AND, NOR, and NAND gates. Although the hydrogels respond to different types of stimuli, their outputs are the same: a change in size of the hydrogel. Hence, we show that the logic gates can be integrated easily (e.g., by connecting an AND gate to an OR gate). In addition, we fabricated a standalone system with the size of a normal drug tablet (i.e., a "smart tablet") that can analyze (or diagnose) different stimuli and control the release of a chemical (or drug) via the logic gates.

Ever since the pioneering work by de Silva et al.,[1] researchers have fabricated many different types of "chemical logic gates:" molecules (or macromolecules) that detect and analyze one or more input signals (e.g., a chemical species) and produce a logical output.[2–4] Chemical logic gates can have a wide variety of applications, such as for information technology (e.g., computation), memory devices,[5] large-scale identification of small (e.g., micron-sized) objects,[6] molecular lock,[7] microfluidics,[8] diagnostics,[9,10] photodynamic therapy,[11,12] prodrug activation,[13] and delivery.[14–19] For example, in order for a drug to be delivered specifically to cancer cells, it is desirable for the drug carrier to be responsive to both pH and temperature—that is, an AND gate is required.[20] This is because certain malignancies can cause both a localized increase in temperature and a decrease in pH in its local environment. Therefore, in order to target specifically the cancer cells—and reduce targeting of normal cells—it is desirable for the drug carrier to be responsive to both temperature and pH. Fundamentally, logic gates are the basic building blocks for complex systems. In electronics, they are used for the construction of sophisticated machines (e.g., a computer) that, in some cases, can be considered as "intelligent."[21] Hence, the fabrication of individual chemical logic gates is generally regarded as the elementary step in realizing "intelligence" in chemical systems. Because these chemical logic gates are both fundamentally interesting and can have many applications, the field has inspired many exciting works.[22–25] Many different types of chemical logic gates have been fabricated; they can be constructed based on small (e.g., organic or organometallic) molecules,[5,10,13] biological macromolecules (e.g., RNA,[26,27] DNA, DNAzymer, and protein),[28–31] or stimuli-responsive polymeric macromolecules (e.g., hydrogels).[32,33] This field of research has advanced to the stage in which the chemical logic gates can accept multiple types of stimuli as inputs (e.g., light or a chemical species) and perform advanced functions that are equivalent to the assembly of multiple basic logic gates. Examples of these advanced operations include sequential logic operations,[5] half adders,[34,35] half subtractors,[36,37] and multiplexers.[38,39]

The general approach to constructing these chemical logic gates is by synthesizing chemically the molecules that can perform the logical functions. Although current research has produced many amazing molecules that are capable of some basic functions, this general approach has its limitations and challenges. First, the ability to perform advanced operations is greatly limited by the challenges in synthesizing the molecules chemically. For example, although some half-adders have been constructed out of small molecules, their function is equivalent to only two logic gates. More complex functions (e.g., a full adder or other simple types of numerical operations) can involve dramatically a lot more logic gates than two. In electronics, a simple program may consist of thousands or many more logic gates. In addition, the number of types of external inputs that the molecules or macromolecules can detect is usually limited to two or three. In some rare cases, the molecules or macromolecules can detect up to four specific combination of inputs.[40–44] In general, it is a challenging task to synthesize these functional molecules chemically. There is surely a balance between the complexity of the operations that the molecule can perform versus the complexity at which the synthesis of the molecule remains reasonably achievable. Another challenge is the connection between the logic gates. For many chemical

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DOI: 10.1002/adma.201606483

logic gates, they cannot be integrated because the output of one logic gate is not compatible to the input of the other logic gate.[2,3,14] Because of these challenges, the goal of constructing chemical systems at the level of sophistication that can be considered as "intelligent" seems far away.

Our approach involves using stimuli-responsive hydrogels that respond to only one type of stimulus for constructing the logic gates. Stimuli-responsive hydrogels are a class of macromolecule that can expand or contract under the influence of an external stimulus. These hydrogels have been investigated widely for many decades and can now be fabricated to respond to a wide range of external stimuli, such as temperature, pH, electric field, magnetic field, light, pressure, gases, ions, salt, alcohol, glucose, and many types of biomolecules (e.g., enzymes and antigens).[45–49] Fundamentally, our approach involves the use of these hydrogels and the functional design (e.g., geometry) of the system for fabricating the logic gates.

