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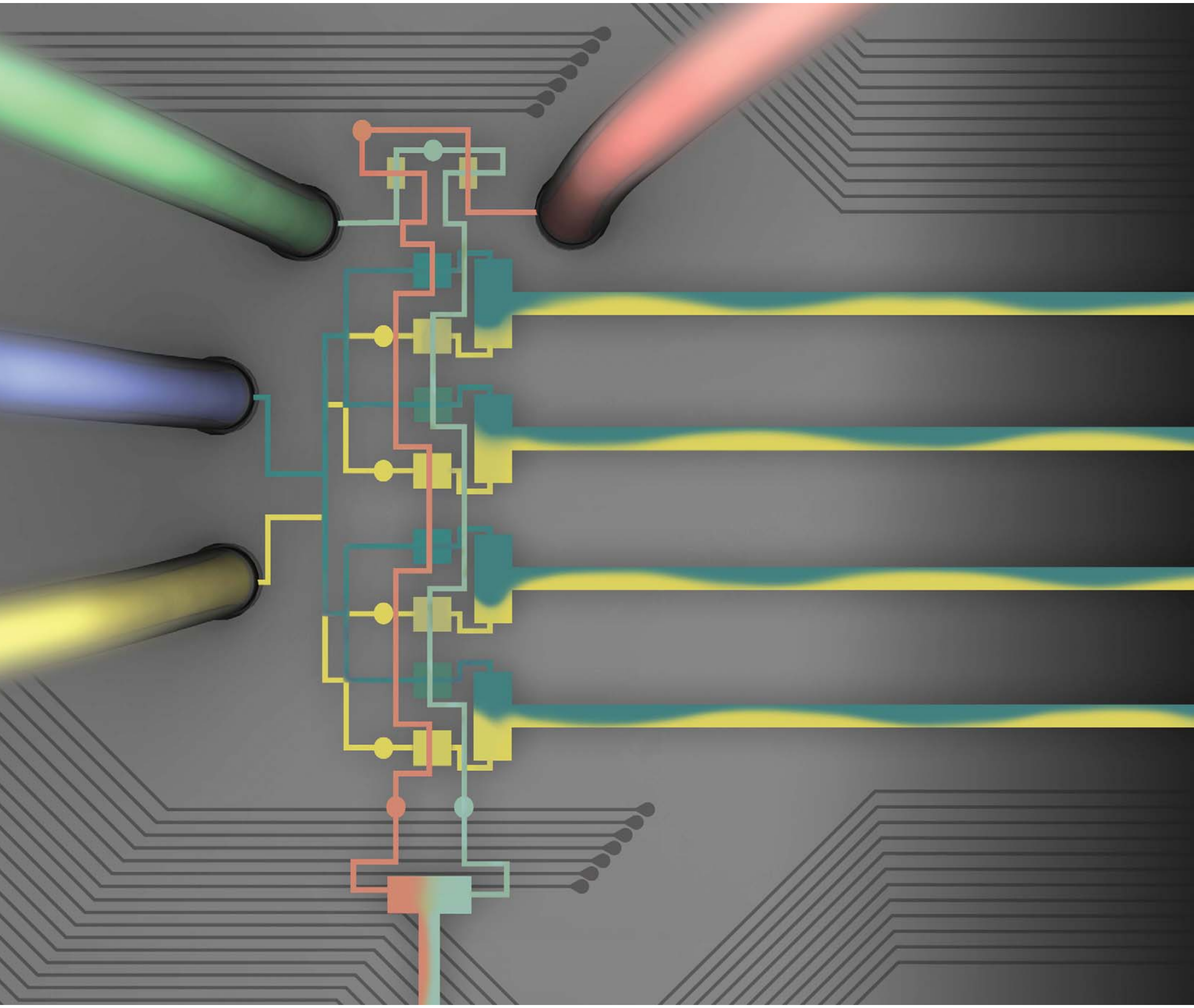

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Next-generation integrated microfluidic circuits

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Next-generation integrated microfluidic circuits

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This mini-review provides a brief overview of recent devices that use networks of elastomeric valves to minimize or eliminate the need for interconnections between microfluidic chips and external instruction lines that send flow control signals. Conventional microfluidic control mechanisms convey instruction signals in a parallel manner such that the number of instruction lines must increase as the number of independently operated valves increases. The devices described here circumvent this "tyranny of microfluidic interconnects" by the serial encoding of information to enable instruction of an arbitrary number of independent valves with a set number of control lines, or by the microfluidic circuit-embedded encoding of instructions to eliminate control lines altogether. Because the parallel instruction chips are the most historical and straightforward to design, they are still the most commonly used approach today. As requirements for instruction complexity, chip-to-chip communication, and real-time on-chip feedback flow control arise, the next generation of integrated microfluidic circuits will need to incorporate these latest interconnect flow control approaches.

