Programmable Fluidic Networks on Centrifugal Microfluidic Discs

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ABSTRACT

Background:

Biomedical diagnostic and lab automation solutions built on the Lab-on-a-Disc (LoaD) platform has great potential due to their independence from specialized micro-pumps and their ease of integration, through direct pipetting, with manual or automated workflows. However, a challenge for all microfluidic chips is their cost of manufacture when each microfluidic disc must be customized for a specific application. In this paper, we present centrifugal discs with programmable fluidic networks.

Results:

Based on dissolvable film valves, we present two technologies. The first, based on recently introduced pulse-actuated dissolvable film valves, is a centrifugal disc which, depending on how it is loaded, is configured to perform either six sequential reagent releases through one reaction chamber or three sequential reagent releases through two reaction chambers. In the second approach, we use the previously introduced electronic Lab-on-a-Disc (eLoaD) wireless valve array, which can actuate up to 128 centrifugo-pneumatic dissolvable film valves in a pre-defined sequence. In this approach we present a disc which can deliver any one of 8 reagent washes to any one of four reaction chambers. We use identical discs to demonstrate the first four sequential washes through two reaction chambers and then two sequential washes through four reaction chambers.

Significance:

These programmable fluidic networks have the potential to allow a single disc architecture to be applied to multiple different assay types and so can offer a lower-cost and more integrated alternative to the standard combination of micro-titre plate and liquid handling robot. Indeed, it may even be possible to conduct multiple different assays concurrently. This can have the effect of reducing manufacturing costs and streamlining supply-chains and so results in a more accessible diagnostic platform.

1. Introduction

The Lab-on-a-Disc (LoaD) [1–10] offers great potential for point-of-care and point-of-use lab-on-a-chip applications. Some of the key application areas include biomedical diagnostics [1] and environmental

monitoring [11]. A significant advantage of the LoaD platform is the ability to perform complex sample preparation steps in an automated fashion, including blood processing [12,13] and solid phase purification of nucleic acids [14–17]. The LoaD platform sits at the interface between low-cost, highly manufacturable and widely used microfluidic diagnostic tests which have little sample preparation requirements, such as lateral flow tests for pregnancy or COVID-19 [18], and specialised and complex diagnostic tests best conducted using liquid handling robotics and specialised instrumentation in centralised facilities.

A key reason for the LoaD's potential is excellent 'world-to-chip' interfacing [16]. The LoaD does not require specialised micro-pumps to operate, nor does it need to be connected to a pressure source (pump) to operate. It does not require bleeding of trapped air prior to operation or any special liquid loading protocols. In many cases, once loaded with sample and/or reagents (most often through direct manual pipetting), the discs can often be fully sealed from the atmosphere prior to operation and can remain sealed during disposal. This can protect on-disc samples from contamination from the surrounding environment. It can also protect the surrounding environment/laboratory from contamination by samples, particularly critical for highly sensitive nucleic acid amplification-based assays (e.g., PCR, LAMP, RPA). Ease of sample loading also permits integration of automated robotics system with centrifugal microfluidic [19].

The increasing availability of low-cost micro-controllers and electronics, primarily driven by the smartphone, has made combining the Lab-on-a-Disc with co-rotating electronics feasible. While these platforms, broadly called Electronic Lab-on-a-Disc (eLoaD) [20], can use electrical slip rings [21], they typically use wireless power transfer and wireless communication protocols such as Bluetooth or WiFi. A key advantage of this approach is it enables easier measurement from the disc, as sensors can co-rotate with the microfluidic disc. Applications of providing power and communication to the disc have included electrochemical measurements [21–23], chemiluminescence [24], colorimetric measurements [25], centripetal pumping [26,27], nucleic acid amplification [28,29], and flow control [12,30].

As centrifugation applies pressure to all liquids on the LoaD, reliable valving technology is critical to automating laboratory assays. Passive valves such as capillary valves [31] are opened by stepped increases in disc spin-rate, while siphon valves [32] are opened by decreases in disc spin-rate. Due to limitations of passive valves, mainly driven by a limit in the number of valves which can be accurately controlled in a defined sequence (and so placing a limit on the number of laboratory operations which can be automated), active valves, which use additional instrumentation to interact with the disc to open or close a valve, have been of increased recent interest [33]. The integration of dissolvable films (DF) into the LoaD [34], and particularly the development of DF-enabled pneumatic networks called event-triggered valves [17], has allowed increased complexity of on-disc liquid flow control using motor-only control. Conventional DF valves have been applied to colorimetric measurements [35] and cancer diagnostics [36,37] while even-triggered valves have been applied to epilepsy [38], immunoassays [39–41], white blood cell isolation [42], serial dilutions [43] and solid phase purification of nucleic acids [16,17,44]. Furthermore, liquid-specific dissolvable films (i.e. dissolving in oil rather than water) have also been used to automate assays [45]. In an active valving approach, DF valves have also been

integrated with the eLoaD concept [12], allowing up to 64 valves be wirelessly opened on demand. Recently, Mishra et al. [46] introduced a new type of DF valve called 'digital pulse actuated' (PA-DF) valves. Here, the event-triggered network is combined with DFs in recessed gas pockets such that the architecture of the disc defines the sequence valves open while short, pulsed increases in disc spin-rate control the timing of valve actuation.