As a demonstration of our concept, we fabricated (macroscopic) systems that consisted of a reservoir of dye, a channel (200 µm in diameter) that allowed the dye to be released, a piece of polymer (i.e., the "valve") that controlled the opening of the channel, and the stimuli-responsive hydrogels (see Sections S1–S3 in the Supporting Information for more details on the materials and methods). In our notation, we assign an input of 0 for the state when the hydrogel contracted, and an input of 1 for the state when the hydrogel expanded. When the dye released normally via the channel, we assign an output of 0; when the dye did not release, we assign an output of 1. We first demonstrated our approach by fabricating the YES logic gate through using a pH-responsive hydrogel (**Figure 1**a). When the hydrogel was exposed to a solution of pH 2, it contracted (input 0), and the dye released via the channel (output 0). At pH 12, the hydrogel expanded (input 1), and pushed a thin film of polymer (50 µm in thickness; polydimethylsiloxane, PDMS) toward the channel; hence, the channel was blocked and the dye did not diffuse out of its reservoir (output 1). The process was reversible: when the hydrogel contracted (after expansion), the elastic polymeric film returned to its nonstretched state, and dye released again.

A NOT gate can be fabricated by replacing the thin polymeric film (i.e., the valve) with a block of polymer (PDMS) that has a geometry as illustrated in Figure 1c. In this case, we used a temperature-responsive hydrogel. At 40 °C, the hydrogel contracted (input 0), and the piece of PDMS blocked the channel; thus, the dye did not release (output 1). At 4 °C, the hydrogel expanded (input 1). This expansion pushed the piece of polymer away from the channel and allowed the dye to release (output 0).

Through specific design of the system, more complex logic gates can be constructed. **Figure 2** illustrates the methods for fabricating the OR, AND, NAND, and NOR gates. A typical setup consists of two stimuli-responsive hydrogels; each one of them responds to a different stimulus (Figure 2a). In our experiments, we used a pH-responsive hydrogel and a temperature-responsive hydrogel. For the OR gate, the two hydrogels were placed next to each other (Figure 2b). Whenever anyone (or both) hydrogel expanded under the influence of either one (or both) of the stimulus, the thin polymeric film was pushed forward; thus, the channel was blocked. For the AND gate, we left a space between the two hydrogels (Figure 2c). When only one of the hydrogels expanded, it merely expanded into the space without pushing the thin polymeric film forward. Hence, the polymeric film could be pushed forward only when both the hydrogels expanded. The NAND and NOR gates were constructed based on these principles together with the block of polymer (i.e., the valve) used for the NOT gate (Figure 2d–f). We verified experimentally that these four logic gates performed as expected for all the four input states. Using only these four "basic" logic gates, it is possible to construct all other types of logic gates by assembling a combination of these gates together.

As a control experiment, we determined that the different stimuli-responsive hydrogels used in the logic gates were able to change their sizes sufficiently under the influence of the respective stimuli to fully open or block the channel (Section S4, Supporting Information). In addition, we measured the times of response of the logic gates when the respective stimuli were applied (Section S5, Supporting Information). We observed that the logic gates were able to switch reversibly between states for ten cycles without any decrease in performance (Section S6, Supporting Information).

