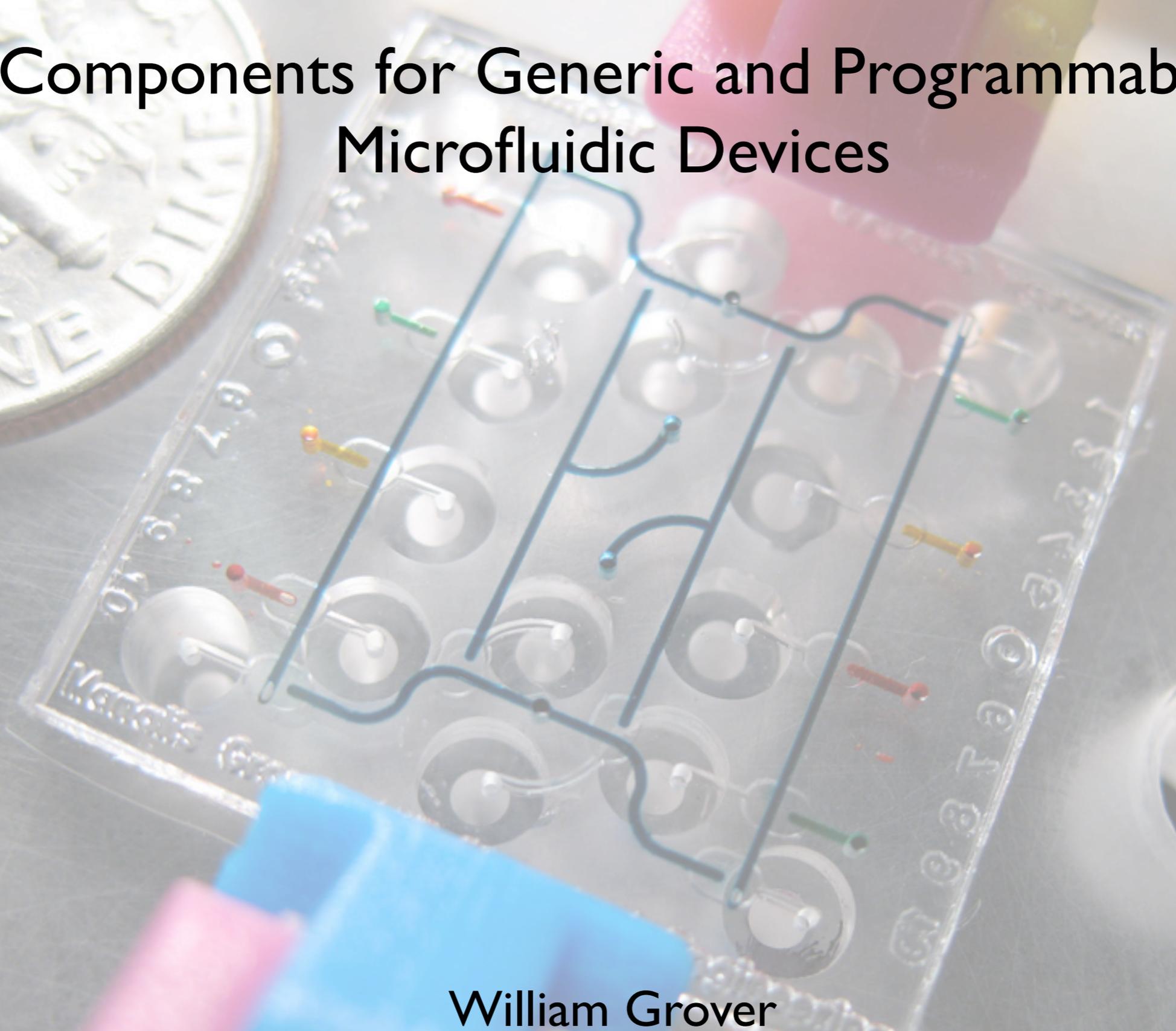


Components for Generic and Programmable Microfluidic Devices



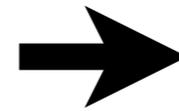
William Grover
Manalis Group, Biological Engineering Division
Massachusetts Institute of Technology

Lessons from the history of computing



Vannevar Bush and Differential Analyzer, MIT, 1931

- Single-purpose machines
- New application requires new machine
- No standard components

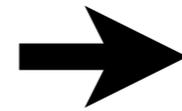


- **General**-purpose machines
- New application requires only a **new program**
- Made from **standard components**

Lessons from the history of computing



Vannevar Bush and Differential Analyzer, MIT, 1931



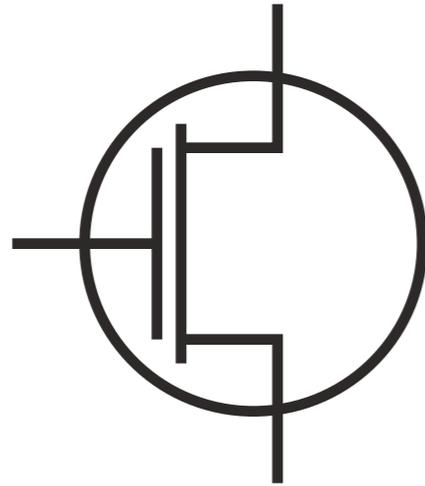
- Single-purpose machines
- New application requires new machine
- No standard components

- **General**-purpose machines
- New application requires only a **new program**
- Made from **standard components**

Standard toolkit of components (control, readout, etc.) that can be assembled into any useful circuit according to logical rules

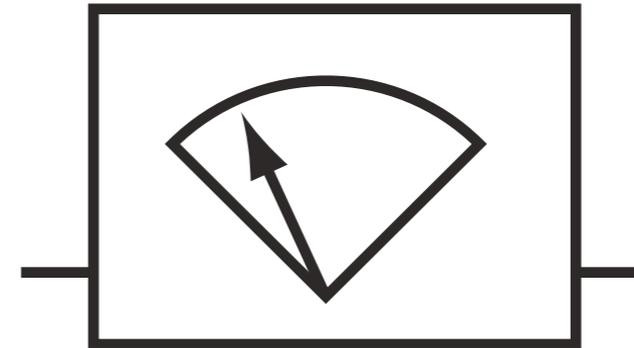
Processors that can run many different programs using the same generic hardware

Two components for microfluidic processors



Transistor

Valve-based pneumatic logic circuits
for device control and operation
(Mathies Group,
University of California, Berkeley)

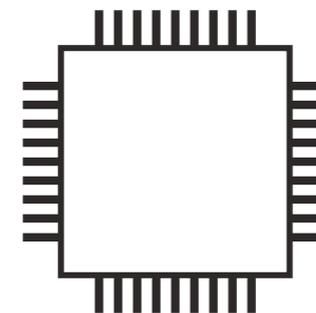


Readout

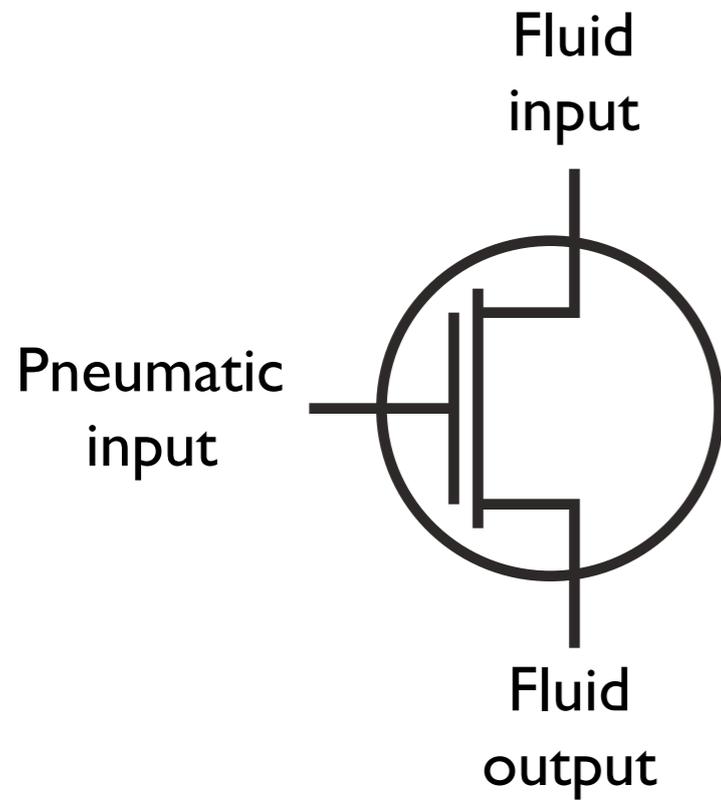
Suspended Microchannel Resonators
as generic mass/density sensors
(Manalis Group,
Massachusetts Institute of Technology)

Generic microfluidic processor

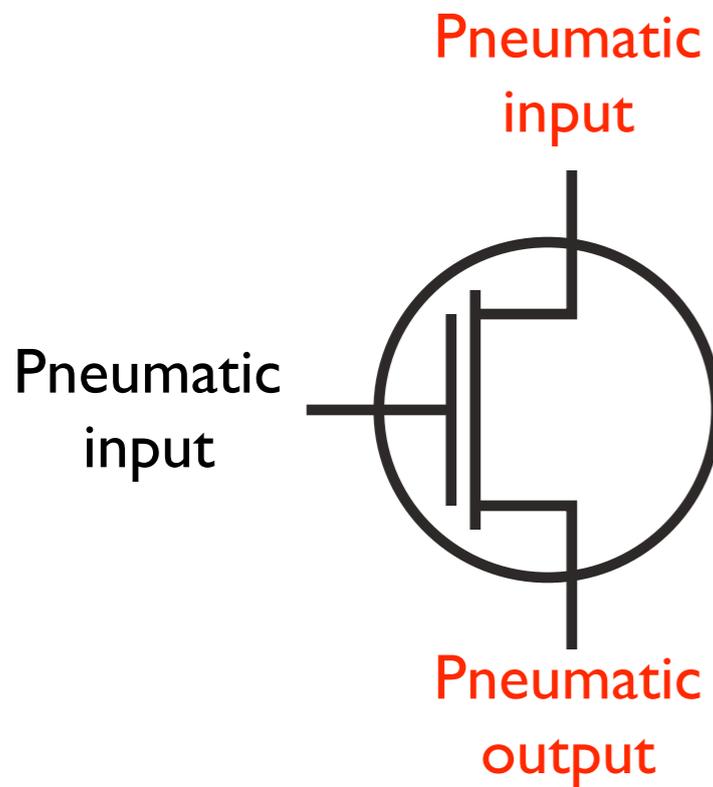
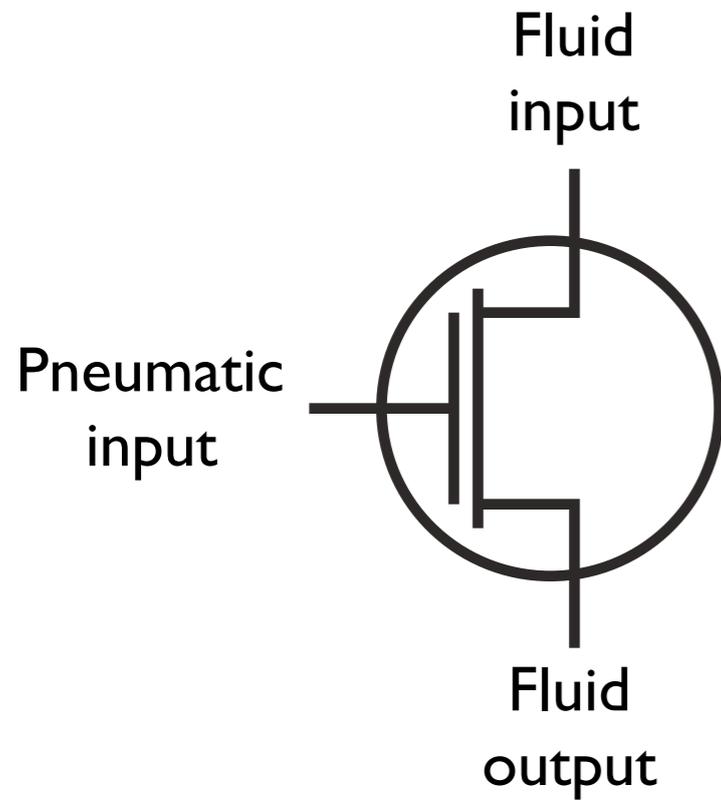
Autosampler chip
(Manalis Group)