Programmable fluid networks have been presented by the microfluidics community in several different forms. Lutz et al. [47] demonstrated the use of programmable elements in paper microfluidics to vary the timing of an assay. Zhakypov [48] create programmable fluidic networks by using a robot to fold an origami structure into different configurations. Tsuda et al. [49] demonstrated a plug-and-play approach using 3D printed components while Zucchelli et al. [50] have described on-demand creation of networks of connecting microchannels using laser ablation in centrifugal microfluidics.

This work presents two approaches to creating a programmable fluidic network on a LoaD. These programmable networks, which leveraging pre-existing valve platforms, represent the key novelty of this work. We demonstrate how the behaviour of a disc can be programmed using control software (software defined network using the eLoaD) and then how a disc can be programmed using the sequence and loading of reagents on-disc (reagent defined network).

While Zucchelli et al. [50] implement programmable networks on the LoaD, their system, based on laser ablation, would not be suitable for applications at point-of-care or point-of-use. The eLoaD implementation presented here is designed as a low-cost instrument solution for use in resource limited settings while the reagent-defined system needs just a low-cost spindle motor to operate.

Firstly, we build on the previously introduced LoaD-controlled Parafilm™ valve platform [12] to present a system which can be defined using software control (wirelessly over Bluetooth ™ or similar). This expands the capability of the eLoaD valving technology and, as far as we are aware, introduces an entirely novel approach to defining disc architectures. In our second approach, we combine our recently introduced pulse-actuated DF valves [46] in a novel fashion with AND and OR conditional actuation to define disc architectures based on order in which reagents are loaded on-disc.

For the eLoaD-controlled platform , the disc is aligned with an array of co-rotating microheaters. These microheaters can melt a Parafilm™ (wax) seal, which triggers the release of liquid through a dissolvable film. In this disc, we have 8 reagent chambers (numbered 1-8) and four reaction chambers(labelled A-D). Between each reagent chamber is four valves and, by opening one of these valves, the liquid can be routed to the appropriate reaction chamber. Thus, by opening the valves in a defined sequence, any combination of reagents can be routed to any combination of valves. To demonstrate this functionality, we first configure the disc such that Reagents 1-4 are routed to Chamber A and Reagents 5-8 are routed to Chamber B. Then, using an identical disc, we configure the system such that Regents 1-2 are routed to Chamber C, Reagents 3-4 to Chamber B, Reagents 5-6 to Chamber A, and Reagents 7-8 to Chamber D (Figure 1 and Figure 2).

Our architecture based on pulse-actuated DF valves [46] leverages the ability of these DF-based vales to implement AND and OR conditional actuation. This provides a system which is controlled by reagents loaded on disc. The disc has seven reagent chambers. Loading chambers 1-6 results in a sequential release, with each pulse in spin-rate, of reagents in chambers 1-6. However, loading chambers 1-3 and 5-7 , on an identical disc, results in parallel release of reagent from chambers 1 and 7 on the first pulse, chambers 2 and 6 on the second pulse, and chambers 3 and 5 on the third pulse (Figure 3 and Figure 4). Thus, it is possible to complete two different sets of liquid handling operations using the same disc architecture.

In this paper, we describe the design and architecture of these programmable fluidic networks and, as a first step, demonstrate their functionality using dyed water. We then discuss their potential, with further advancement, to provide a flexible complimentary technology to the microplate where the ability to program a microfluidic chip to be compatible with a wide range of assays can allow the discs to be mass manufactured at a low-cost. The architectures presented here represent a first step towards flexible fluidic networks which, with further refinement, may be suitable for applications across a wide range of different bio-assays.

2. Materials and Methods

2.1 Disc Manufacture and Assembly

The microfluidic discs used in this study were assembled from either eight or twelve layers of material, depending on if they used PA-DF or eLoaD actuated DF valves, respectively. As previously described by Kinahan et al. [17], for PA-DF valves, these layers were four layers of 0.086 mm pressure sensitive adhesive (PSA) (Adhesives Research, Limerick, Ireland) and four layers of poly(methyl methacrylate) (PMMA). The PMMA layers were laser cut (Epilog Zing, USA) to generate air-vents, reservoirs for liquids, and connecting holes vertically through the disc while microchannels were created in the PSA using a knife cutter (Graphtec, Yokohama, Japan). Briefly and listed from the top, Layer 1 (0.5 mm PMMA) contains loading and air vents. Layer 2 (PSA) contains upper-level microchannels for liquid movement and pneumatic venting, Layer 3 (1.5 mm PMMA) primarily defined large reservoirs for liquid, Layer 4 (PSA) and Layer 5 (PSA) were layers to sandwich and support DF tabs, Layer 6 (0.5 mm PMMA) contained through-holes and Layer 7 (PSA) contained microchannels for liquid movement and pneumatic venting. Finally, Layer 8 (PMMA 0.5mm) was the sealing layer on the underside of the disc.