Introduction

The field of microfluidics emerged in part from fabrication techniques developed for integrated electronic circuits (IECs).[1] The IEC was a revolution that enabled multiple (up to billions today) electrical switches to be fabricated on a single, small substrate. Initially used for specialized space and defense applications, decreases in cost and increases in capability have led to the permeation of electronic circuits in many common devices. Similar grand hopes are provoked with the term integrated microfluidic circuits (IMCs). IMCs today, however, fall short of such hopes. In this article, we focus on one possible roadblock, and the recent advances towards clearing the way forward through this obstacle. The obstacle is microfluidic flow control.

IECs are of course controlled by electrical means. Importantly, IECs are also powered, as well as receive inputs and produce outputs, by electrical means. There is a seamless integration of all necessary components within a single semiconductor material substrate, and smooth exchange of signals between the components. IMCs, on the other hand, are typically comprised of an assortment of electrical, mechanical and fluidic components. Instruction signals originating from electrical control circuits must be converted to mechanical actuation signals that are then further translated to flow control events.[2] In these conglomerate systems, the fluidic conduits and valves may be integrated in a single substrate (*e.g.* polydimethylsiloxane or PDMS) but the controller is in a separate electrical unit (interfacing computer) and the mechanical means of enacting the controls in yet another device (*e.g.* solenoid valves). Thus, a major obstacle for microfluidic devices is interfacing and converting the instructions given by the electrical components to the actual fluids in the microfluidic components. Furthermore, whereas IMCs are designed to effectively convert electrical signals into fluid actuation events, the converse of converting fluid flow signals back into electrical signals to allow closed loop feedback control is difficult.

This review provides an overview of the most recent development towards overcoming these challenges in microfluidic control. We categorize these microfluidic control approaches using concepts akin to modern instructional delivery approaches of electronic circuits (Fig. 1): parallel instruction, serial instruction, and embedded-instruction. Emphasis is given particularly on the latter two approaches since they are the more recent developments. Although serial instruction or embedded-instruction strategies have begun to be adopted by other types of microfluidic systems as well,[3–5] this mini-review will focus on devices that use networks of elastomeric valves to implement these types of control systems.

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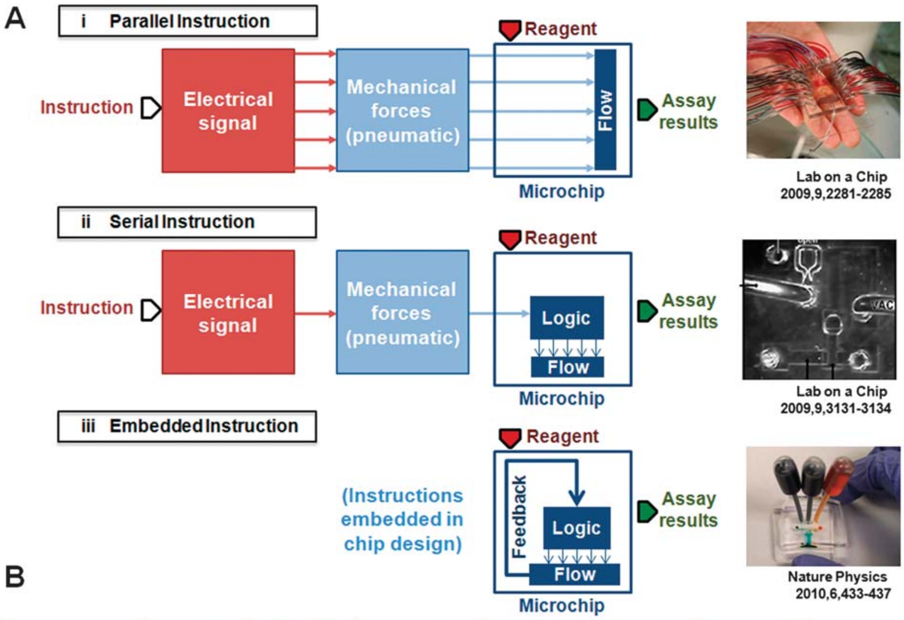