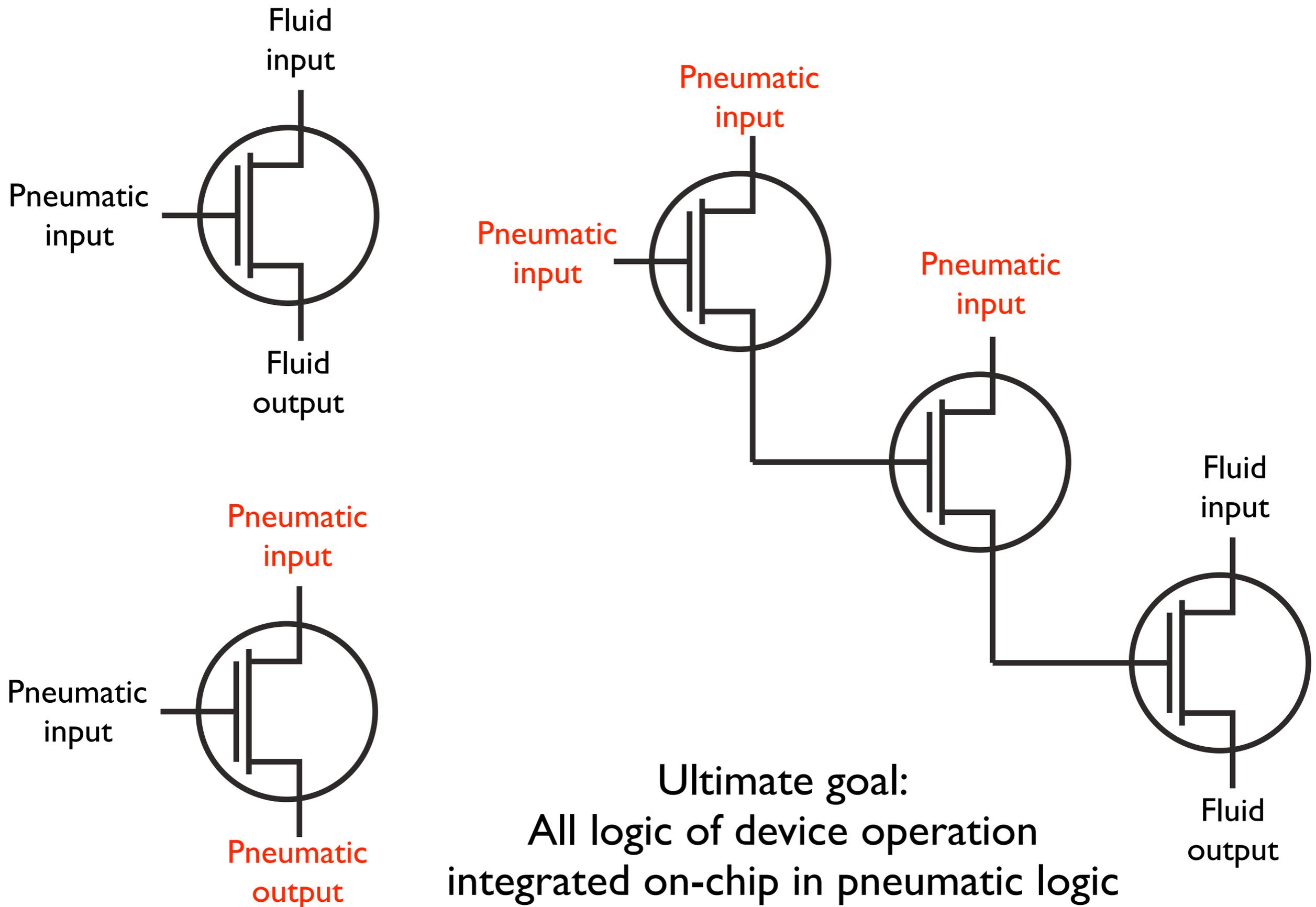
Valve-based pneumatic logic

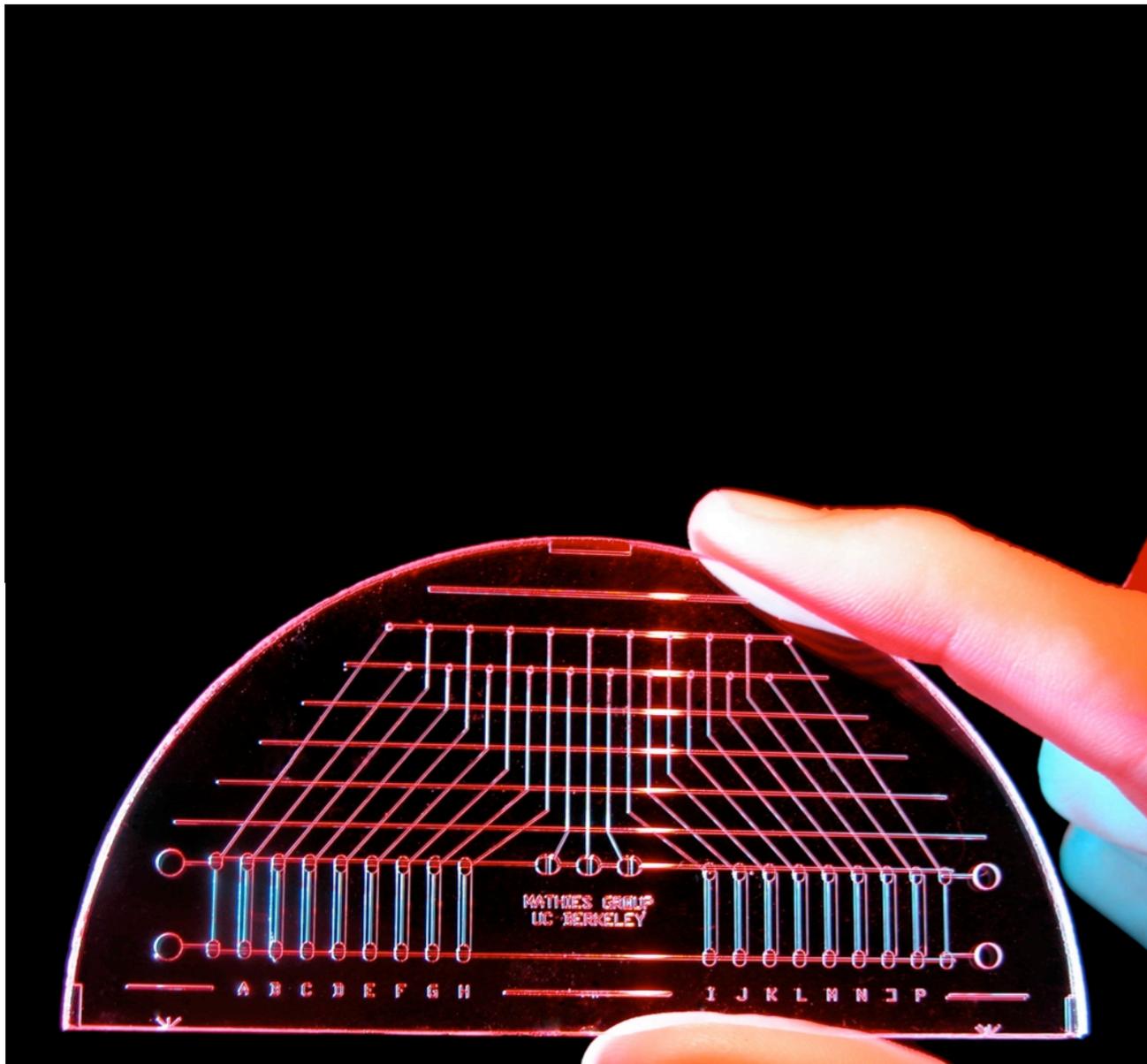


Valve-based pneumatic logic

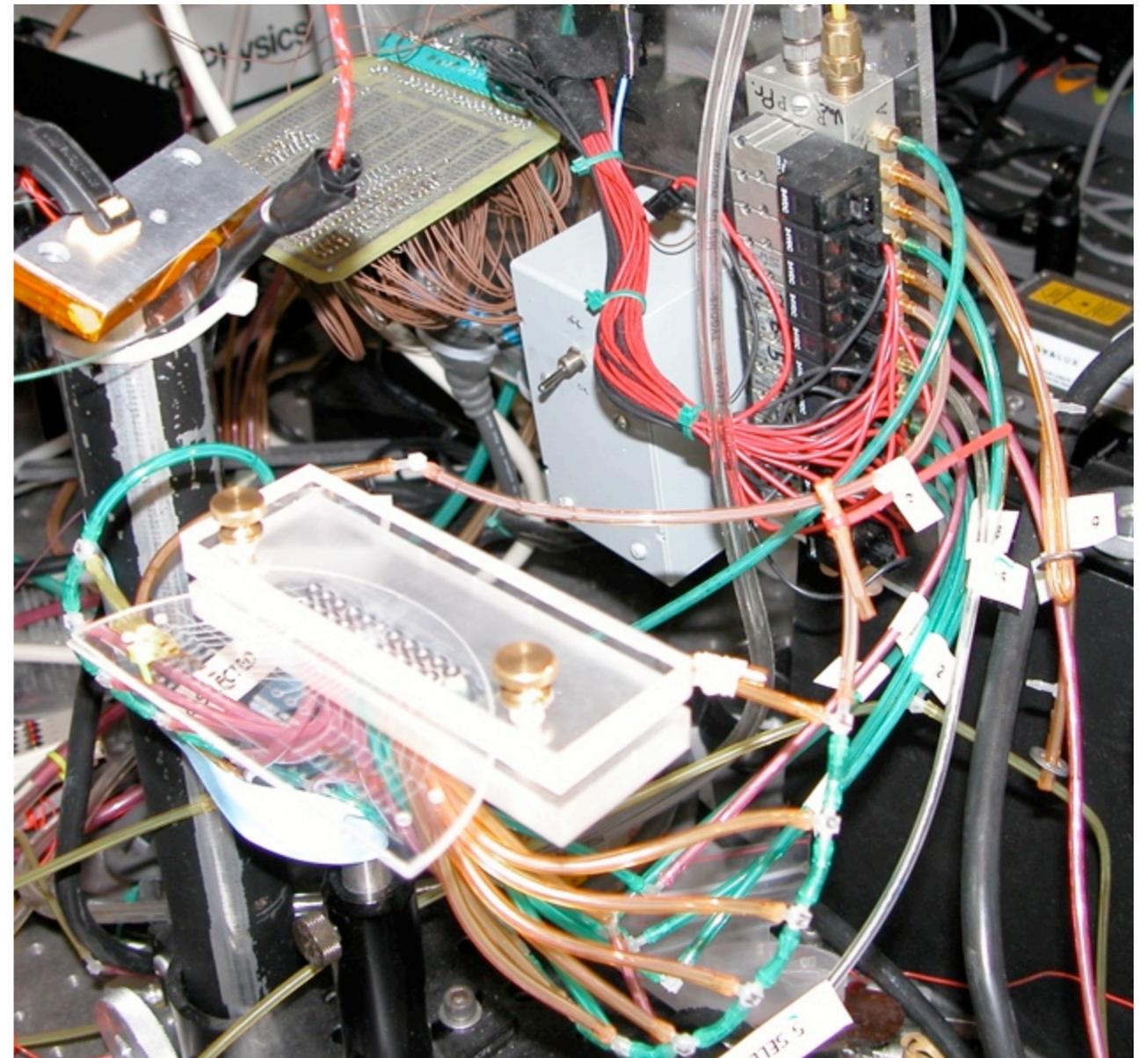


Valve-based pneumatic logic





The pretty picture

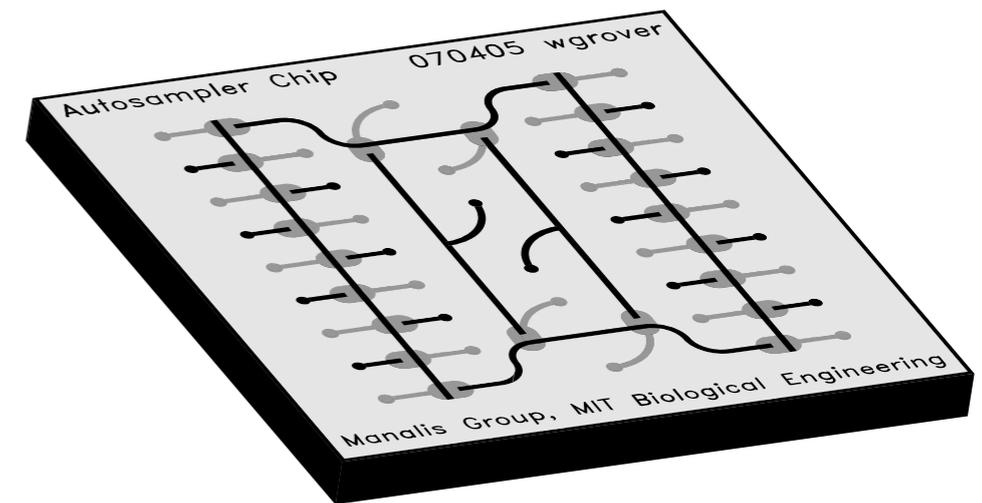
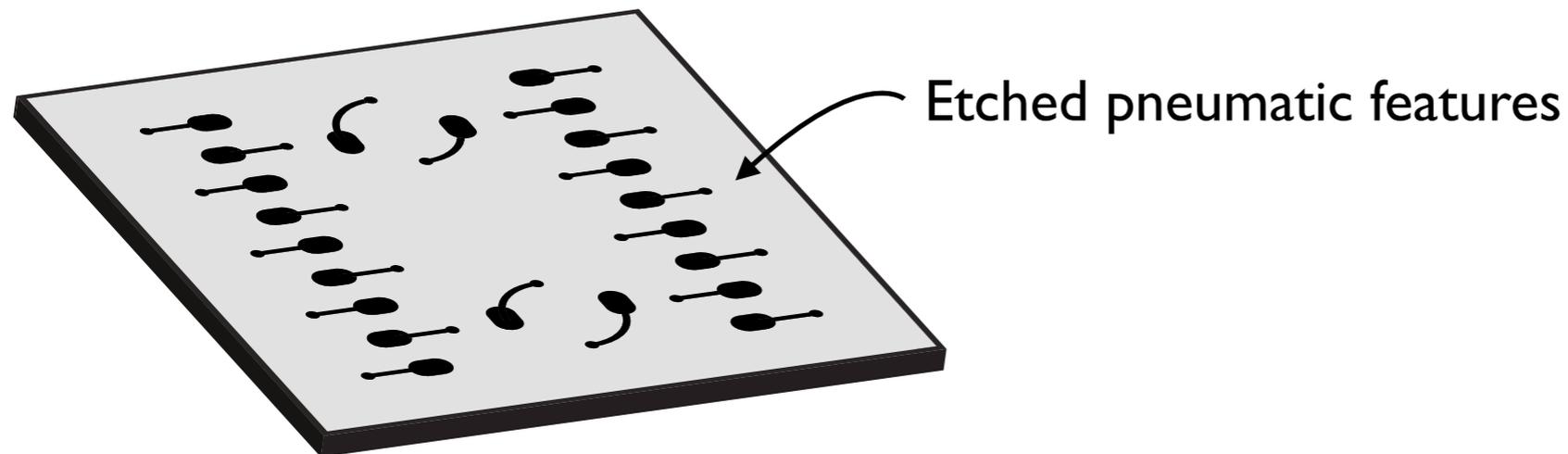
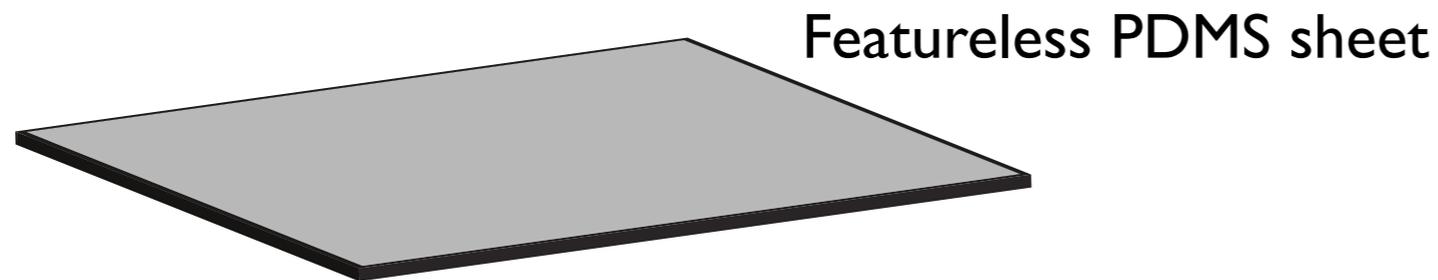
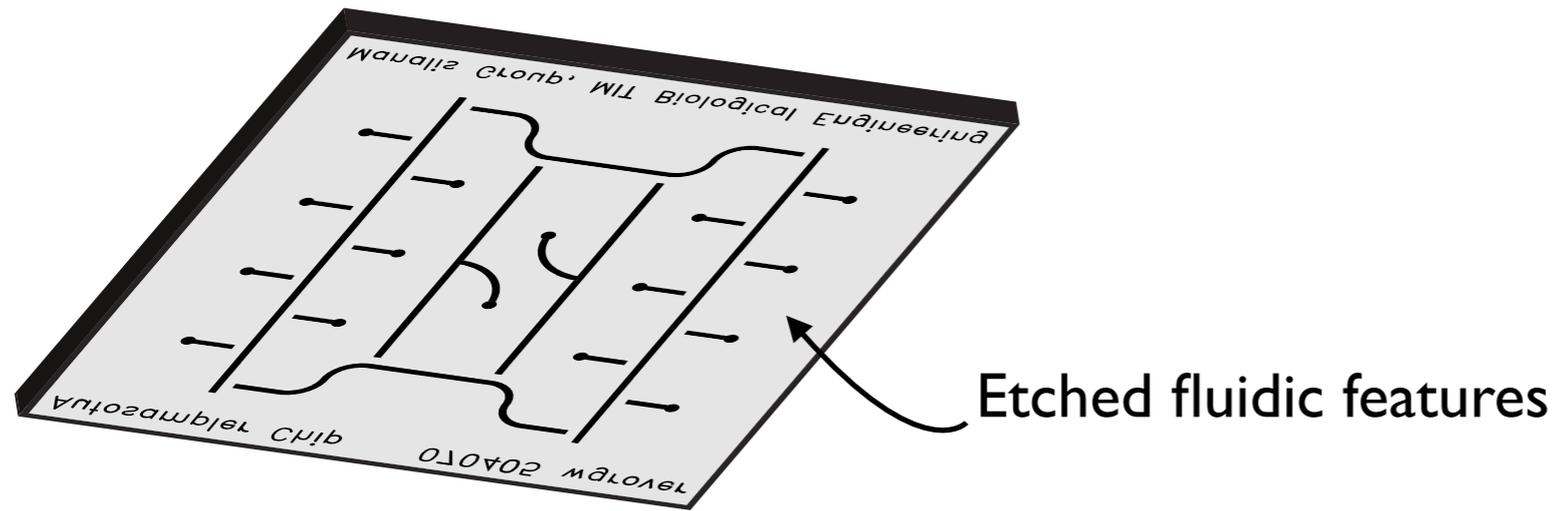