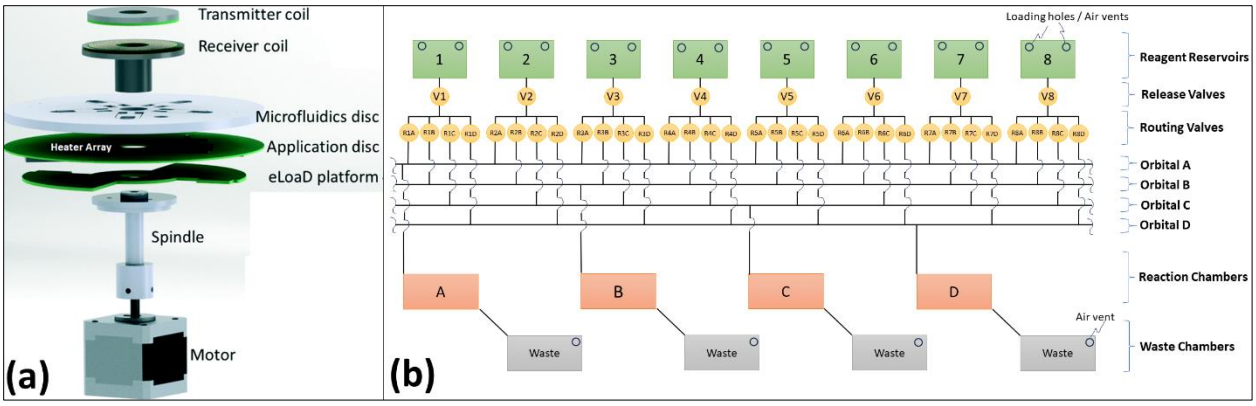

Figure 1: Configuration of the wireless eLoaD platform (Reproduced from Ref. [24] with permission from the Royal Society of Chemistry) (b) schematic of the fluidic network enabled by the eLoaD platform

For the eLoaD actuated DF valves, a similar architecture was used, which was adapted from that presented by Delgado et al. [12]. The first seven layers of this disc have a similar configuration to that described above; however, for the eLoaD actuated valves, Layer 8 (0.5 mm PMMA) contains through-holes which can act as pneumatic venting holes. Layer 9 (PSA) and Layer 11 (PSA), and Layer 12 (0.5 mm PMMA) mirrored the heater elements on the eLoaD application disc while Layer 10 (Parafilm™) is a single layer of wax Parafilm™ which seals the valves on the disc.

2.2 Test Stand and eLoaD

The discs used in this study were imaged using a test-stand which is previously described **[12]**. Briefly, a spindle motor (Festo EMME-AS-55-M-LS-TS, Esslingen, Germany) is synchronised with a sensitive, short-exposure time camera (Basler Ace 2040-90uc, Basler, Germany) and a stroboscopic light source (Drelloscop 3244, Drello, Germany) using a trigger output signal from the motor. A series of still images are acquired at 5 Hz and, due to synchronisation, it can appear the disc is stationary. These images are later used to create videos provided in ESI. This system is controlled using a custom LabVIEW program.

The eLoaD [12,20,24,25,27] comprises an Arduino compatible microcontroller and a wireless power receiver. The receiver is part of the 5W-series of Qi Standard for wireless power transfer. Power transmission is from a standard wireless phone charger amounted above the disc as previously described [12,24]. The 'application disc', fitted to the eLoaD, is a 120 mm diameter PCB board with 128 micro-heaters, and, as previously described, each of these heaters can be individually activated remotely using Bluetooth control via custom software [12].