Although different stimuli-responsive hydrogels detect different types of external stimuli, their outputs are the same: the pushing of the pieces of polymer. Thus, we can connect multiple logic gates together for performing more advanced operations. In the first demonstration, we connected an AND gate to an OR gate (**Figure 3**a). The AND gate consisted of a thin polymeric film, a pH-responsive hydrogel, a temperature-responsive hydrogel, and a space in the gate as discussed in Figure 2c. The OR gate consisted of a thin polymeric film and a salt-responsive hydrogel (i.e., a hydrogel that expands in deionized water and contracts in a solution containing salt) without any space in it. When both the pH-responsive and the temperature-responsive hydrogels expanded, they pushed the thin polymeric film of the AND gate forward. This polymeric film then pushed the salt-responsive hydrogel and the thin polymeric film of the OR gate forward, thus blocking the channel. Since there was no space in the OR gate, the channel was blocked regardless whether the salt-responsive hydrogel was in its expanded (in deionized water) or contracted state (in a 1 M NaCl solution). Similarly, when the salt-responsive hydrogel expanded, the channel was blocked regardless whether the thin polymeric film of the AND was pushed forward. In our design, the salt-responsive hydrogel was fabricated to have a slightly larger width than the length of the thin polymeric film of the AND gate. When the salt-responsive hydrogel expanded, it could not push the polymeric film of the AND gate backward due to the two PDMS supports at the ends of the thin polymeric film. We verified experimentally that this system of two logic gates performed as expected for all the eight input states (Figure 3b). We also demonstrated a system that consisted of an AND gate connected to a NOR gate (Figure 3c). Similarly, we left a space between the pH-responsive hydrogel and the temperature-responsive hydrogel for the AND gate; however, there was no space in the NOR gate. Again, we verified experimentally that the logic gates performed as expected for all the eight input states (Figure 3d).