The reality

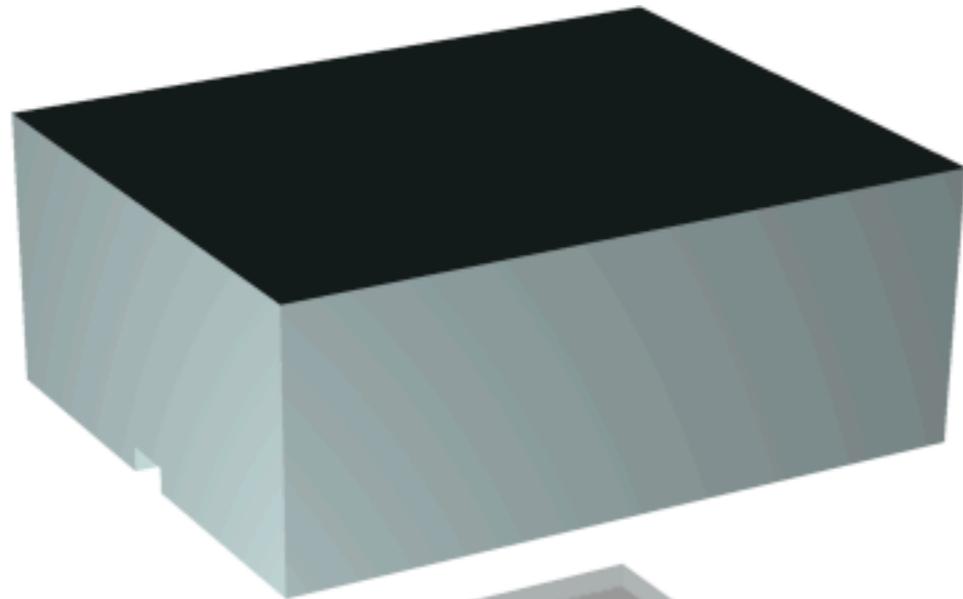
Off-chip controllers for on-chip pneumatic valves and pumps cost more \$ and consume more **power** and **space** than the chip itself.

The next thing to go on-chip is the **logic** of device operation

Monolithic membrane valves



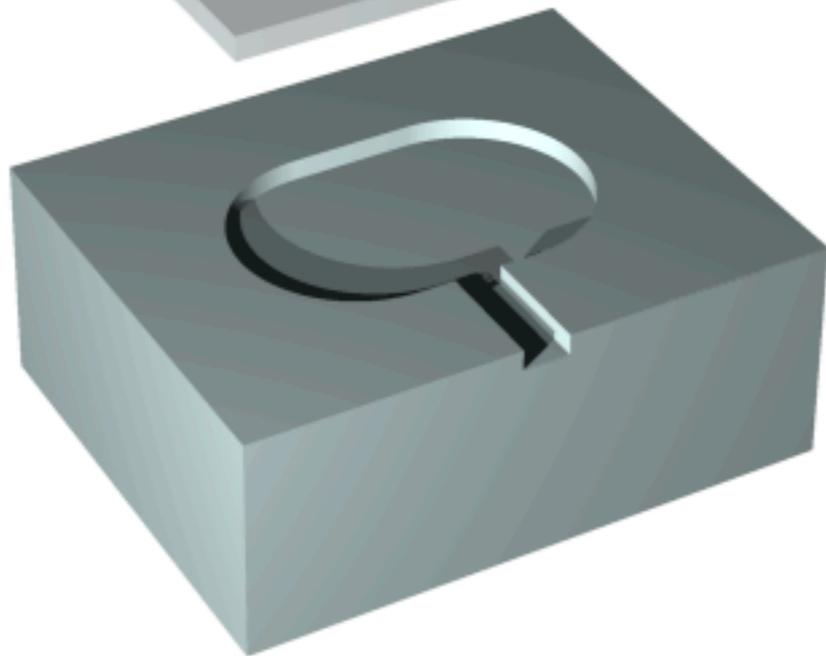
Monolithic membrane valves



Fluidic wafer
(etched discontinuity or valve seat)

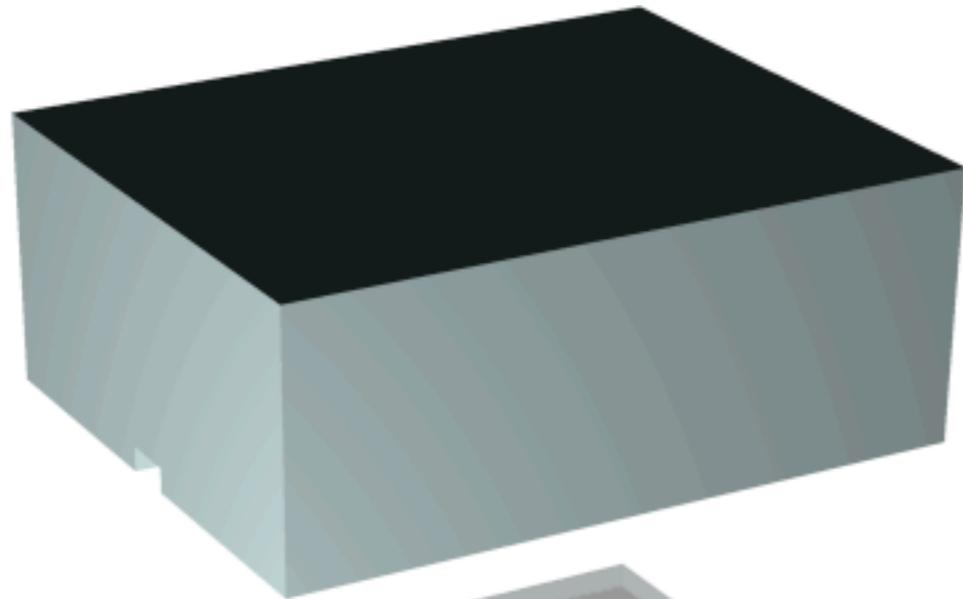


PDMS (polydimethylsiloxane) membrane



Pneumatic wafer
(etched displacement chamber)

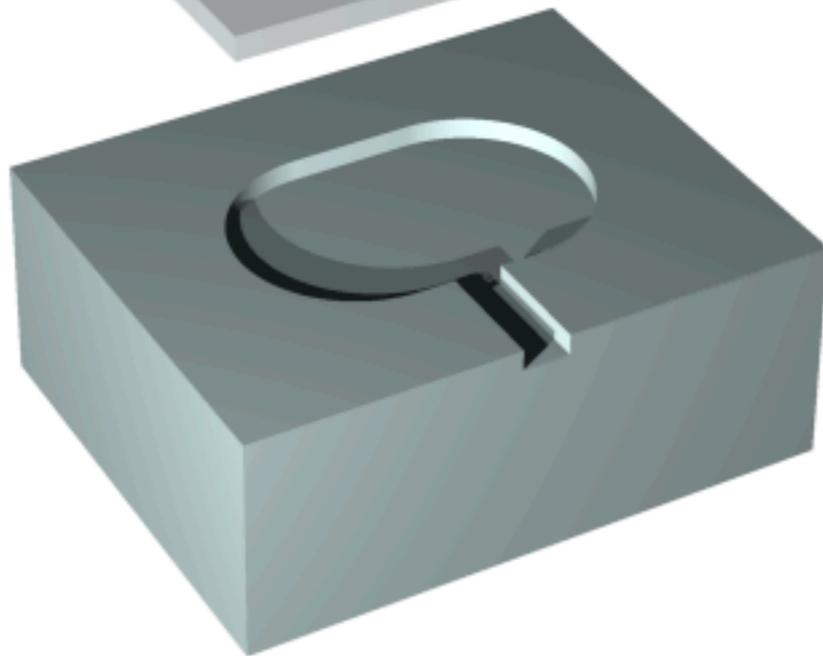
Monolithic membrane valves



Fluidic wafer
(etched discontinuity or valve seat)

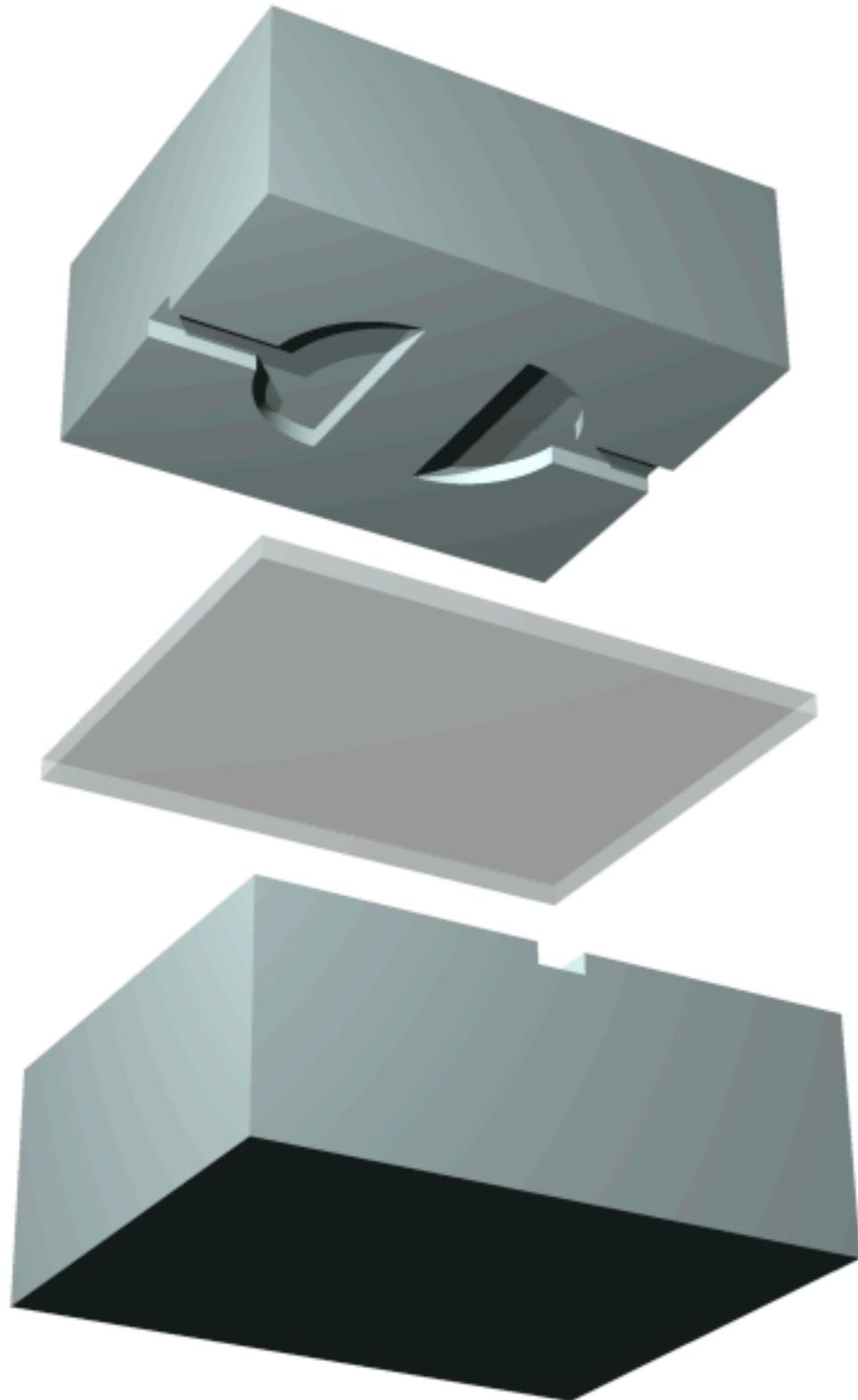


PDMS (polydimethylsiloxane) membrane

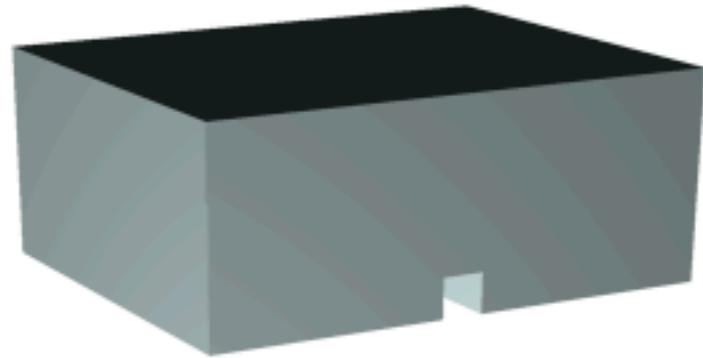


Pneumatic wafer
(etched displacement chamber)