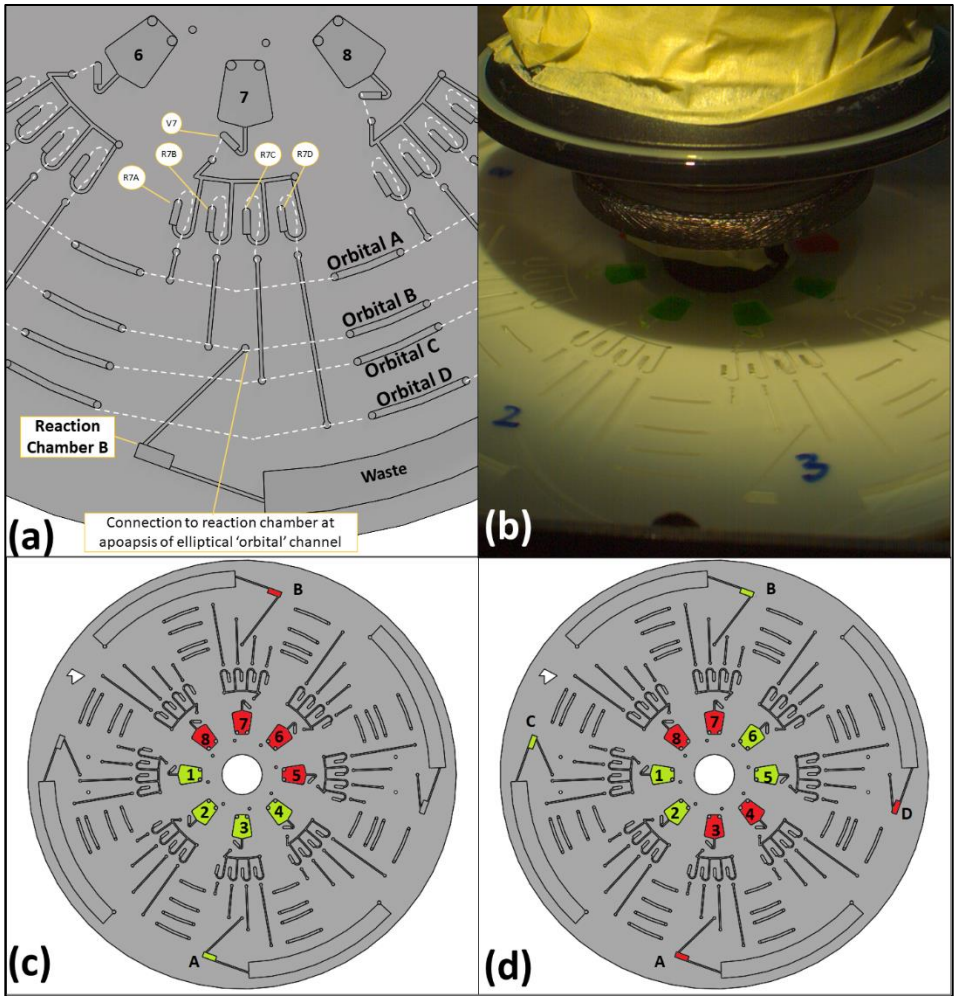

Figure 2: The operation of the programmable fluidic networks using the eLoaD system. (a) shows a detail of one of the reservoirs on the Lab-on-a-Disc. Each reservoir is closed with a DF valve which can be activated by a heater on the eLoaD. After this valve, the fluid is connected via four valves to four 'orbital' channels, which extend around the entire disc. These orbitals are connected at their periapsis to a reaction chamber (b) shows the disc mounted on the eLoaD system with power transmission from above via a commercial phone charger (c-d) show schematics of the entire discs (c) is configured to wash two reaction chambers with four reagents (d) is configured to wash four reaction chambers with two reagents each (see ESI Movie 1, 1a, 2and 2a)

When testing the Pulse-Actuated programmable networks, the discs are fitted directly to the spindle motor, and the camera is in a top-down orientation. However, for testing with the ferro-wax controlled valves, the discs are alighted with the eLoaD application disc using alignment pins and then placed on the spindle motor. The transmitter is then placed above the discs. Due to the positioning of the transmitter, the camera and the strobe are oriented at an angle to image as much of the disc as possible.

3. Operation of Programmable Networks

Programmable Fluidic Network using eLoaD

The programmable fluidic network using the eLoaD consists of 8 reservoirs located at the centre of the disc, which can be connected in any combination to four reaction chambers located radially outwards (Figure 1 and Figure 2). Each reservoir is sealed by a corresponding valve (i.e. V1 through V8) which can

be actuated by the eLoaD system and is used for reagent release (reagent valve). Past this valve, the channel splits into four and each of these channels is sealed by valves which are used for routing (routing valve) (in the case of Reservoir 1, referred to as R1A, R1B, R1C and R1D). Each of these valves is, in turn, connected to an elliptical channel, which is connected all around the disc, which we refer to as an orbital channel. R1A, along with R2A through R8A, are all connected to Orbital A. Orbitals B-D are all connected in a similar manner. At the radially outwards location of these orbitals (i.e. the periapsis), there is a reaction to the corresponding reaction chamber and waste chamber. The connection at the periapsis ensures that the reservoirs empty through the reaction chamber in an efficient manner.