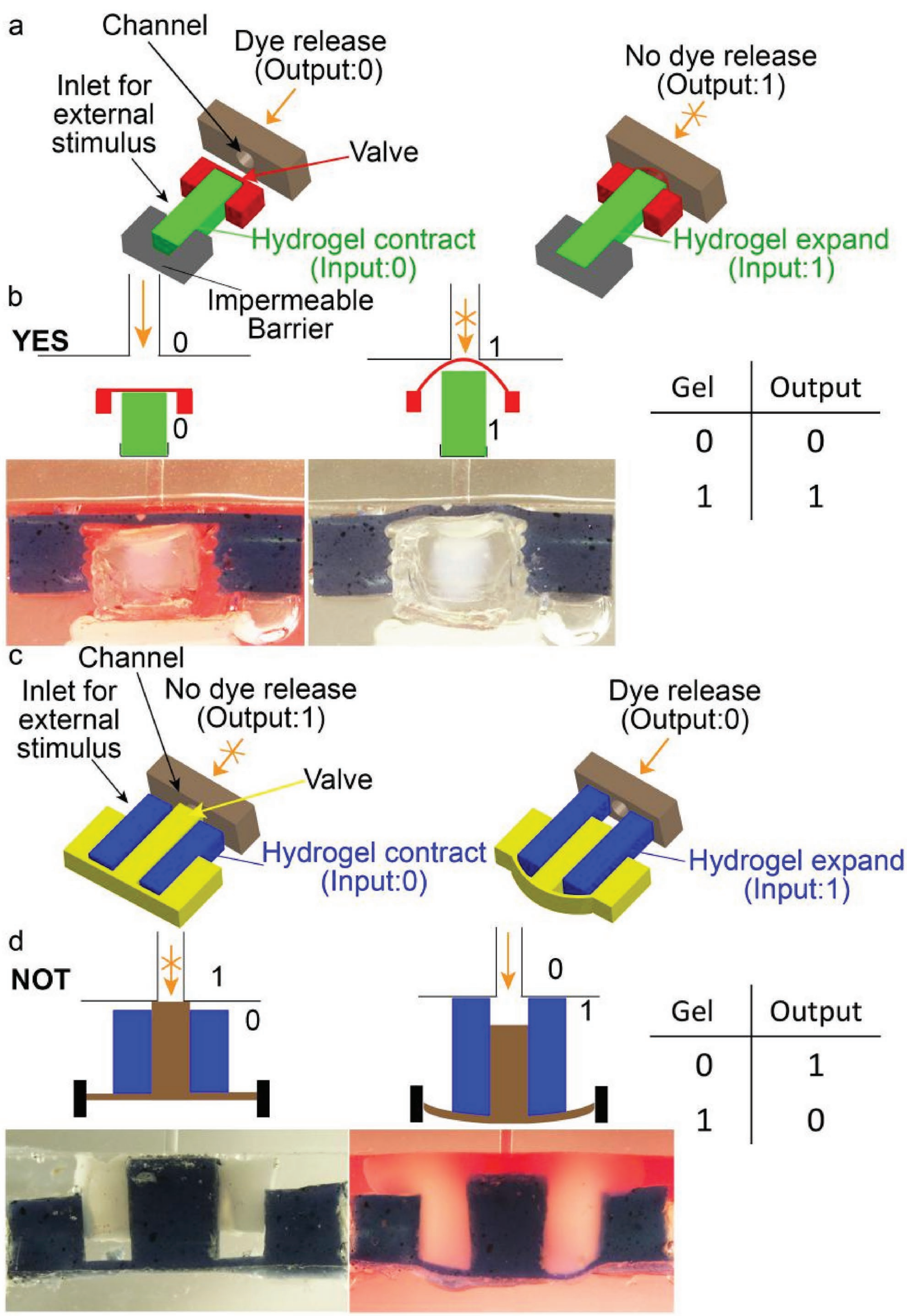

Figure 1. The design of the YES gate and the NOT gate using stimuli-responsive hydrogels. Input 0 represents the state when the hydrogel contracted, and input 1 represents the state when the hydrogel expanded. Output 0 represents the state when the dye released normally, and output 1 represents the state when the channel was blocked and no dye was released. Schemes illustrating a) the YES gate, and c) the NOT gate. Simplified representations of the different states of b) the YES gate and d) the NOT gate, and the truth tables. The images at the bottom show the respective logic gates fabricated experimentally at different states. The pieces of polymer (polydimethylsiloxane, PDMS) for blocking the channel were dyed blue for clarity. Red color indicates that the dye released.

One important application of chemical logic gates is drug delivery. It would be desirable for the drug-delivery system to be able to analyze—and hence diagnose—the conditions of the human body. In this way, the release of the drug can be controlled by the diagnosis. The ability to perform advanced analysis can also be useful for targeting a specific region of the body as discussed (e.g., the local environment of a tumor site). Experimentally, we fabricated a standalone system (Section S7, Supporting Information) with an overall size of a typical drug tablet (≈1 cm). It consisted of a reservoir of