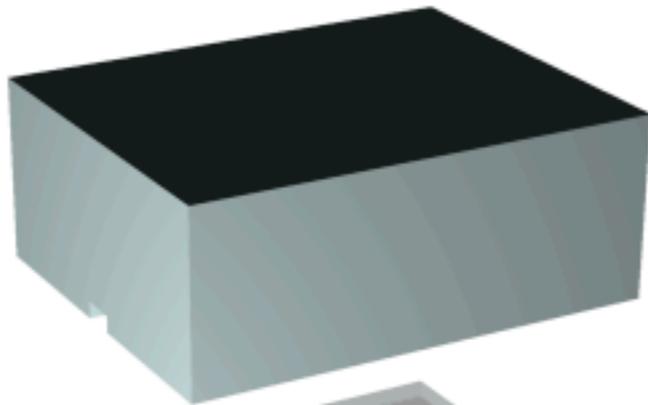
Monolithic membrane valves



4-layer monolithic membrane valves



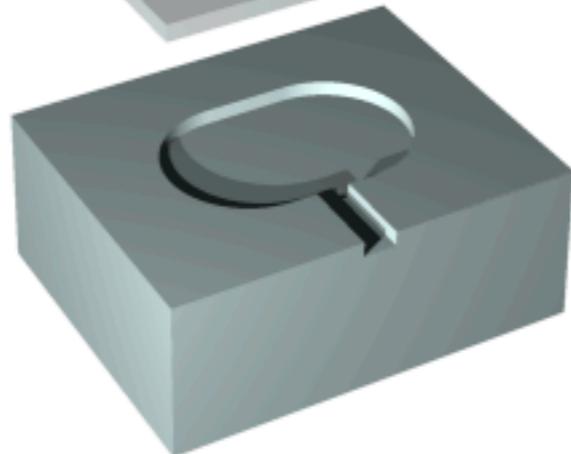
All-glass fluidic wafer



Hybrid glass-PDMS fluidic wafer

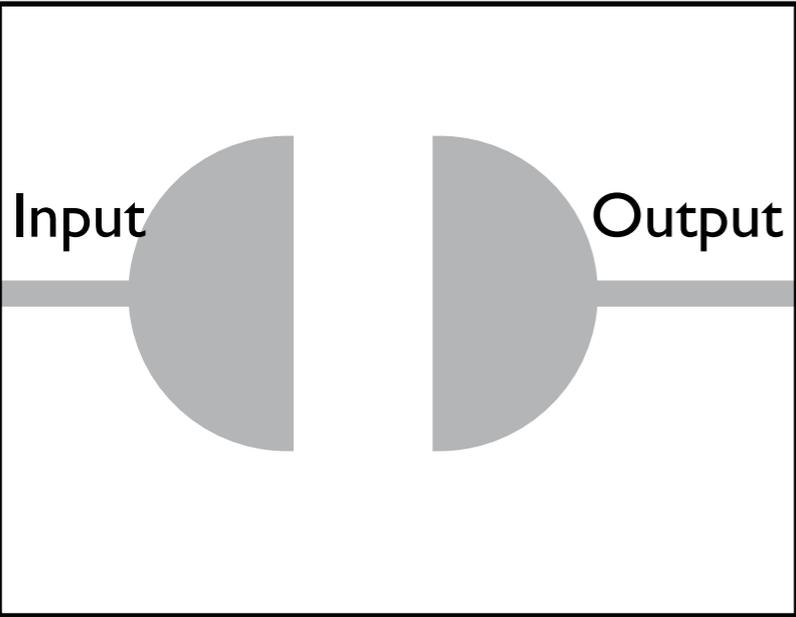


PDMS membrane



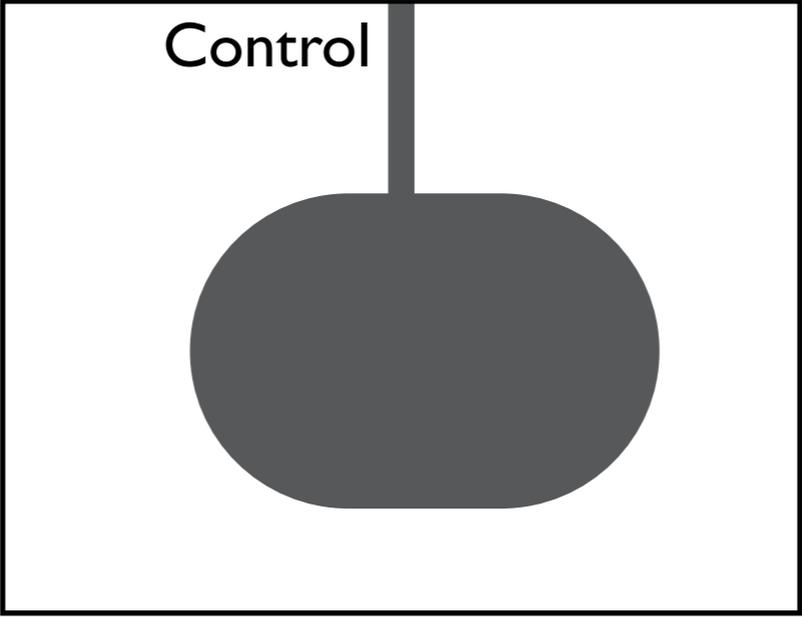
Pneumatic wafer

Valve operation



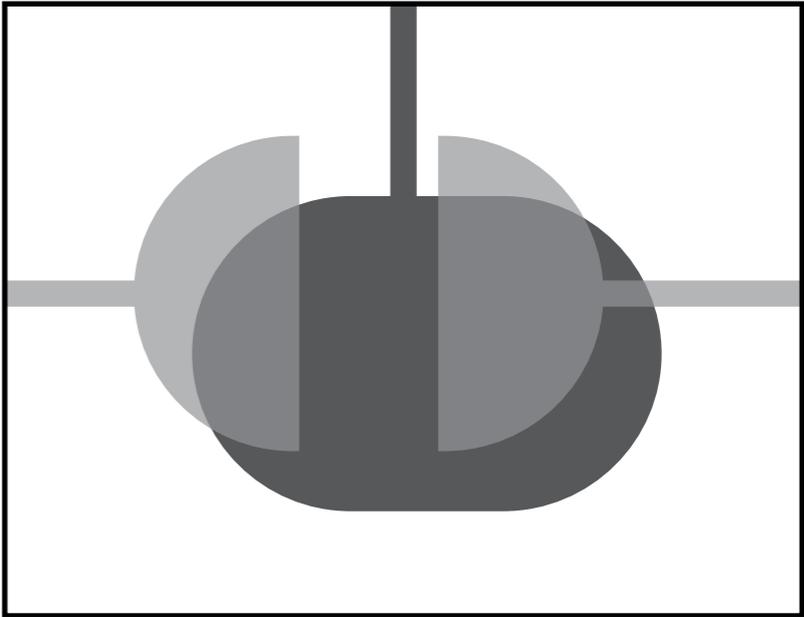
Fluidic wafer
(channel discontinuity)

+

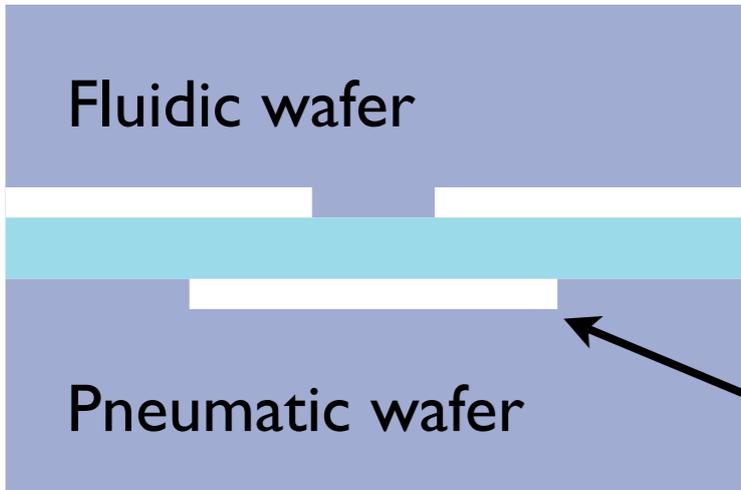


Pneumatic wafer
(displacement chamber)

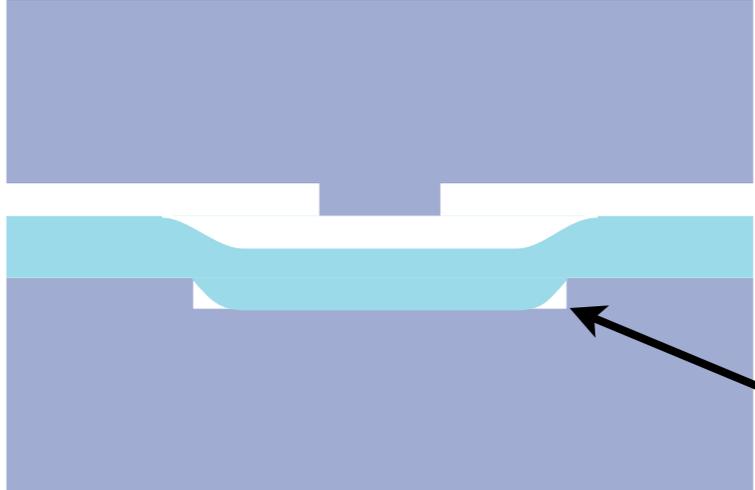
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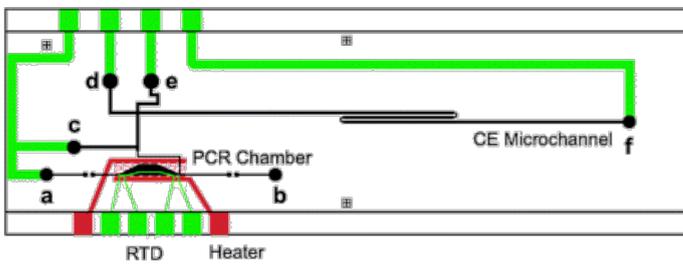
Assembled monolithic
membrane valve



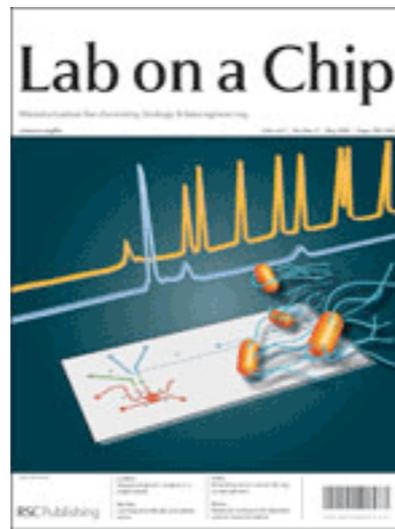
Valve closed



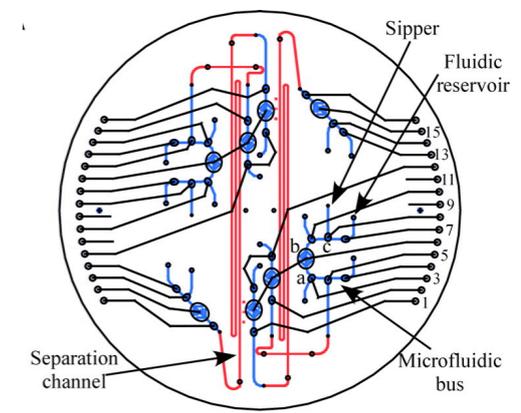
Valve open



Integrated portable genetic analysis microsystem for pathogen/infectious disease detection. E.T. Lagally et al., *Analytical Chemistry* **76**, 3162 (2004).



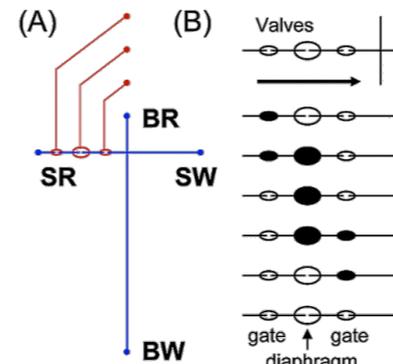
On-chip pressure injection for integration of infrared-mediated DNA amplification with electrophoretic separation. C.J. Easley, J.M. Karlinsey, and J.P. Landers, *Lab on a Chip* **6**, 601 (2006).



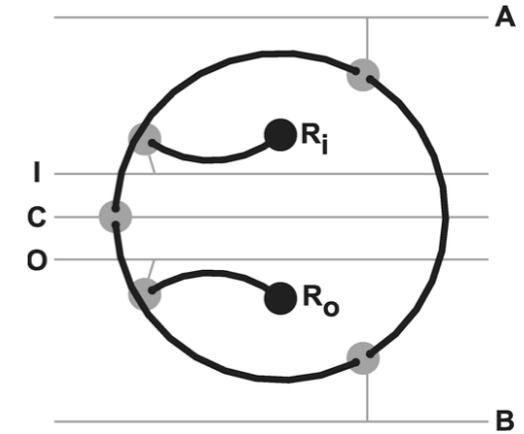
Development and evaluation of a microdevice for amino acid biomarker detection and analysis on Mars. A.M. Skelley et al., *Proceedings of the National Academy of Sciences of the USA* **102**, 1041 (2005).



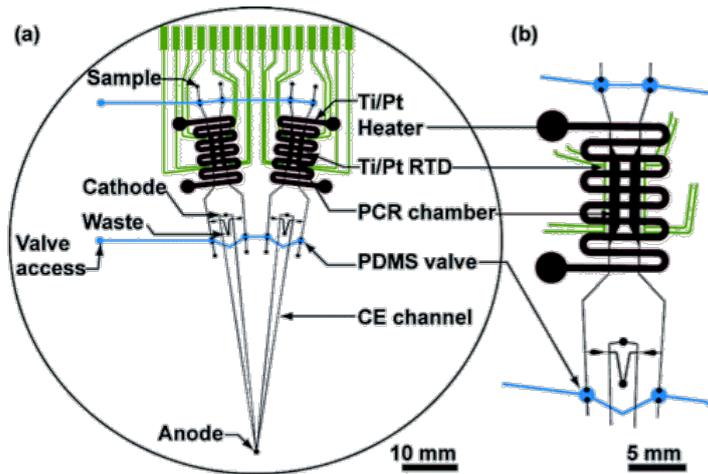
Microfabricated bioprocessor for integrated nanoliter-scale Sanger DNA sequencing. R.G. Blazej et al., *Proceedings of the National Academy of Sciences of the USA* **103**, 7240 (2006).



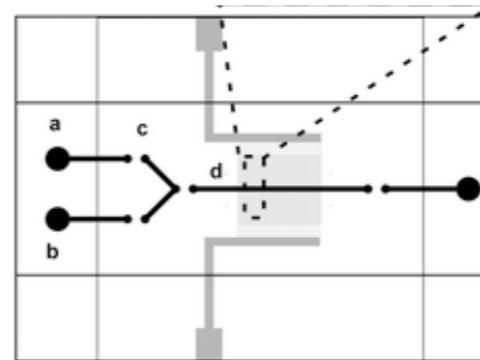
Pressure injection on a valved microdevice for electrophoretic analysis of submicroliter samples. J.M. Karlinsey et al., *Analytical Chemistry* **77**, 3637 (2005).



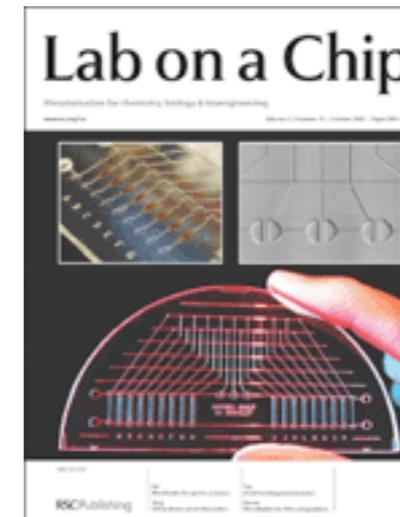
Microfluidic serial transfer circuit: Automated evolution of RNA catalysts B.M. Paegel et al., *Analytical Chemistry*, in press.



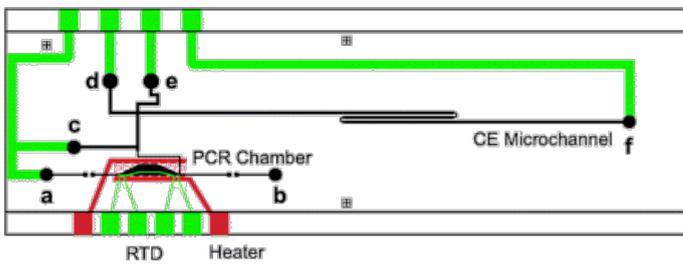
Multichannel PCR-CE Microdevice for Genetic Analysis. C.N. Liu, N.M. Toriello, and R.A. Mathies, *Analytical Chemistry* **78**, 5474 (2006).



Integrated microsystem for dielectrophoretic cell concentration and genetic detection. E.T. Lagally, S.H. Lee, and H.T. Soh, *Lab on a Chip* **5**, 2005.



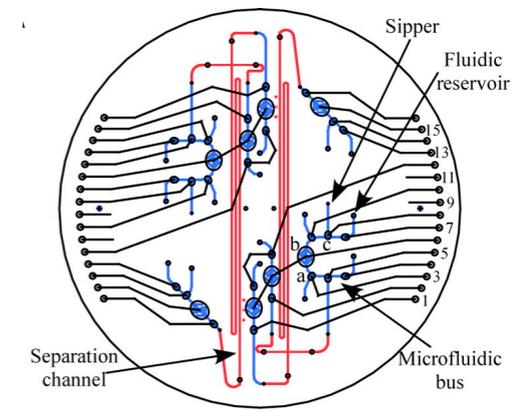
An integrated microfluidic processor for single nucleotide polymorphism-based DNA computing. W.H. Grover and R.A. Mathies, *Lab on a Chip* **5**, 1033 (2005).