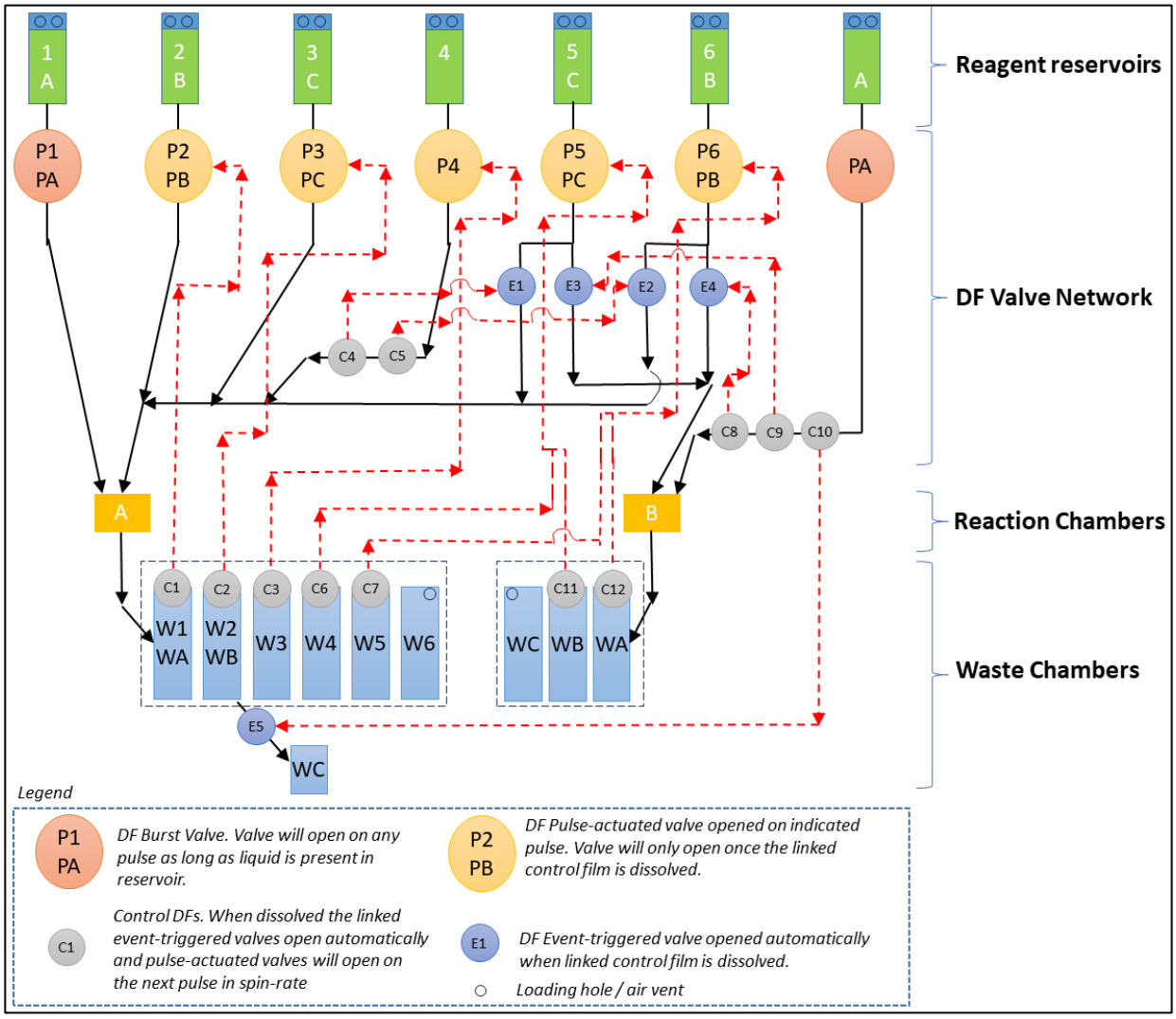

Figure 3: Schematic of the fluidic network which enabling the rotational controlled disc

To operate the disc in the configuration shown in Figure 2c (see also ESI Movie 1), the disc is mounted on the eLoaD system, and the chambers are loaded. Next, the Parafilm™ wax sealing valves R1A, R2A, R3A and R4A are melted using the corresponding heaters on the eLoaD. R5B, R6B, R7B and R8B are also opened. With this configuration in place, opening V1 will release the liquid in Reservoir 1 to flow into and through valve R1A and on into Reaction Chamber A. Reservoirs 2-4 can, in turn, be opened on-demand (i.e. programmatically or using a UI) and will all be routed to Chamber A. Reservoirs 5-7 can also be opened on-demand and routed through Reaction Chamber B.

For the configuration shown in Figure 2d (see also ESI Movie 2), where four reaction chambers are washed with two reagents each, the routing valves R1B, R2B, R3A, R4A, R5C, R6C, R7D and R8D are used to program the fluidic network. From here, as each valve is actuated, the liquid is directed through the correct routing chamber. Note that in ESI Movie 2, Valve 2 fails to open due to a manufacturing defect associated with the manual assembly of these discs. It should also be noted that this same liquid handling sequence can be managed by just the routing valves if the reagent valves were removed or pre-opened. However, we have conceptually divided the design into valves which define fluidic routing / disc architecture (routing valves) and those which define the assay release.