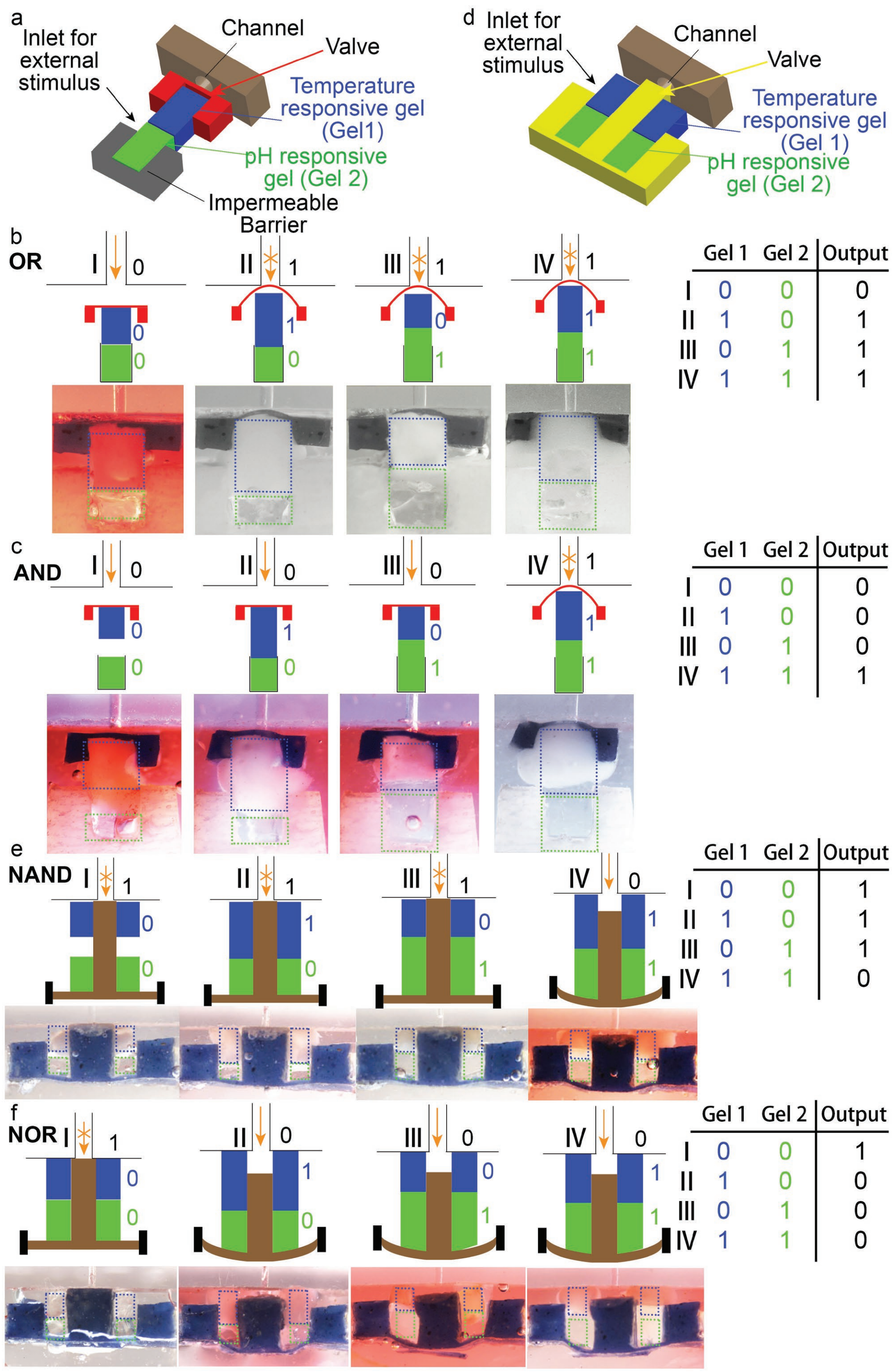

Figure 2. The design of the logic gates that detect two external stimuli. Schemes illustrating the designs of a) the OR and the AND gates, and d) the NAND and the NOR gates. The simplified representations, truth tables, and experimental images for b) the OR gate, c) the AND gate, e) the NAND gate, and f) the NOR gate.

chemical (i.e., a red dye) and the logic gates for controlling the release. We first demonstrated the concept using an OR gate that consisted of a temperature-responsive hydrogel and a pH-responsive hydrogel (**Figure 4**a,b). The "tablet" stopped releasing chemical when either one or both of the hydrogels expanded. We also demonstrated the concept using an AND gate connected to an OR gate (**Figure 5**a,b). In all cases, we took samples and determined the amount of chemical