Integrated portable genetic analysis microsystem for pathogen/infectious disease detection. E.T. Lagally et al., *Analytical Chemistry* **76**, 3162 (2004).



On-chip pressure injection for integration of infrared-mediated DNA amplification with electrophoretic separation. C.J. Easley, J.M. Karlinsey, and J.P. Landers, *Lab on a Chip* **6**, 601 (2006).

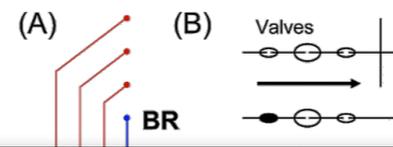


Development and evaluation of a microdevice for amino acid biomarker detection and analysis on Mars. A.M. Skelley et al., *Proceedings of the National Academy of Sciences of the USA* **102**, 1041 (2005).



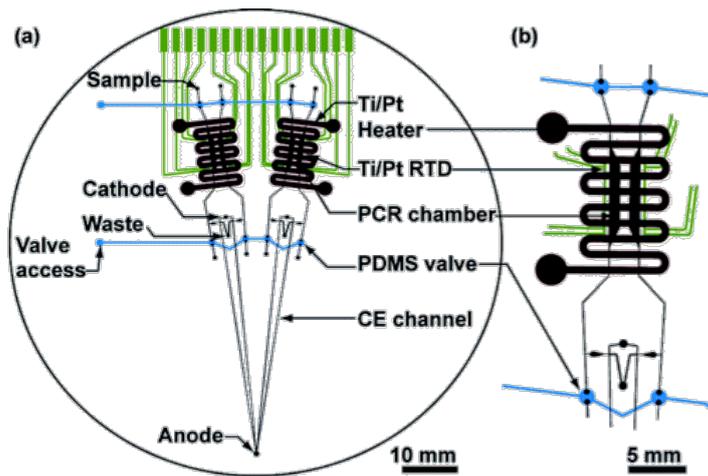
Microfabricated

If we want more independent valves on-chip or reduced cost, size, or power consumption, the logic of device operation must be integrated on-chip.

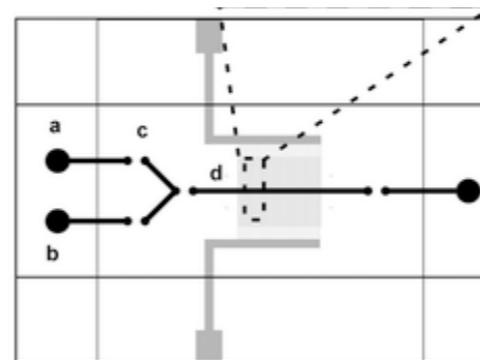


Analytical Chemistry **77**, 3637 (2005).

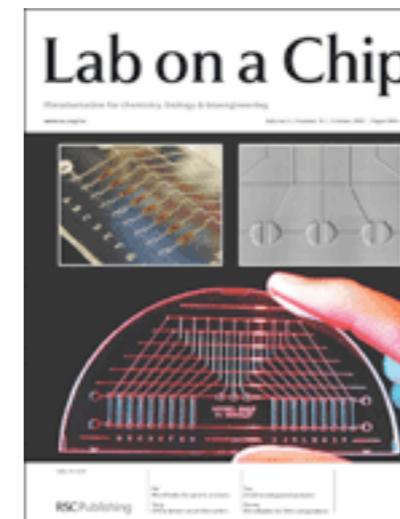
Microfluidic serial transfer circuit: Automated evolution of RNA catalysts B.M. Paegel et al., *Analytical Chemistry*, in press.



Multichannel PCR-CE Microdevice for Genetic Analysis. C.N. Liu, N.M. Toriello, and R.A. Mathies, *Analytical Chemistry* **78**, 5474 (2006).



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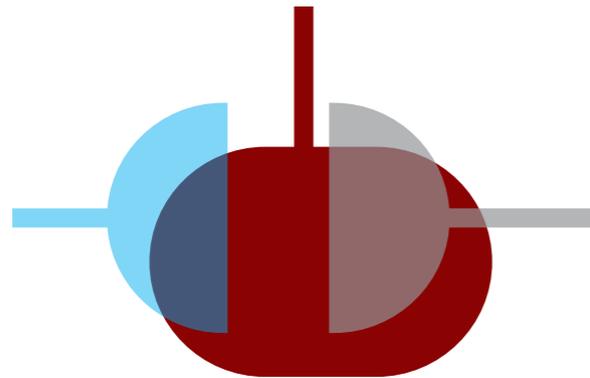


An integrated microfluidic processor for single nucleotide polymorphism-based DNA computing. W.H. Grover and R.A. Mathies, *Lab on a Chip* **5**, 1033 (2005).

Pneumatic Valve "Truth Table"

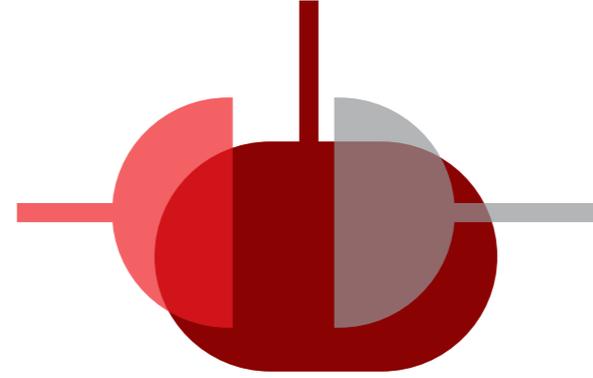
Pressure

Vacuum



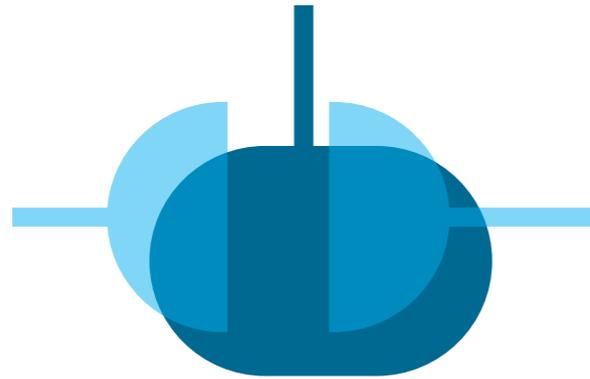
Pressure

Pressure



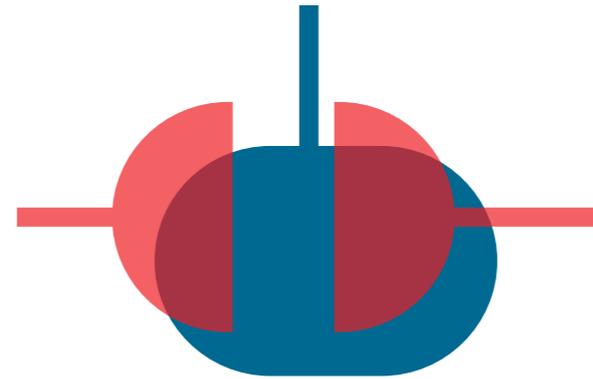
Vacuum

Vacuum



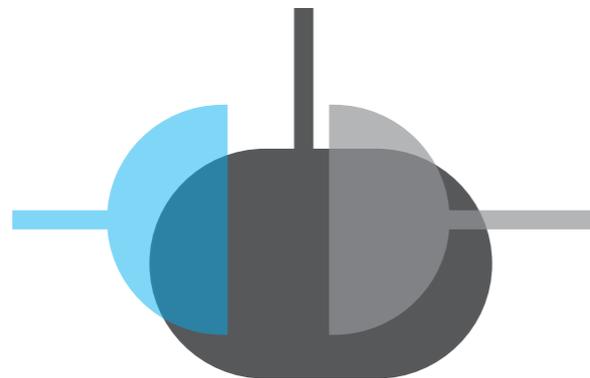
Vacuum

Pressure



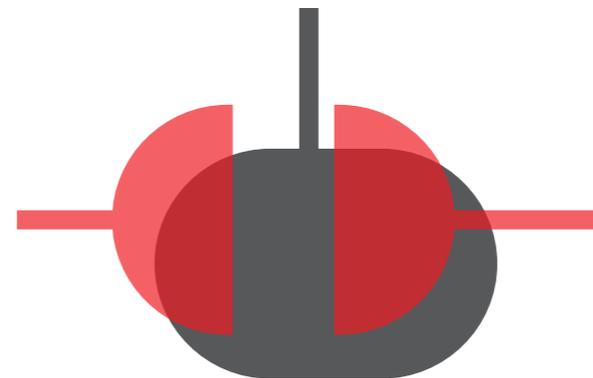
No connection

Vacuum

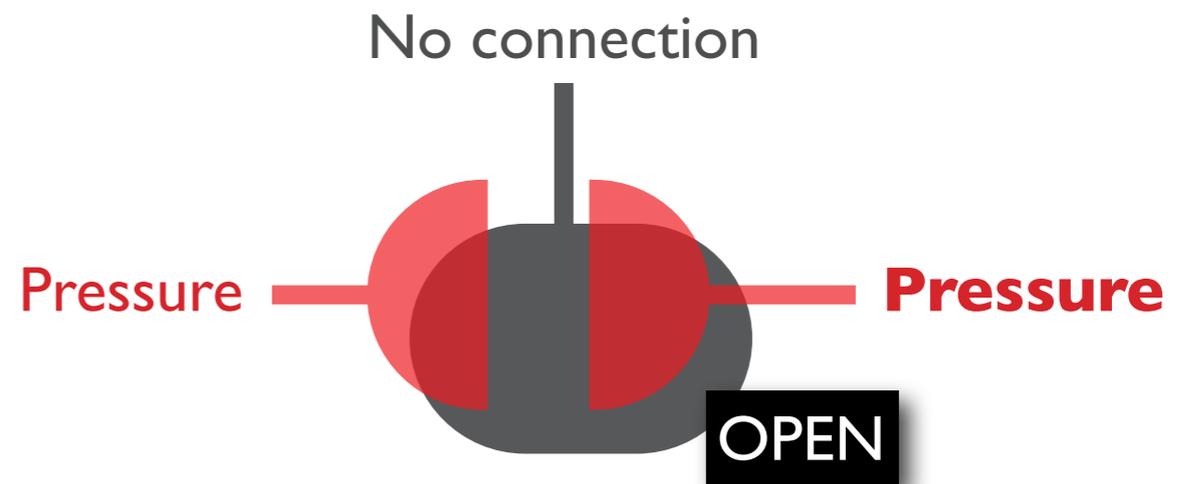
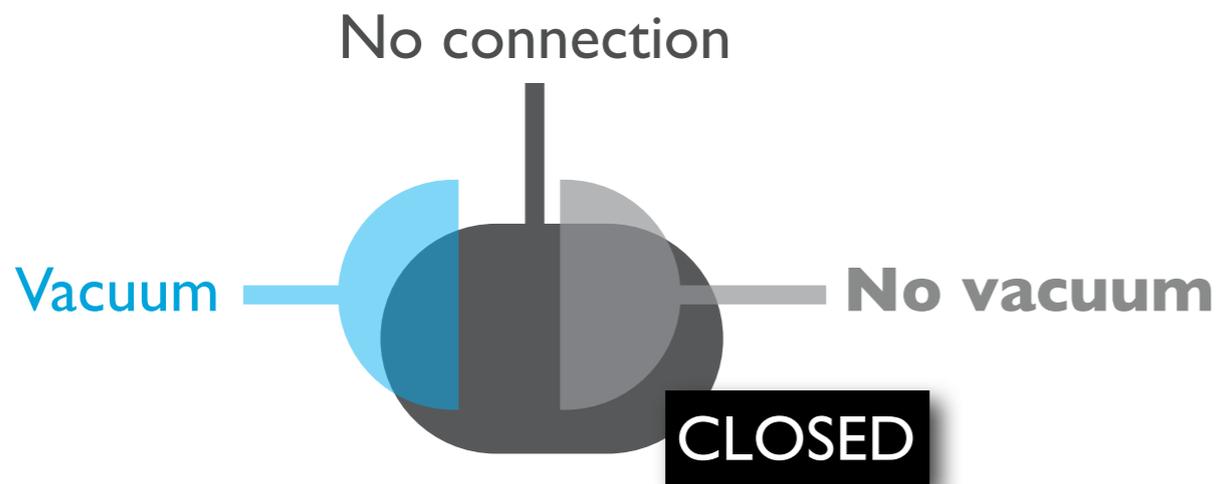
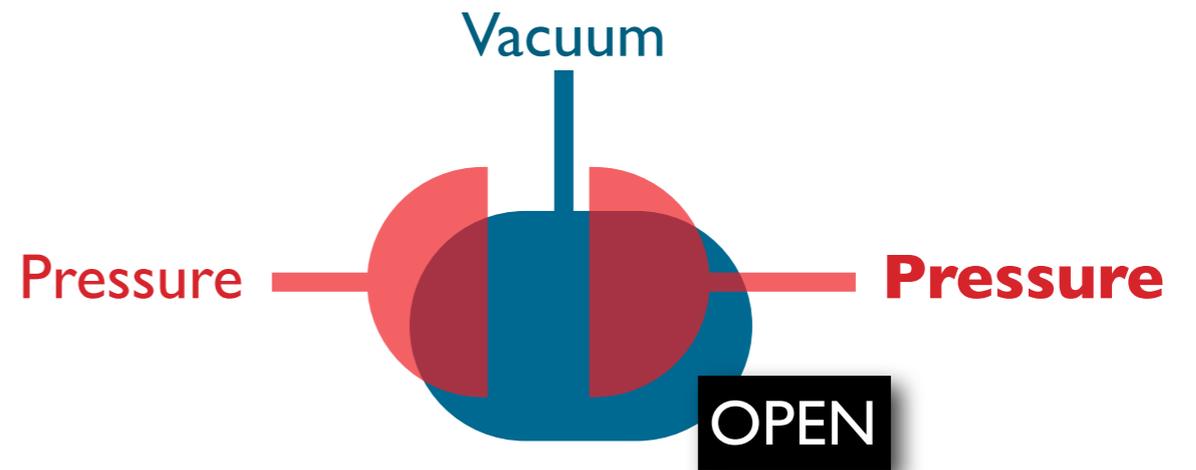
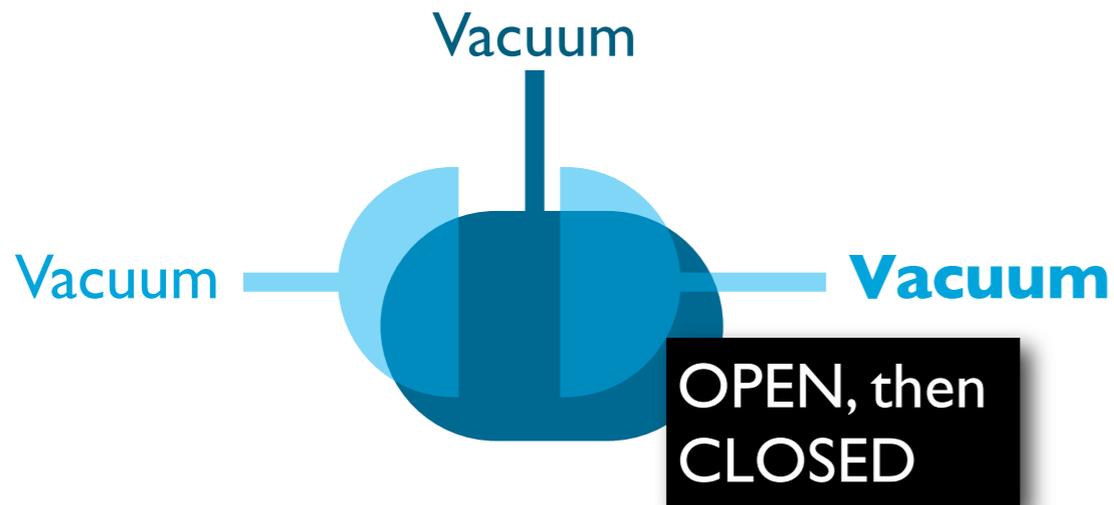
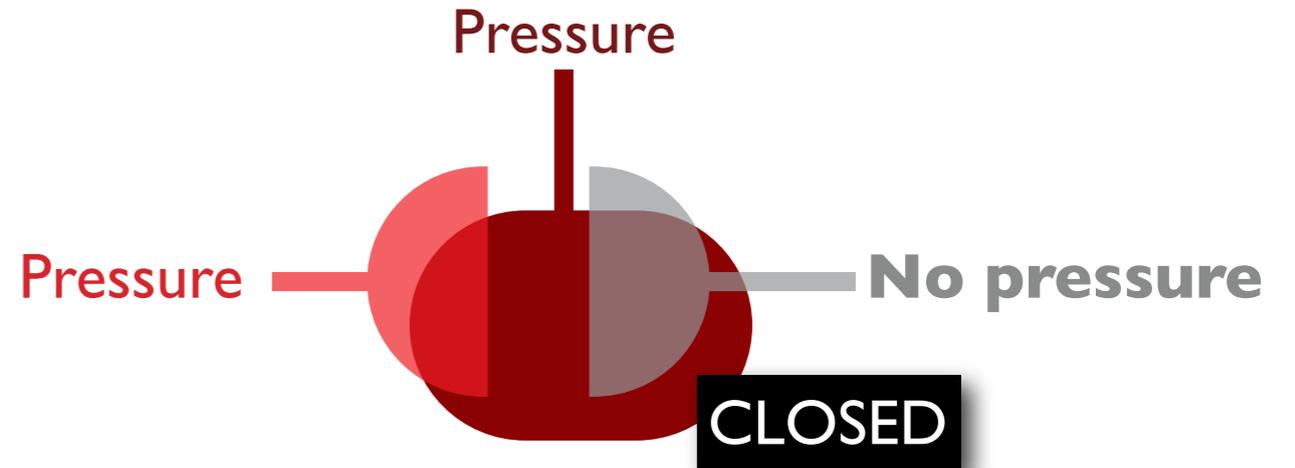
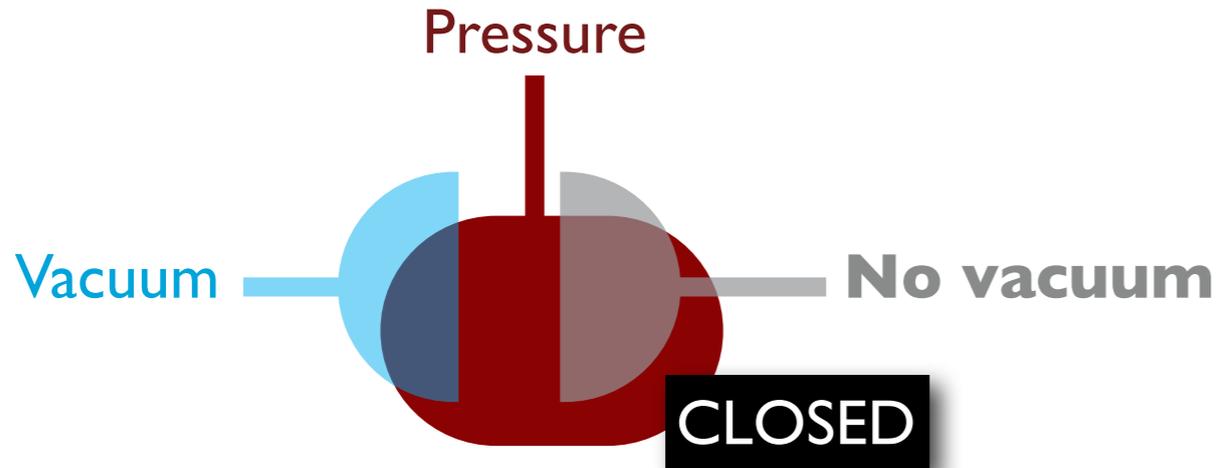