B

Approach	Intuitive Design	Small On-Chip Valve Footprint	Small # of External Components	Speed of Fluid Regulation	Sample Feedback	User Interface	Overall Ease of Setup
Parallel Instruction	★★★	★★★	★	★★★	★	★★	★
Serial Instruction	★★	★	★★	★	★★	★★★	★★
Embedded Instruction	★	★★	★★★	★★	★★★	★	★★★

Fig. 1 Approaches to microfluidic flow control. (A) Conceptual sketches of flow control methods and example microfluidic devices. (A-i) Parallel instruction provides multiple signals simultaneously and each signal can be individually controlled at any given time point. This type of signaling is currently the most commonly used for microfluidic circuits. (A-ii) Serial instruction delivers bits of information one at a time and the device itself decodes/organizes that information based on a known clocking cycle. (A-iii) Embedded instruction uses integrated self-regulating components that control the flow of reagents without any external instructional signals (power to infuse the reagents is still needed). (B) Relative ranking (more stars indicate a higher ranking) of the three approaches in part A for various design parameters.

Approach 1: parallel instruction

Currently, the majority of microfluidic devices that possess valves to be switched on and off in arbitrary sequences have control signals relayed to each valve separately through parallel instruction lines regulated by electronic controllers (Fig. 1A).[1,6,7] Advantages of this approach include conceptual simplicity and the direct, quick response of the fluidic valves to external signals. Many complex and functional devices have been demonstrated using this concept over the last 10 years.[6,8–10] To reduce the need for each valve to have its own control line, multiplexed valving schemes have been developed.[10–14] The two main approaches have been to either design valves that actuate at multiple threshold pressure values (*i.e.* ternary or quaternary multiplexing)[12,14] or by multiplexing the control lines themselves instead of the fluid channels.[10,11,13] These schemes can be very effective for devices incorporating large numbers of flow channels (*i.e.* 1024 flow channels can be controlled by 10 external control lines for the case of quaternary multiplexing) however additional regulatory equipment is needed to accurately supply the correct threshold pressure. A general disadvantage of this approach, however, is that regardless of multiplexing, the number of required external control lines still increases as the number of valves to be *independently* actuated increases. This complexity of external equipment and connections may be one reason why the use of this technology is not more widespread. In addition to challenges of scalability, the direct external instruction scheme also lacks the conceptual framework for on-chip fluidic feedback control that can further enhance fluidic operation functionality and robustness.

Approach 2: serial instruction

In recognition of the hardware limitations in the parallel instruction approach, microfluidic logic circuits and control strategies have been developed that can decode serial instructions sent to the microfluidic circuit.[7,15–17] Specifically, consecutive high/low pressure/vacuum inputs can be translated by embedded microfluidic components into discrete sets of parallel instructions that then regulate fluid flow within the device. There have been several different methods developed to accomplish the design of these valve-based serial instruction microfluidic devices (Fig. 2, 3). The main distinction between these various serial

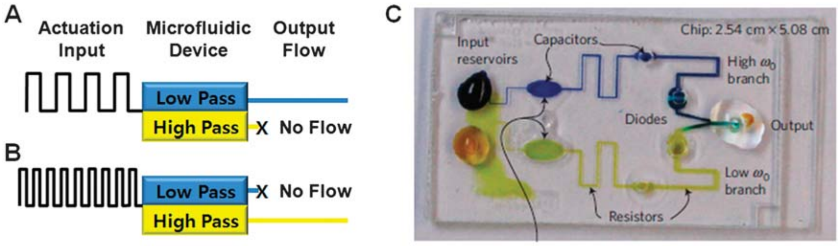

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Fig. 2 Frequency responsive flow control. (A and B) Schematic of flow control by having parallel RC circuit components for separate fluids actuated simultaneously by a single serial actuation input signal. (C) Image of a frequency responsive microfluidic device that switches flow between two distinct fluids.

instructional methods is the manner in which the serial signal is delivered and decoded.