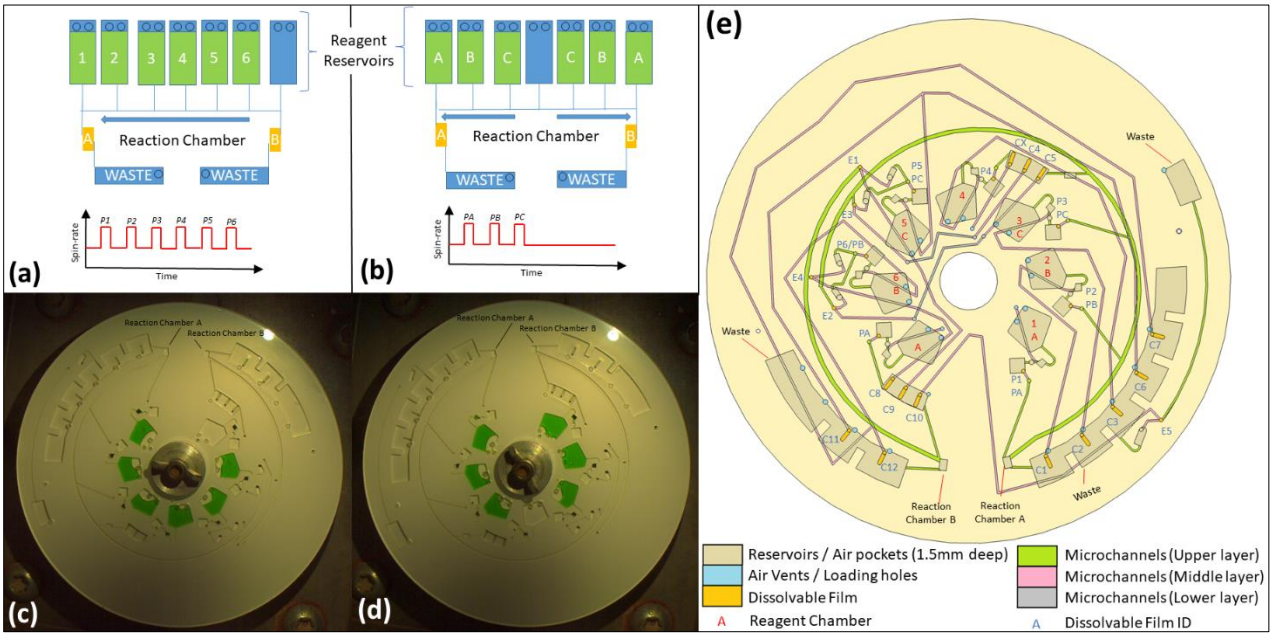

Figure 4: The operation of the programmable fluidic network using pulse actuated dissolvable film valves. Here, the way the disc is loaded determines the sequence of reagent release. These are (a) six regents through one reservoir and (b) three reagents through two reservoirs. In (a), chambers 1-6 are loaded and six digital pulses are used to wash the content of the six reservoirs through reaction chamber A, while (b) shows a configuration where chambers 1-3 and 5-7 are loaded. Here, three pulses will wash the contents of chambers 1-3 through reaction chamber A and the contents of chambers 7-5 (in that order) through reaction chamber B. Note in the 6x1 configuration, the pulses are P1-P6 while in the 3x2 configuration, we refer to the three pulses as PA, PB and PC respectively. (c) and (d) show the discs loaded to operate in the 6x1 and 3x2 configurations, respectively (see also ESI Movie 3, 3a, 4 and4a) (e) shows detail colour coded schematic of the fluidic network including intermediate and lower connecting channels not shown in other figures.

Programmable Fluidic Network using Pulse Actuated Valves

As described previously, DF-based event-triggered valves can be configured to enable AND and OR operations on-disc [17]. In an alternative approach to using the eLoaD, we have combined this principle with pulse actuated DF valves [46] to develop a disc which can be programmed based on how the reagents are loaded. Namely, as shown in Figures 3 and 4, an identical disc can be loaded to release reagents in a 6x1 configuration (six reagents through one reaction chamber) or 3x2, where three reagents are each released through two reaction chambers. In this description, we adapt the terminology used previously [46] to describe the pulse actuated valves and use four key terms which are highlighted in the legend shown in Figure 3.