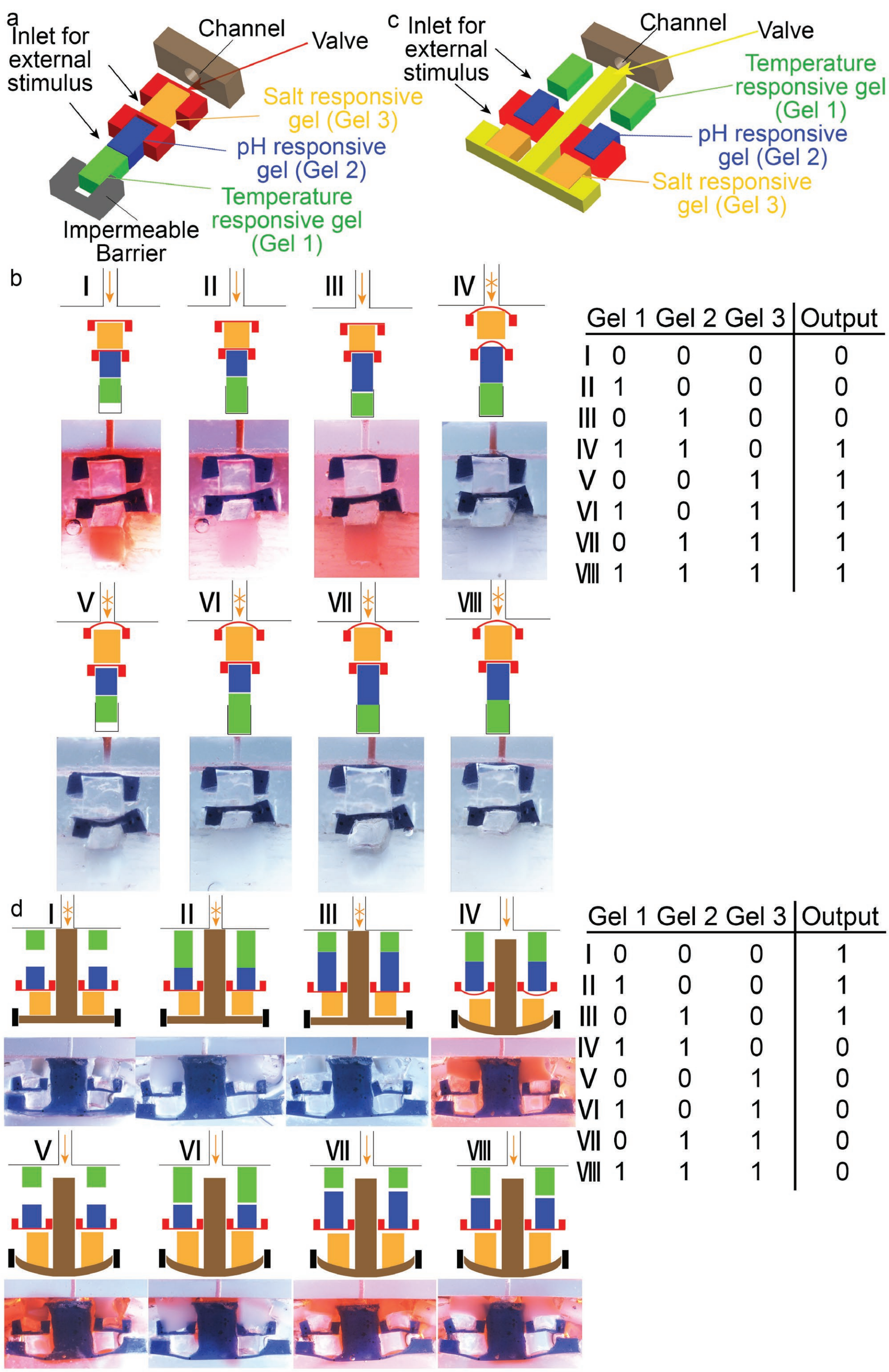

Figure 3. The designs of the systems that consisted of two logic gates connected together. a,b) An AND gate connected to an OR gate and c,d) an AND gate connected to a NOR gate.

released by UV–vis spectroscopy for 2 h. We verified that all the inputs corresponded to the logical outputs experimentally (Figures 4c and 5c).

In conclusion, these demonstrations show that through designing the system (e.g., the positions of the stimuli-responsive hydrogels and the geometries of the valves), it is possible to construct different types of chemical logic gates. This approach has a few advantages over other chemical logic gates reported in previous studies. First, we used stimuli-responsive hydrogels that respond to only one