One method for using a single instruction line to control two or more flow paths is to engineer systems with different resonant frequencies.[4,17] A single conduit connected to all channels can then actuate one channel selectively based on the frequency of the input signal (Fig. 2A and B). For elastomeric valve-based systems,[17] fluidic capacitors (flexible membrane chambers) and resistors (channels of different lengths/widths) define each channel's resonant frequency (Fig. 2C). Normally closed valves that open at

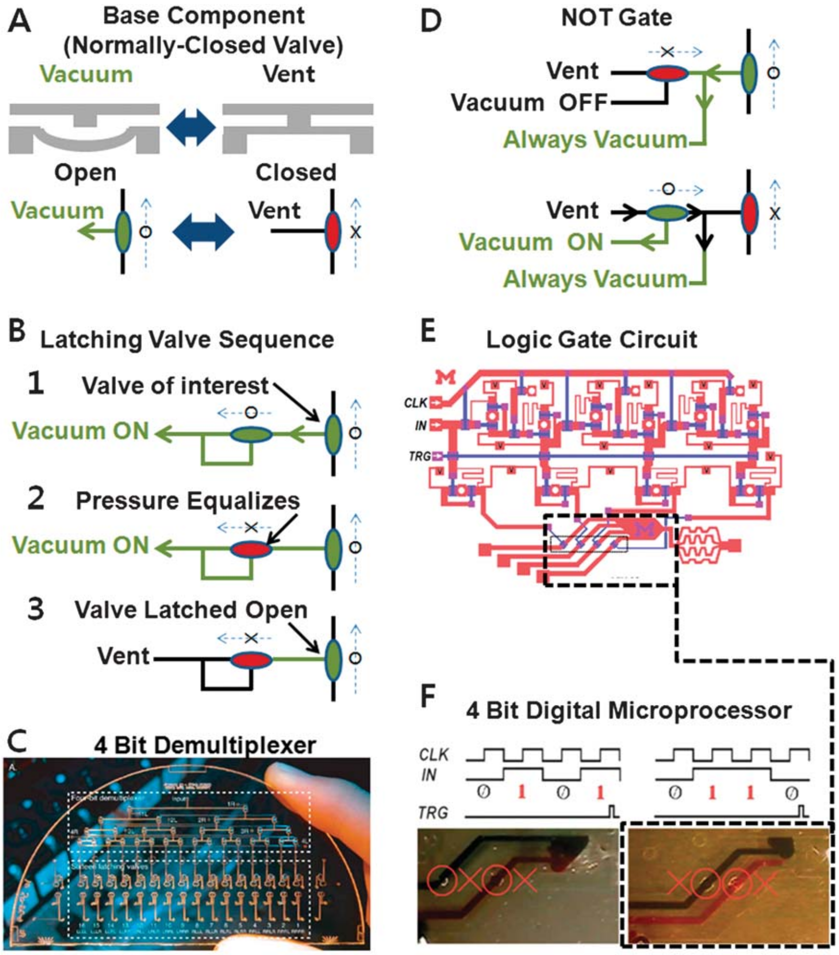

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Fig. 3 Flow control using latching valves and logic gates. (A) Schematic of both states of the normally closed valve with its corresponding symbol. (B) Steps to form a latching valve by combining normally close valves such that a vacuum pulse temporarily opens each valve until the pressure equilibrates on the first valve which causes it to close but maintains the second valve open. (C) Actual device that has a four bit-demultiplexer controlling 16 independent latching valves. (D) Schematic of both states of the NOT gate that has the inverse output of its input (built using same normally closed valve in part (A)). (E) Larger logic circuits are made by combining logic gates. (F) A 4 bit digital microprocessor that regulates fluid flow of dyed solutions is shown.

a threshold positive pressure but remain closed with negative pressure provide a diode-like function to rectify the oscillating signal. The advantage of this system is that only a single control line is required. The current challenge for this approach is that the inherently broad frequency response of the elastomeric components makes clean switching of flow between different channels difficult.[18] However, as stated by the authors, there are many avenues that can enable more precise tuning of device's frequency response including the use of stiffer materials and fluidic inductors.[17]