No connection

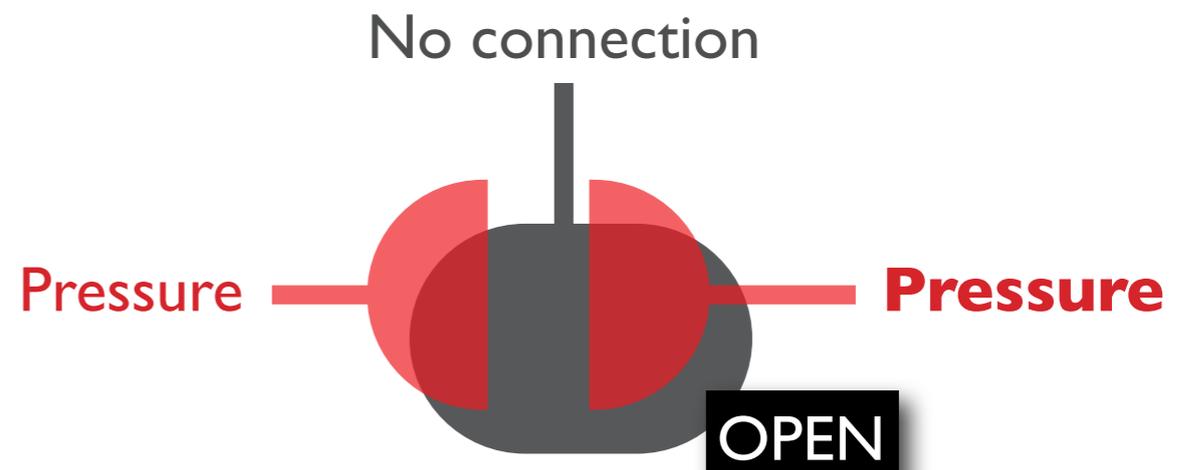
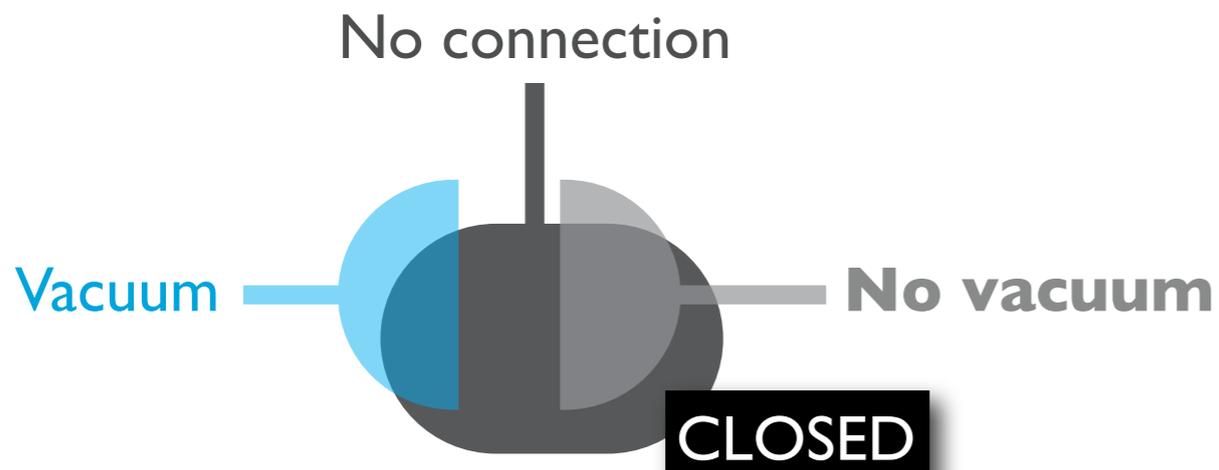
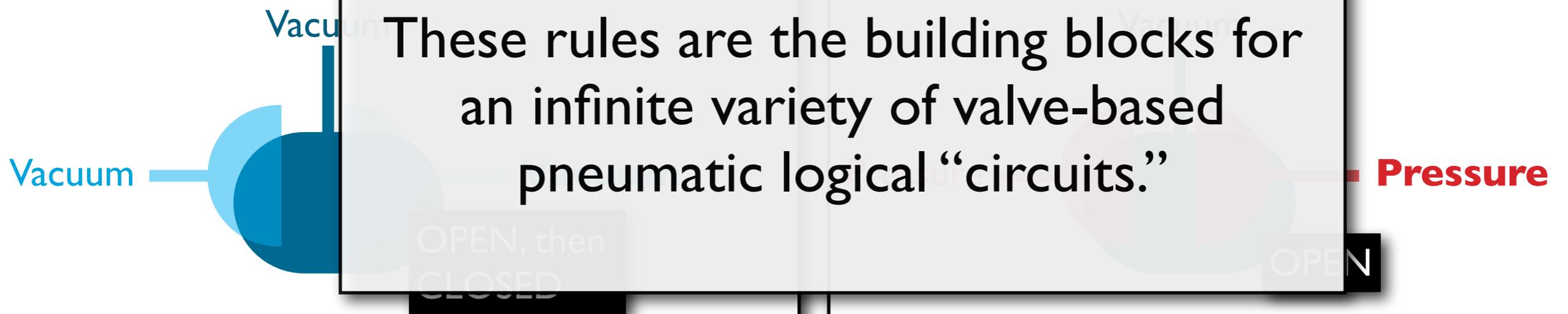
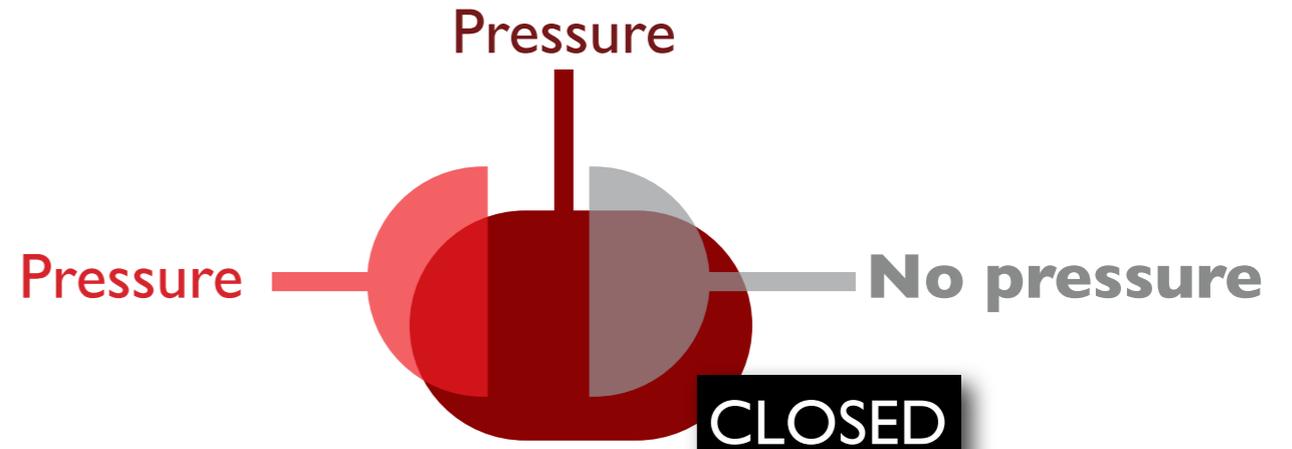
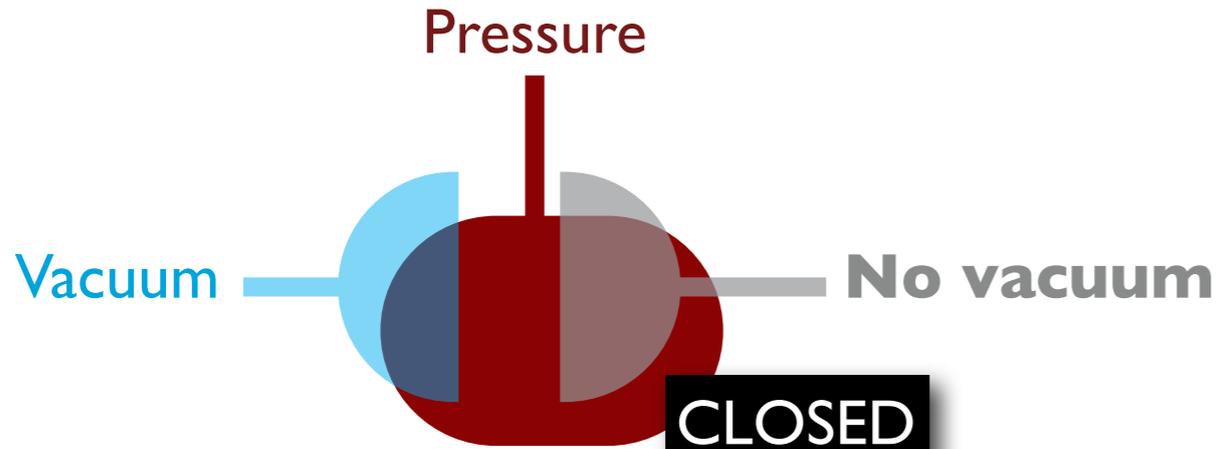
Pressure



Pneumatic Valve "Truth Table"

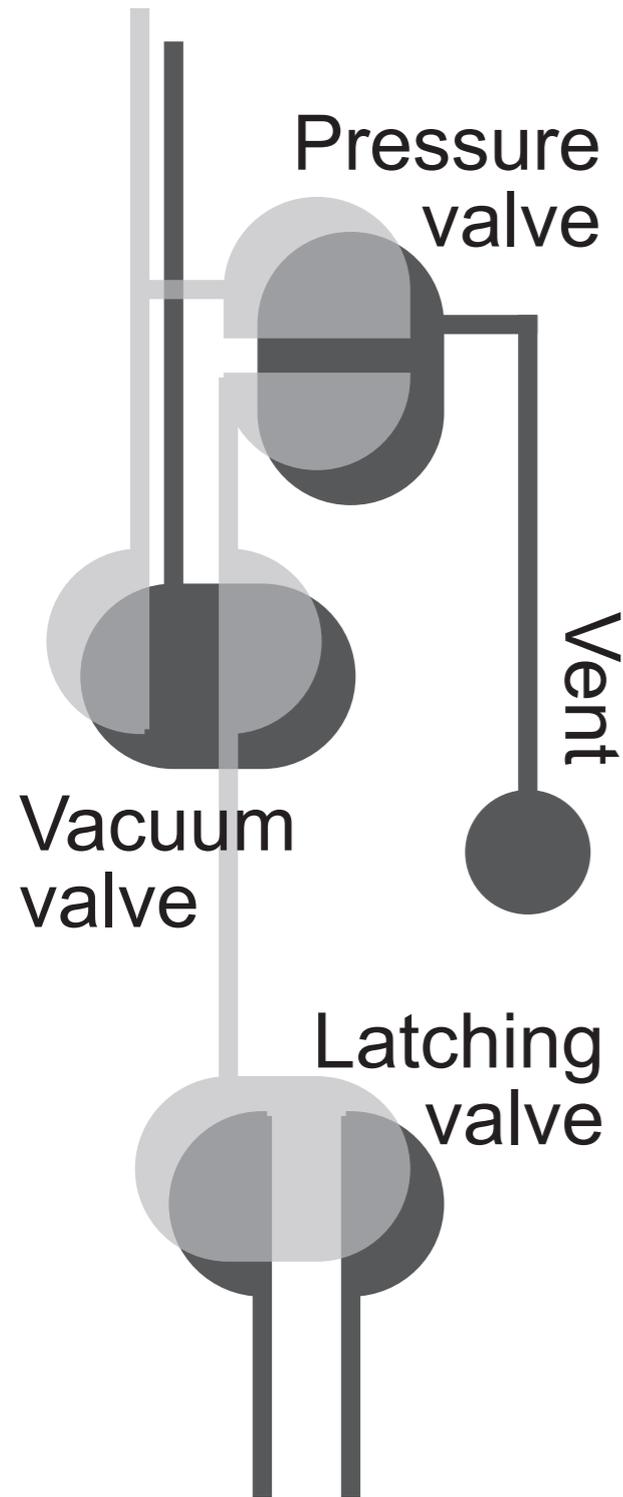


Pneumatic Valve "Truth Table"