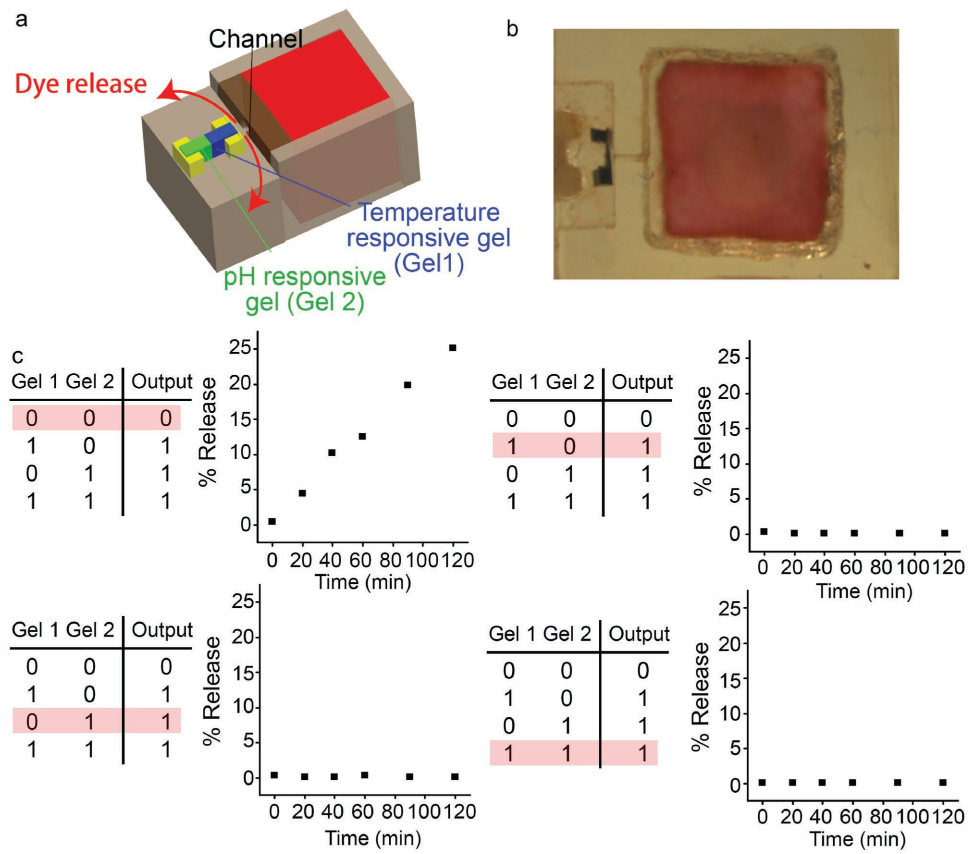

Figure 4. Analysis and delivery of a chemical using an OR gate. a) A standalone chemical-delivery system with the size of a drug tablet (≈1 cm) was fabricated by assembling a reservoir of dye with an OR gate. Depending on the temperature (40 °C: input 0, 4 °C: input 1) and the pH (pH 2: input 0, pH 12: input 1) of the surrounding solution, the logic gate analyzed and controlled the release of the dye. b) Top-down experimental image of the system. c) Verifying that the release of dye was controlled by the logic gate.

type of stimulus; importantly, the preparation of these hydrogels is much easier than the synthesis of many molecules that are reported to have the functions of a few logic gates. Second, the output of one logic gate can be connected simply to the input of another logic gate as demonstrated. Advanced operations require many logic gates to be connected and integrated into complex systems; however, integration of logic gates has been an important challenge for molecules reported in previous studies.[2,3,14] Third, this approach allows many different combinations of the stimuli to be detected by assembling the appropriate types and number of stimuli-responsive hydrogels together; hence, there is no need to synthesize other molecules that can detect specifically the desired combination and number of stimuli. In terms of size, recent rapid technological advancement has enabled fabrication at the small scale—especially at the nanoscale—to be technically much easier than before.[50,51] Therefore, together with the simplicity of fabrication and the capability to integrate the logic gates, it is potentially feasible to produce massive number of these logic gates at a small scale for performing complex analyses or calculations. This is the approach used in electronics and is proven to be very successful for building highly advanced electronic equipment, such as computers. Hence, the same approach can potentially pave the way for constructing chemical systems that can be regarded as "intelligent." For example, it may be possible to build a smart drug carrier that is able to perform on-board diagnostics for controlling the release of drugs—this futuristic goal may be realizable by incorporating many logic gates in a single drug-carrying particle.

This study essentially demonstrated the basic principles of using elementary responsive building blocks for constructing the logic gates. In general, there is a wide range of flexibility in this approach. Further work can involve other creative designs of the valves and the hydrogels (e.g., different geometries, sizes, positions, and chemical compositions) for the construction of other types of logic gates or other complex operations. At the same time, different designs can lead to different ways of integrating the logic gates. Another example of the flexibility of the approach is that the release of dye can be designed differently; the system may consist of multiple channels, a channel with multiple valves, or a combination of both. Besides binary output, these systems may provide continuously varying responses (e.g., the extent of the opening of the channel). Interesting applications can potentially be achieved through exploring different aspects of the system and integrating a combination of many of the same type (i.e., similar to electronic devices in which the same electrical stimulus is used for controlling the logic gates) and different types of hydrogels.