Another single-instruction-line method uses a signal that is delivered at precise times using normally closed valves (Fig. 3A).[14] Cleverly connecting three or more such valves enables construction of latching valves—a valve that remembers and maintains its fully open state for a limited time (<2 min).[7] Fig. 3B shows a simplified implementation of a latching valve comprised of two normally closed valves in which the valve of interest is maintained open (the alternative three valve design demonstrated by Grover *et al.* allows for active control to reclose the valves).[14] When a vacuum signal is applied (Fig. 3B-1), both valves are opened due to a negative pressure acting on the deformable membrane (as shown in Fig. 3A). After approximately 120 ms, the pressure on the deformable membrane of the first valve equalizes and the valve closes (Fig. 3B-2). The vacuum signal can now be removed but the negative pressure acting on the membrane of the valve of interest is maintained since the first valve is in a closed position (Fig. 3B-3). The specific latching valve demonstrated by Grover *et al.* maintains its open position for ~2 min due to the permeability of PDMS to gases.[14] These latching valve components have been used to perform serial instruction by means of a demultiplexer that routes vacuum pulses, delivered through a single port, to a set of parallel latching valves (Fig. 3C). The demultiplexer allows *n* external valves to control $2^{(n-1)}$ parallel latching valves.

An alternative to using a demultiplexer is to use logic gates to transform a series of input signals into a parallel set of control actions. This type of serial instruction interpretation has been demonstrated using two different types of microfluidic valves.[15,16] One method uses the normally closed elastomeric valves (shown in Fig. 3A) with a pneumatic actuation system,[15] and the second method uses a normally open elastomeric valves with a hydraulic actuation system (Fig. 4A).[16] Both of these methods use shift registers to parallelize the serially encoded signals so that temporally spaced inputs are translated into spatially distinct states of multiple valves (Fig. 3E). Although these two methods operate on the same concept, their implementation has been achieved by different means. The first method uses serially delivered vacuum pulses that are decoded by microfluidic logic components (*e.g.*, NOT gates, flip-flops, shift registers) to produce parallel signals that will either open or close fluidic valves in the test channels (Fig. 3E). The second method uses serial hydraulic pressure inputs that activate "gain valves" that are directly connected to, and thereby subsequently closing or letting remain open, non-gain valves that are in the test channels (Fig. 4B and C). Implementations of only the simple NOT gate (Fig. 3D) and AND gate (Fig. 4B) are shown in detail here; more complex components integrate a combination of several such components together (Fig. 3F).

The advantages of the digital logic-based serial instruction strategies include robust digital operation and the conceptually straightforward transfer of digital circuit design strategies from microelectronics. In addition, only a single input line (along with a clocking and trigger signal) is needed to control a theoretically infinite number of on-chip valves. However, attenuation of control signals as they propagate through the device can be a significant issue, as it is in electronic circuits, and therefore designs need to incorporate adequate signal buffering and amplification.

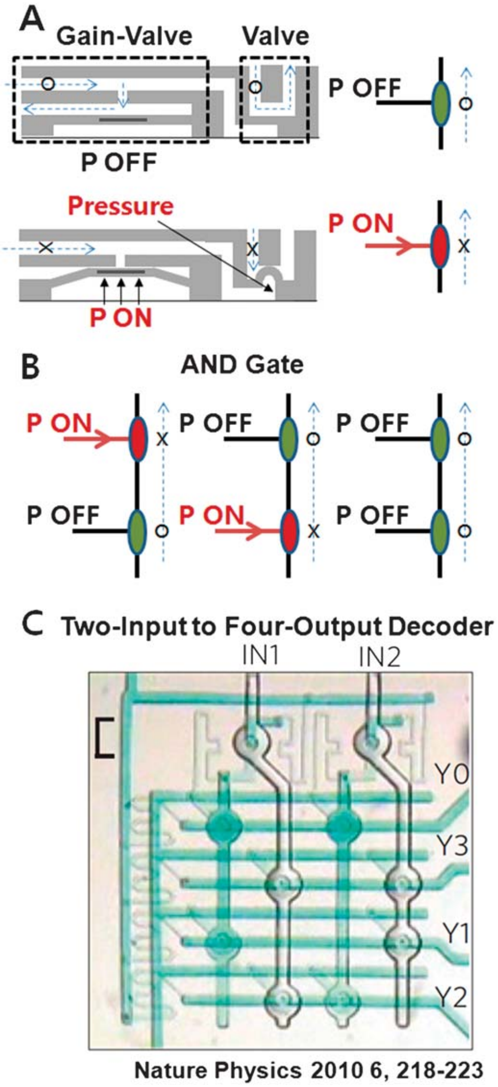

Fig. 4 Microfluidic logic-gates made by normally open gain-valves. (A) Schematic of both states of the gain-valve that regulates another elastomeric valve that directly controls a desired sample solution. (B) Implementation of the gain-valve as an AND gate is done by combining Gain-Valves in series such that flow of the desired solution only occurs when both Gain-Valves are OFF. (C) Larger logic circuits are made by combining logic gates. Inverters and AND gates are combined to make a 2 input to 4 output decoder.