Latching valve operation

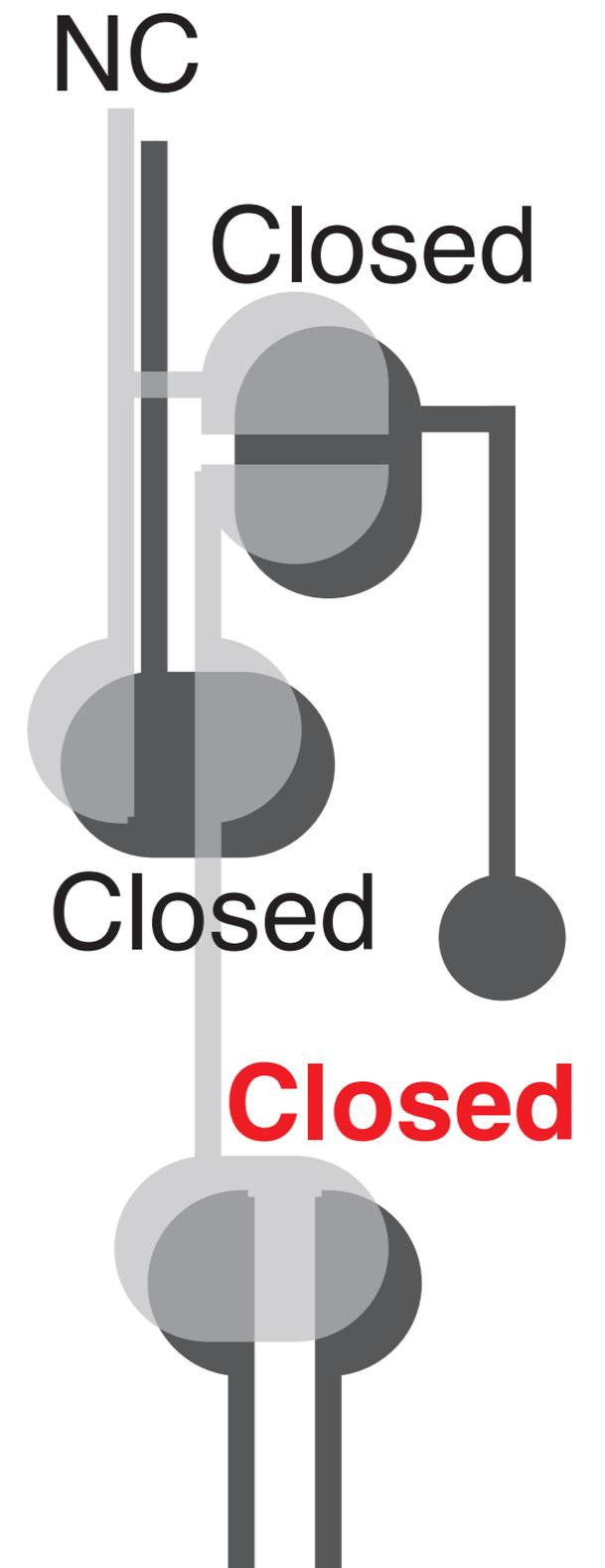
Set input



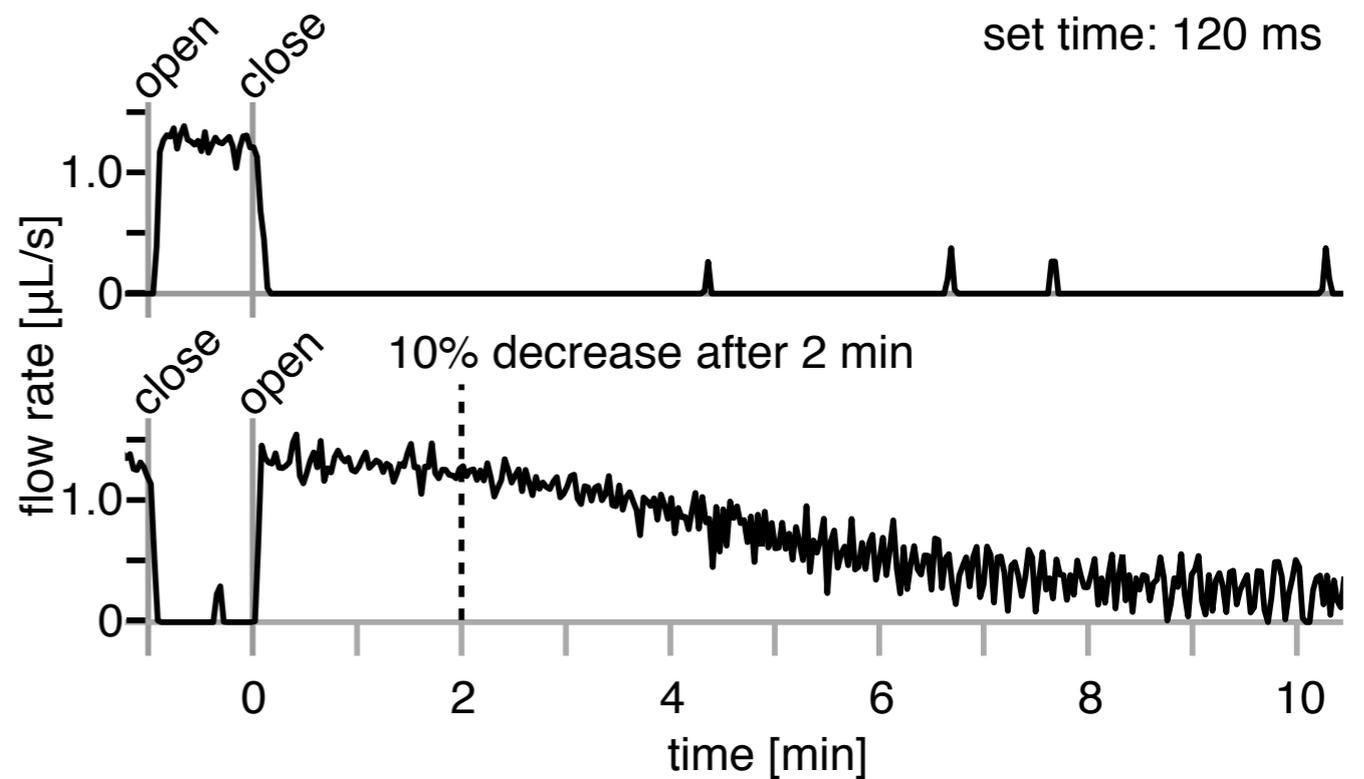
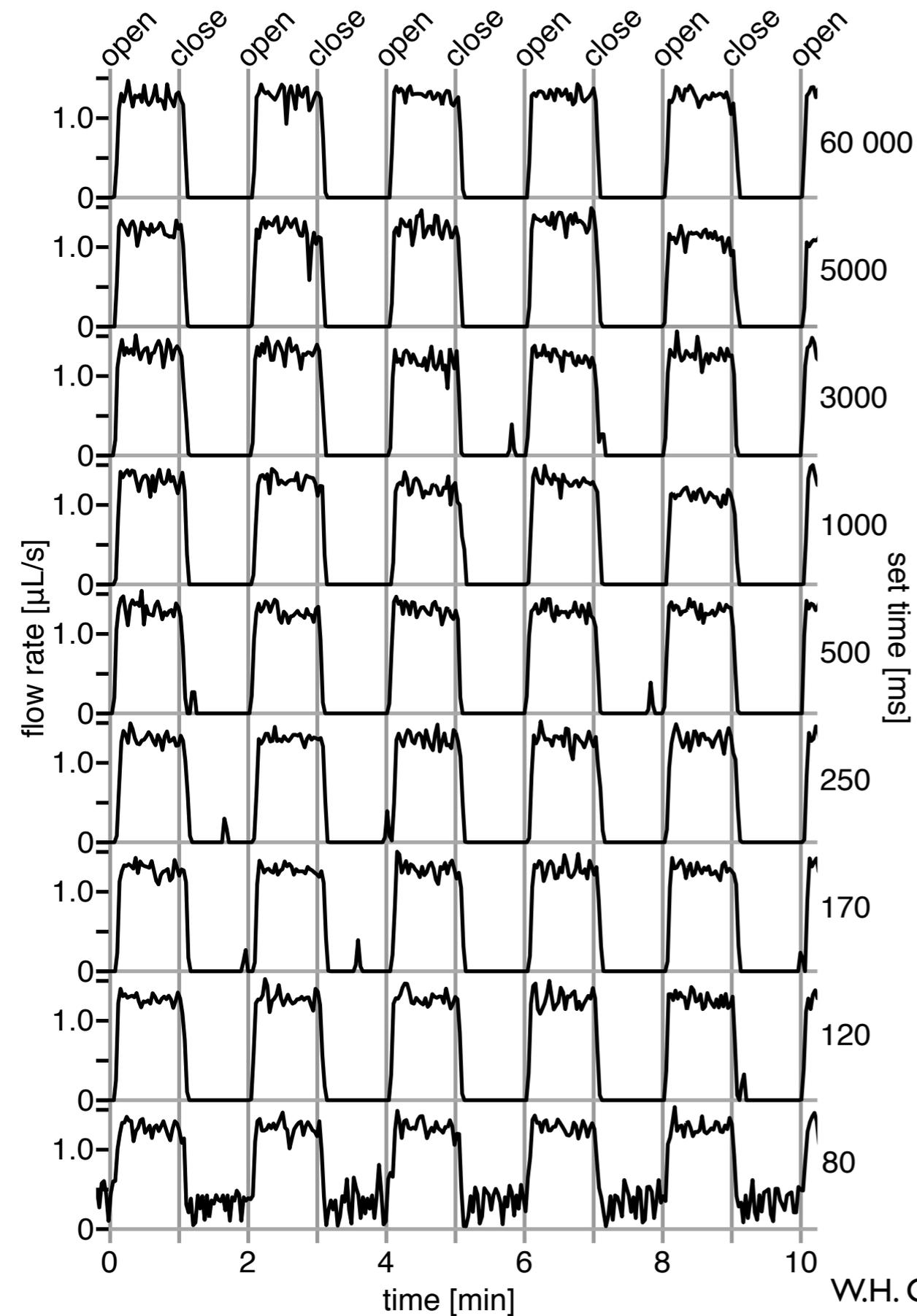
NC



NC



Characterizing a single latching valve

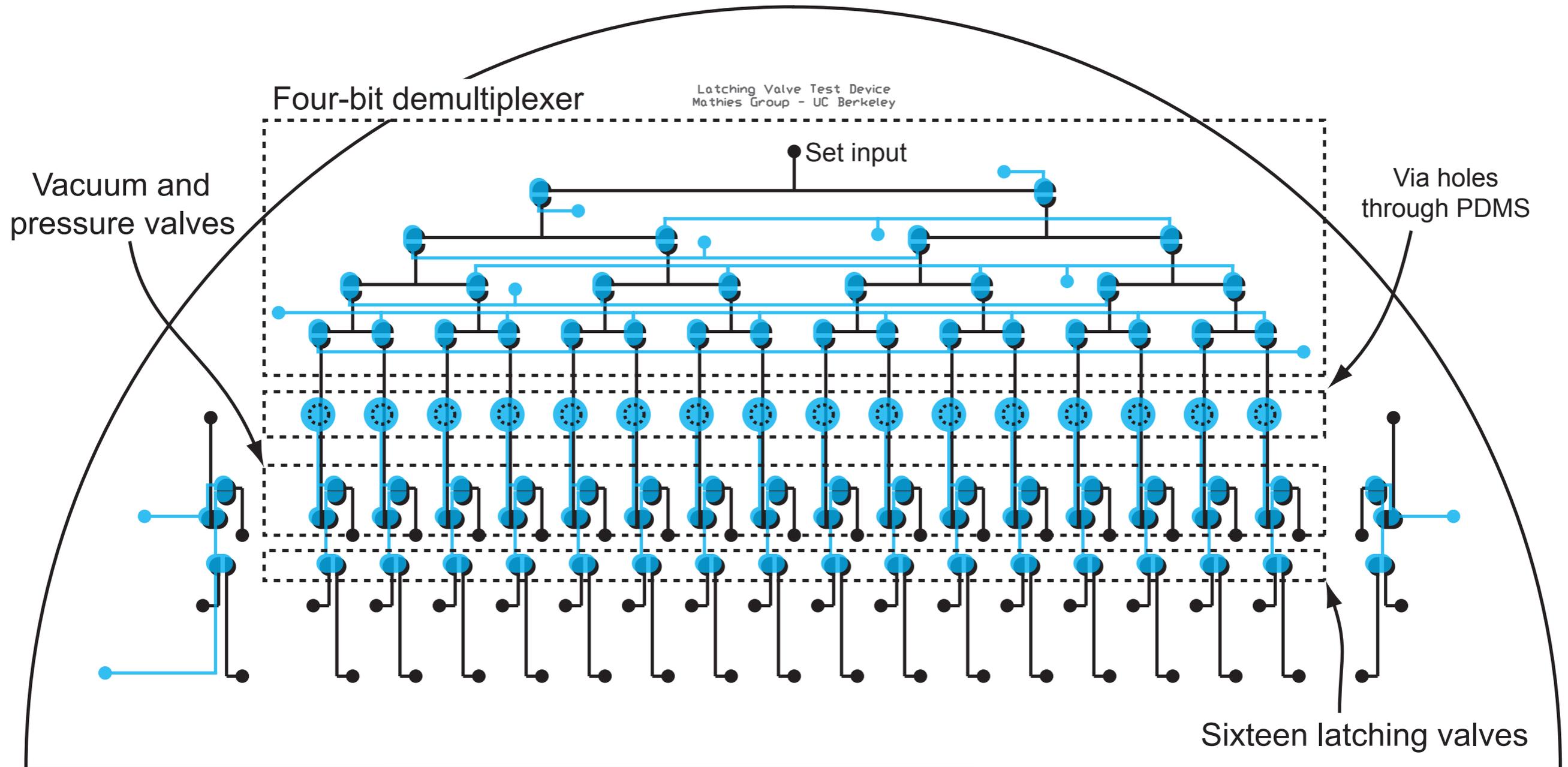


120 ms V/P pulse holds valve open or closed for 2 minutes.

Time for 1000 valves to be actuated in 2 min.