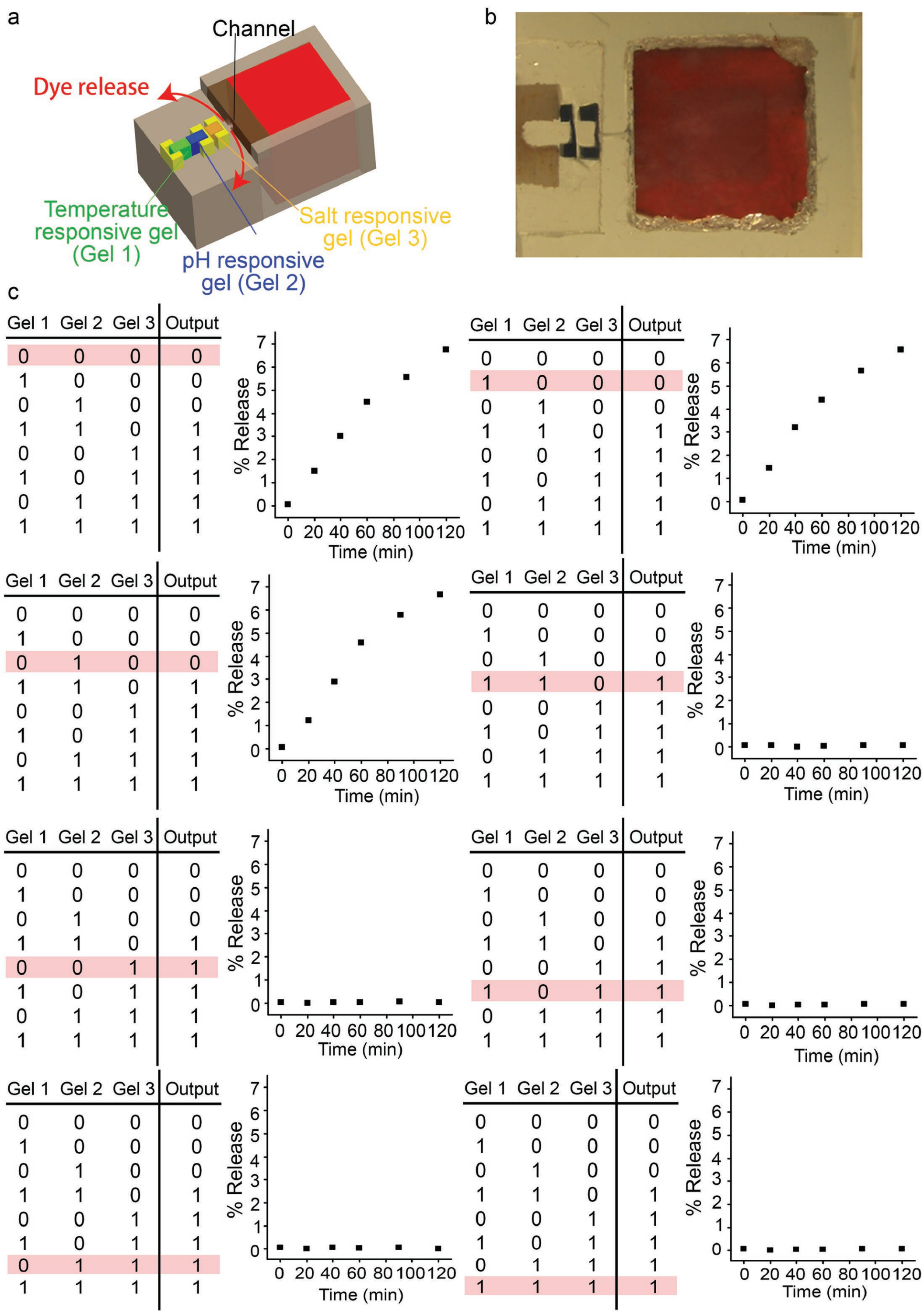

Figure 5. Analysis and delivery of a chemical using an AND gate connected to an OR gate. a) A standalone chemical-delivery system of the size of a drug tablet (≈1 cm) was fabricated by assembling a reservoir of dye with the logic gates. Depending on the temperature (40 °C: input 0, 4 °C: input 1), the pH (pH 2: input 0, pH 12: input 1), and the concentration of salt (1 M NaCl: input 0, deionized water: input 1) of the surrounding solution, the logic gates analyzed and controlled the release of the dye. b) Top-down experimental image of the system. c) Verifying that the release of dye was controlled by the logic gates.

COMMUNICATION

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

This work was financially supported by the Ministry of Education, Singapore, under grant R-279-000-398-133.

Received: November 30, 2016
Revised: January 23, 2017
Published online: March 1, 2017

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