- DF Burst valves are opened when the disc exceeds a design opening spin frequency. Here, the DF is recessed in an air pocket as previously described [34,36].
- DF Pulse-actuatedValves valves [46] are composed of two DFs. The Load film (LF) is the DF through which the liquid is released, while the control film (CF) vents part of the valve. For pulse actuated valves, when the CF is sealed, the vales will not open at any spin frequency within the design envelope of the disc (in our case, it will not open at any speed below 100 Hz). With the CF dissolved, the valve partially vents and so can be opened, in a manner like a burst valve, by exceeding a design spin-rate (in our case, 40 Hz). We refer to this as putting the valve in a 'ready' state. Opening the valves with a digital pulse (an acceleration to 50 Hz and then deceleration to 30 Hz) in a time shorter than it takes for the DFs to dissolve allows each valve to be opened in the designed order. The architecture of the disc determines the order the valves open, while the digital pulses in spin-rate determine the timing of valve actuation. In this work, we use OR relationships whereby a valve may have one Load Film (LF) and two or more control films (CFs). Dissolving just one of these CFs will put the valve in a ready state to open on the next pulse. In the following description, we refer to the Load Films (LFs) by the pulse in which they will open (e.g. P1, P2 etc).
- DF Event-triggered valves [17] are also composed of two DFs referred to as the Load Film (LF) and Control Film (CF). Here, the dissolving of the CF results in the automatic release of liquid through the LF.
- Control DFs (CFs) are the control films referred to which are part of DF Pulse-actuated valves and DF Event-triggered valves. Dissolving these films, by reagent washing over them or by reagent filling a waste chamber, is key to the operation of the pneumatic network.

The programmable network of the disc is described in Figure 3, where the path of liquid is shown in black solid lines while pneumatic venting channels are shown in red dashed lines. Consider first that reservoirs 1-6 are loaded and then released by pulses 1-6. The following sequence takes place:

- On Pulse 1 (P1), the liquid in Reservoir 1 is released and washes through Reaction Chamber A. It flows into waste chamber W1, filling it and dissolving control film C1. With C1 dissolved, valve P2 can open on the next pulse
- On Pulse 2 (P2), the liquid in Reservoir 2 is released and washes through Reaction Chamber A. It flows into waste chamber W1, and because this chamber is full, the liquid overflows and fills waste chamber W2 (i.e. AND criteria), where control film C2 is wetted and dissolves. With C2 dissolved, valve P3 can open on the next pulse.
- On Pulse 3 (P3), the liquid in Reservoir 3 is released and washes through Reaction Chamber A. Combined with the liquid released from Reservoir 1 and Reservoir 2, waste chambers 1, 2 and 3 now fill, and control film C3 is wetted and dissolves. With C3 dissolved, valve P4 can open on the next pulse.
- On Pulse 4 (P4), the liquid in Reservoir 4 is released. Before washing through reaction chamber A, it washes over control films C4 and C5. These open event-triggered valves E1 and E2. With these valves open, the contents of Reservoir 5 and Reservoir 6 will be routed to Reaction Chamber A on subsequent pulses in disc spin-rate. The liquid in Reservoir 4 continues through Reaction Chamber A and fills the waste chambers such that control film C6 is wetted and dissolves. With C6 dissolved, P5 can open on the next pulse. Note that P5 is controlled by an OR

297 relationship whereby dissolving C6 OR C11 will put P5 in a ready state. Note also that CX (not
298 shown in Figure 3 but shown in Figure 4) is also dissolved. This opens this chamber to
299 atmosphere. It is otherwise sealed to prevent reagents released on P1 or P2 backflowing to
300 incorrectly wet C4 or C5.
301 • On Pulse 5 (P6), the liquid in Reservoir 5 is released and is selectively routed (through E1, which
302 was opened in the previous step) to wash through Reaction Chamber A. C7 is now wetted to put
303 P6 in a ready state.
304 • On Pulse 6 (P6), Reservoir 6 is released and is selectively routed (through E2, which was opened
305 in the previous step) to wash through Reaction Chamber A and so completing the protocol.
306
307 In the alternative protocol, where Chamber 1-3 and Chambers 5-7 are loaded, the pulses are referred to
308 as Pulse A, Pulse B and Pulse C:
309
310 • On Pulse A (PA), the liquid is simultaneously released from Reservoir 1 and Reservoir 7 and
311 washes through Reaction Chamber A and Reaction Chamber B, respectively. As the liquid in
312 Reservoir 7 flows to Chamber B, it wets and dissolves control films C8, C9 and C10. C8 and C9
313 open valves E3 and E4, respectively, which will route the liquid in Chamber 6 and Chamber 5 to
314 be routed through Reaction Chamber B. Dissolving C10 opens valve E5. This acts as a failsafe by
315 opening an overflow chamber. This overflow chamber prevents liquid, which is washed through
316 Reaction Chamber A, from wetting control valves C6 or C7 (which would put valves in a ready
317 state in the wrong order). Control films C1 and C12 are wetted, which puts the valves on
318 Reservoir 2 and Reservoir 6 into a ready state.
319 • On Pulse B (PB), the liquid is released from Reservoir 2 and Reservoir 6 and these wash through
320 Reaction Chamber A and Reaction Chamber B, respectively. Control films C2 and C11 are
321 wetted, which puts the valves on Reservoir 3 and Reservoir 5 into a ready state.
322 • On Pulse C (PC), the liquid is released from Reservoir 3 and Reservoir 5 and these wash through
323 Reaction Chamber A and Reaction Chamber B, respectively, and so completing the protocol.
324
325 The operation of the discs in these programmed states is shown in ESI Movie 3 and ESI Movie 4,
326 respectively.
327
328 **4. Conclusions and Outlook**
329 One of the major challenges in the widespread adoption of point-of-care diagnostics tests is the cost of
330 manufacture. High-volume manufacture requires roll-to-roll, injection moulding, and automation (i.e.
331 pick and place etc.), which requires significant upfront capital investment. Minor changes to an assay
332 can require development of an entirely new tooling. In addition, these tooling changes can take
333 significant lead-time and optimisation and so may not be quickly available to address emerging
334 challenges such as the next global pandemic. While disc manufacture by injection moulding has bene
335 demonstrated [51], discs with embedded DFs have not yet been mass-manufactured. However, it is
336 clear that mass manufacture using injection moulding is possible by integrating automated pick-and-
337 place of DF tabs into the production process. Similarly, it is possible to manufacture DF enabled discs
338 using roll-to-roll by multi-lamination manufacture whereby a whole sheet (of relatively low-cost) DF
339 becomes a layer in the disc supported (and in parts shielded from reagents) by PSA.
340
341 Integration of wax membranes into injection moulded discs using pick-and-place, or a full disc sized
342 sheet of wax Parafilm™ in discs made using roll-to-roll, may also applications towards challenges in wet