Approach 3: embedded instruction

As opposed to the directly controlled fluidic circuits described above, the ability to construct self-regulating fluidic circuits is needed for efficient operation of advanced devices. Networks of normally closed elastomeric valves (Fig. 5A) can be designed such

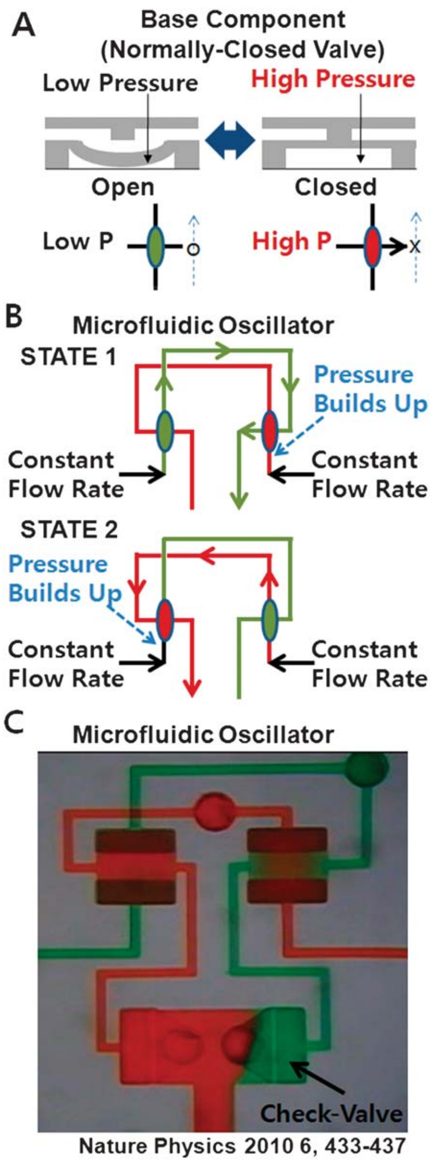

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Fig. 5 Microfluidic devices controlled by embedded instruction. (A) Schematic of both states of a normally closed valve as used in the embedded instruction approach. (B) The two states of a microfluidic oscillator automatically producing an alternating output flow between two distinct solutions that are being simultaneously infused at a constant rate. (C) Image of the microfluidic oscillator outputting a red dye solution. The two additional valves on the bottom are check-valves that negate cross-contamination of solutions.

that they provide auto-regulation of flow (Fig. 5B and C). These valves are similar to the normally closed valves used for pneumatic instruction (Fig. 3A) but use hydraulic feedback from on-chip flow to control valve opening and closing (Fig. 1A-iii and 5B) instead of using external pressure sources. Development of devices with autonomous flow control has been explored by several groups but most systems require some form of user input to set the parameters by which the device will operate.[2,4,19–24] Here, we have focused our discussion on the elastomeric valve based system.[25] In this concept, there are no interconnects for controlling flow; the only input is the direct infusion of the reagents at a constant flow rate. An interconnected network of fluidic capacitors that provide time delays, valves that open and close at defined threshold pressures, and channels that serve as resistors convert the constant input flow to discrete control signals that direct fluid to different parts of the device at defined times. This concept is reminiscent of electronic devices that continually operate based on the instructions encoded by the embedded IEC as long as power (*i.e.* direct current from a battery) is supplied.