reagent storage [45].

Here, we present preliminary work on developing a programmable Lab-on-a-Disc which can be reconfigured to address different liquid handling challenges. We demonstrate this using the low-cost eLaoD platform and using pulse-actuated valves, which only require a spindle motor to function. In this paper, we refer to 'reaction chambers' through which the liquid is washed. The next key step to developing this technology further will be the development of modular reaction chambers. Because the Lab-on-a-Disc does not need to be primed before use, an insert might easily be placed into the Lab-on-a-Disc. This insert might be a silica substrate to enable Solid phase DNA / RNA purification, or it might be an antibody-coated surface to enable an ELISA. The use of such modular inserts, combined with loading the appropriate reagents (which might also occur using modular inserts), would allow the same programmable architecture to be used across a wide range of assays (such as the aforementioned nucleic acid tests or ELISA tests), and so reducing the cost of manufacture. These different assays might be conducted in series (using outputs from one test to inform the second test), or concurrently on the same disc if enough chambers are available. It must be noted that this manuscript demonstrates programmable fluidic networks only the perspective of liquid handling (using dyed water). For next steps, we hope to demonstrate the capability of these platforms to automate two different assays through use of modular reaction chambers discussed above.

A challenge to commercial deployment of this platform is the reliability of (the relatively complex) microfluidic discs. In this work, the reliability of discs (which were manufacture using manual processes) was ~90% for reagent defined discs and ~70% for the discs which couple to the eLoaD. The difference is primarily due to the additional layers using parafilm for these valves. Automated manufacture would greatly improve reliability of this manufacturing. However, event minor design changes might have knock-on effects to disc reliability which in turn may take significant time to identify and engineer out of the system. Thus, the ability to provide a completely standard disc which can be programmed for multiple applications provides scope to greatly increase reliability. Indeed, there may even be potential to include error-correction architectures which compensate for manufacturing errors as they occur.

This technology has great potential in both point-of-care applications and in potential use in laboratory automation. In the first case, these flexible discs might be manufactured as a strategic reserve whereby, in the event of a global health emergency, they can be rapidly loaded with a modular reaction chamber, appropriate reagents, and deployed without the need to start from zero. In the event of a major global emergency, these will act as a stop-gap diagnostic test while cheaper and more specialised options are developed; in the event of a smaller-scale outbreak, their rapid availably might be key to preventing the development of a pandemic. In the case of laboratory automation, with further development, these discs might be integrated into liquid handling units and used as an alternative to micro-titre plates in centralised laboratories. A single-chip architecture which can be applied across a range of tests would greatly minimise cost and logistics while the inherent ability to centrifuge samples on-chip would be particularly useful for hospital labs working on blood samples. While the concept of flexible

programmable networks has great potential, it is also clear that application of a single architecture to a range of different assays will have significant challenges. These include potential regulatory issues along with challenges surrounding reagent storage and metering, surface treatments to suit specific assays, and the challenge of integrating different measurement techniques into a standardised platform. We hope that further research will address some of these challenges.

Furthermore, while a standardised flexible programmable network might address several different assays, no one network will be able to address the entire range of available biomedical diagnostic tests. Indeed, there will also be some assays, such as those requiring long incubations, which cannot be easily addressed by discs which are based on single-use normally closed valves such as the DFs which underpin this paper. From this perspective, there integration of other valve types into the flexible fluidic network, particularly (repeatably) openable / closable valves, leaves significant space for future innovation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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