The main advantage of this method is the self-regulating capability built upon internal feed-back and feed-forward loops. Although the normally closed elastomeric valve structures itself is not new,[7,23,26] this is one of the few, if not the first, demonstration of using such components for self-switching of outlet flow between different solutions. A challenge of this approach is that, similar to analog electronic circuits, operation can fluctuate with changes in fluid flow. For applications that do not require precise timing and simple circuits with few actuation sequences, sufficient flow control can be induced simply by using hand-held clamps.[25] However, the repeatability of this flow method is not sufficient for more complex circuits that require higher stability. Therefore, additional regulatory components such as passive flow rate regulators must be embedded into the circuit to ensure that a constant flow rate is being infused into the system.[21,27] Also, despite the use of fewer components, design of analog circuits and prediction of their behavior are known to be more challenging than digital circuits.

Next-generation design principles

Design of the next generation of IMCs will benefit from understanding the advantages and disadvantages that each microfluidic control approach can provide given its current state of technology as well as what they may be able to provide in the future (Fig. 1B). For any particular application, the key is to prioritize the needed capability, cost, and portability of the device. Currently, microfluidic parallel instruction devices (Approach 1) still remain the most characterized and well developed microfluidic control systems. Parallel instruction is also faster than serial instruction. As the required instructional complexity increases, however, these devices have the drawback of high cost, low portability, and difficulty to control interface standardization. They also have little self-regulation and feedback control capability.

Although these caveats of Approach 1 are expected to improve over time,[28] the newer approaches (Approaches 2 and 3) described in this mini-review will also become more important.[29] Such transitions are seen in microelectronics where the use of parallel ports has given way to serial ports, particularly universal serial bus (USB) ports. The main advantage of serial instruction for microelectronics is that it provides the ability to convey arbitrarily complex instructions from various input devices (*e.g.* keyboard, microphone, *etc.*) as well as between devices using a small, limited number of control lines; parallel ports require an increasing number of lines and connector pins as the complexity of information increases. Therefore serial ports allow a connector of a specific physical geometry to interface with any device, while parallel ports must be specifically designed so that two devices can properly interface. Similarly, for microfluidic systems, as the complexity of the devices increases and the need for device standardization increases, serial device instruction may become more attractive.

One must remember, however, that serially or temporally encoded instructions require a decoder circuit on the microfluidic device, resulting in an increased fluidic circuit complexity. Thus, integrated microfluidic device fabrication capabilities must advance and the associated costs decrease before such concepts become practical.

Similar fabrication limitations exist for the embedded-instruction fluidic circuits as well.[30] Regardless, the potential power of this approach is that complex, timed operations can be preprogrammed to run so the user only needs to plug in the device for it to operate. Furthermore, this type of device naturally allows for real-time, on-chip automatic adjustments and feedback control. Devices are thus envisioned that can modulate assay operations appropriately based on, for example, sample state or reagent feed rates. In addition, exploration into the effects of different material properties will be needed in order to accommodate other applications. Material properties such as stiffness have a direct effect on how the fluid media pressurize and depressurize in the channel features and valve components. PDMS is a convenient material to test these conditions since stiffness can be regulated by varying the mixing ratio of its two components (oligomer base and curing agent). However, PDMS absorbs water and small hydrophobic molecules which can be problematic for devices that need long incubation times.[31] In addition, the relatively high permeability of PDMS to gasses can be a disadvantage for applications requiring controlled micro-environments or long-term latching mechanisms.[7] These facts motivate the need to investigate other materials as either substitutes or hybrids for these devices.

Although there are many applications that could function with a control system designed based on just one of these approaches (parallel, serial, or embedded), the most effective and advantageous strategy for next-generation IMCs may be to exploit a combination of these control approaches. Such is the case in complex microelectronic devices (*e.g.*, computers) where parallel, serial, and fully embedded modes of control co-exist. Microfluidic devices constructed with such a mixture of components will then have the ability to automatically run pre-determined assays combined with the flexibility of user input to customize the procedure. Of course there are obstacles to integrating multiple approaches. Currently the actuation signals vary between approaches in using compressed gas,[6] vacuum,[15] mechanical actuators,[1,32] constant pressure liquid flow,[16] or constant flow rate liquid flow.[25] Clever ways to convert between different types of signals or the standardization to one or few of the actuation signal types may be necessary.

Finally, it is not the device architecture that matters to the end-user but rather the applications it enables. Biologists, chemists, clinicians, environmental scientists, and any other potential end-users are invited to explore opportunities and challenge the operational limits of IMCs. If we observe the development of microelectronics, perhaps it will be when children start playing with microfluidic games that we will know that the next generation of IMCs has fully developed.[33]

Acknowledgements

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