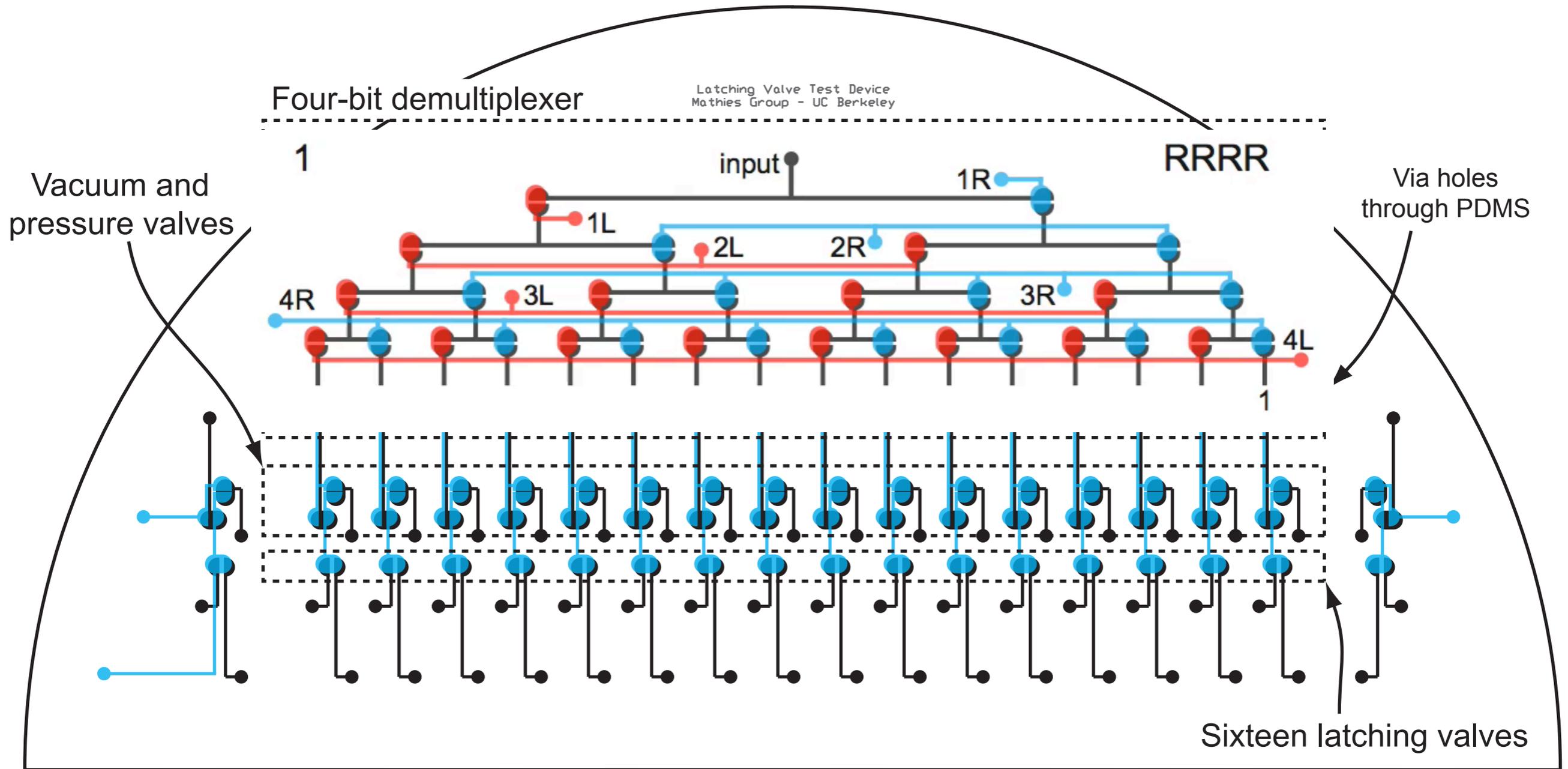
How to actuate 1000 on-chip valves without 1000 off-chip solenoids?

Latch valve/demultiplexer test chip



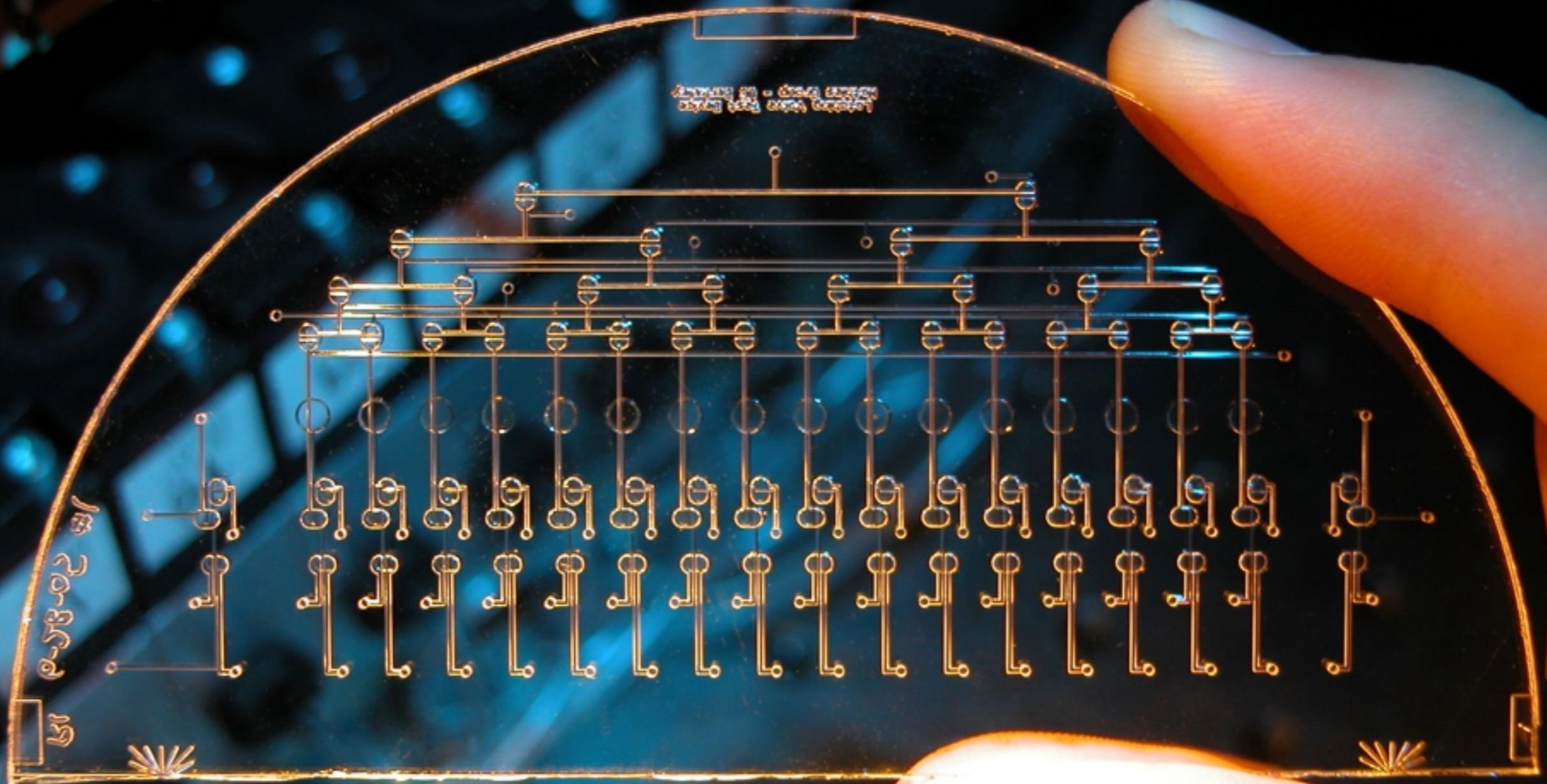
n off-chip controllers: 2^{n-1} independent on-chip valves

Latch valve/demultiplexer test chip

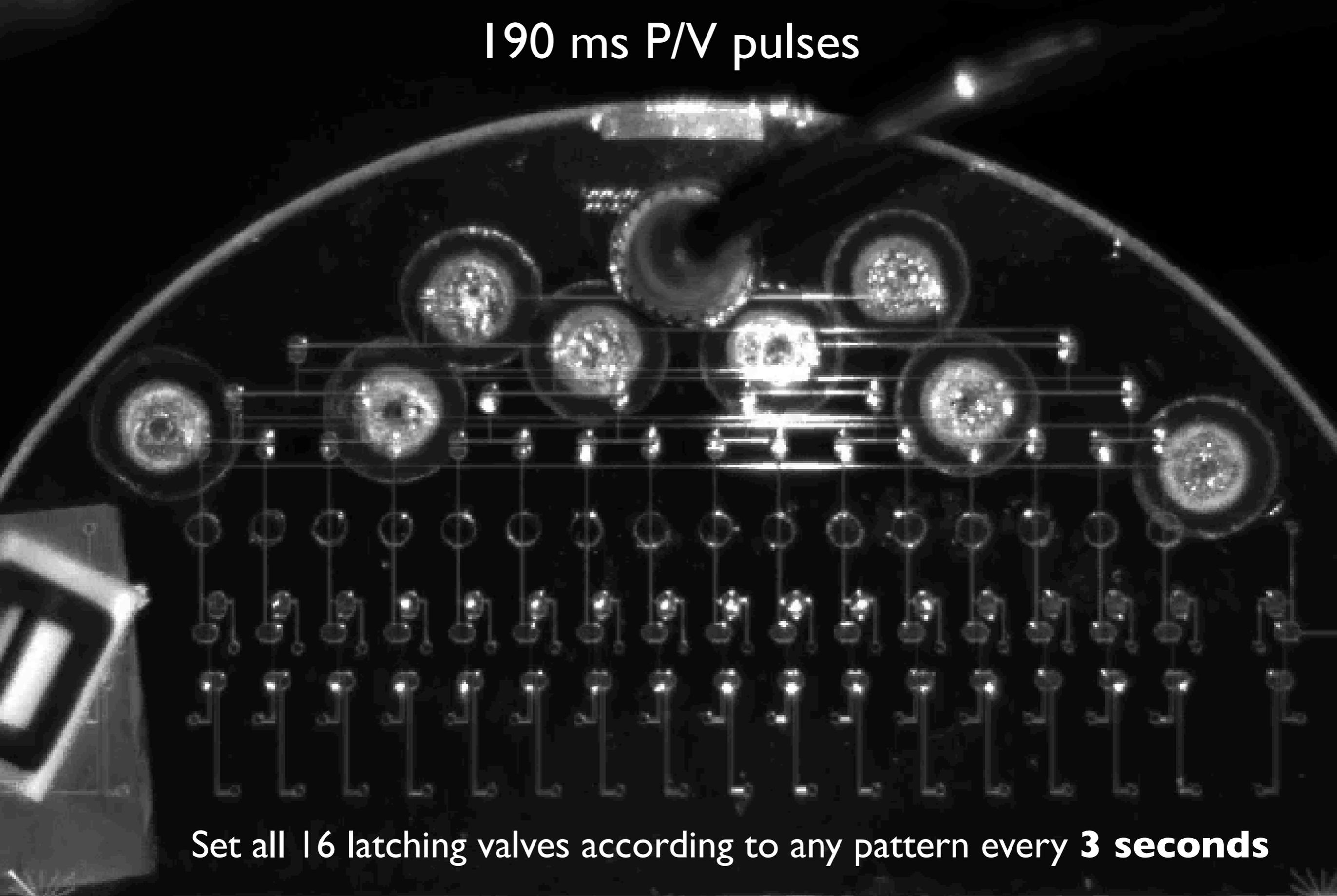


n off-chip controllers: 2^{n-1} independent on-chip valves

Latch valve/demultiplexer test chip



190 ms P/V pulses



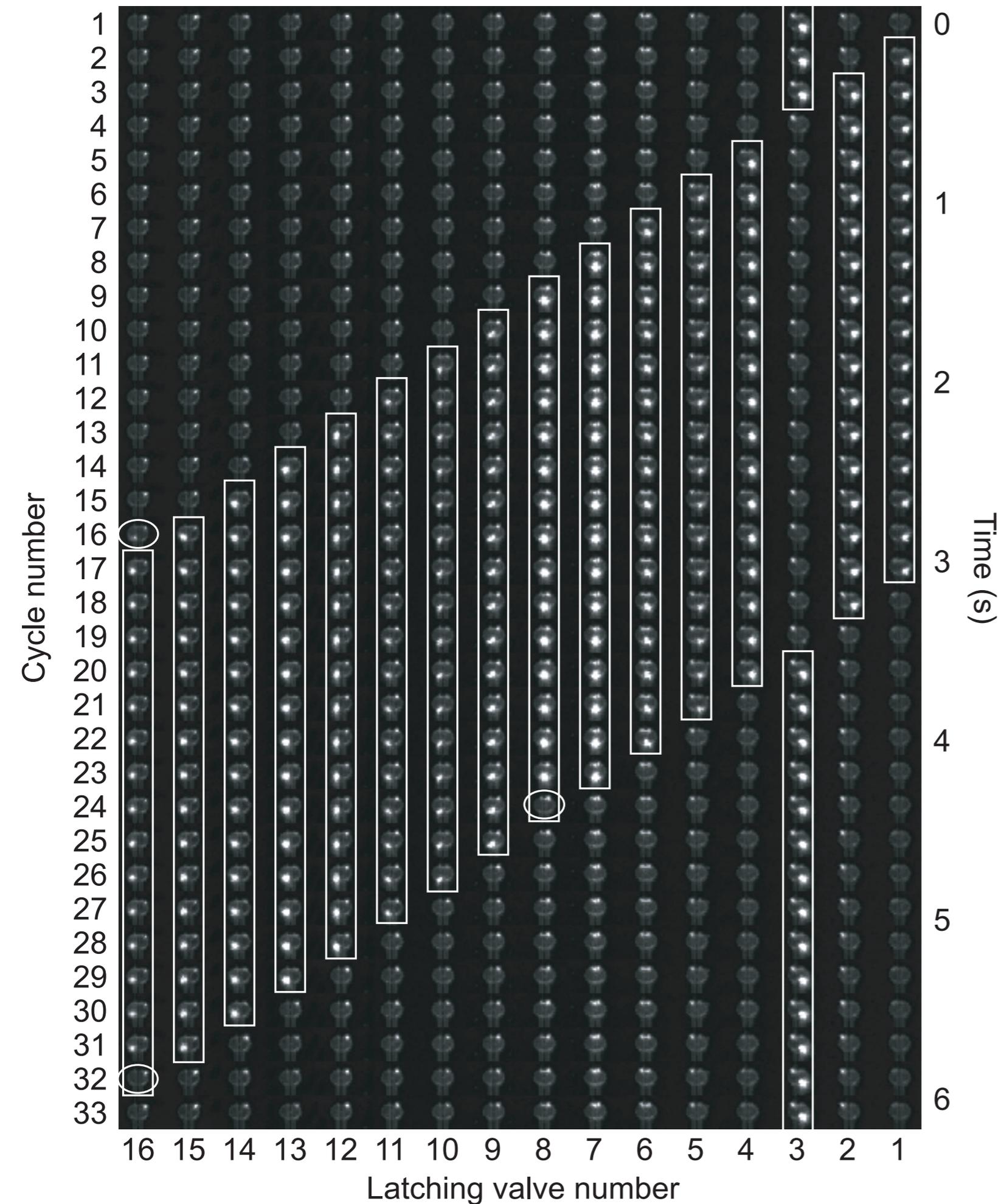
Set all 16 latching valves according to any pattern every **3 seconds**

190 ms pulses, inverted Valve 3

- - Open valves
- - Incorrect valves

All errors consist of a valve changing too early, with its “Least Significant Bit” neighbor.

Need a **software** solution, a different **program...**

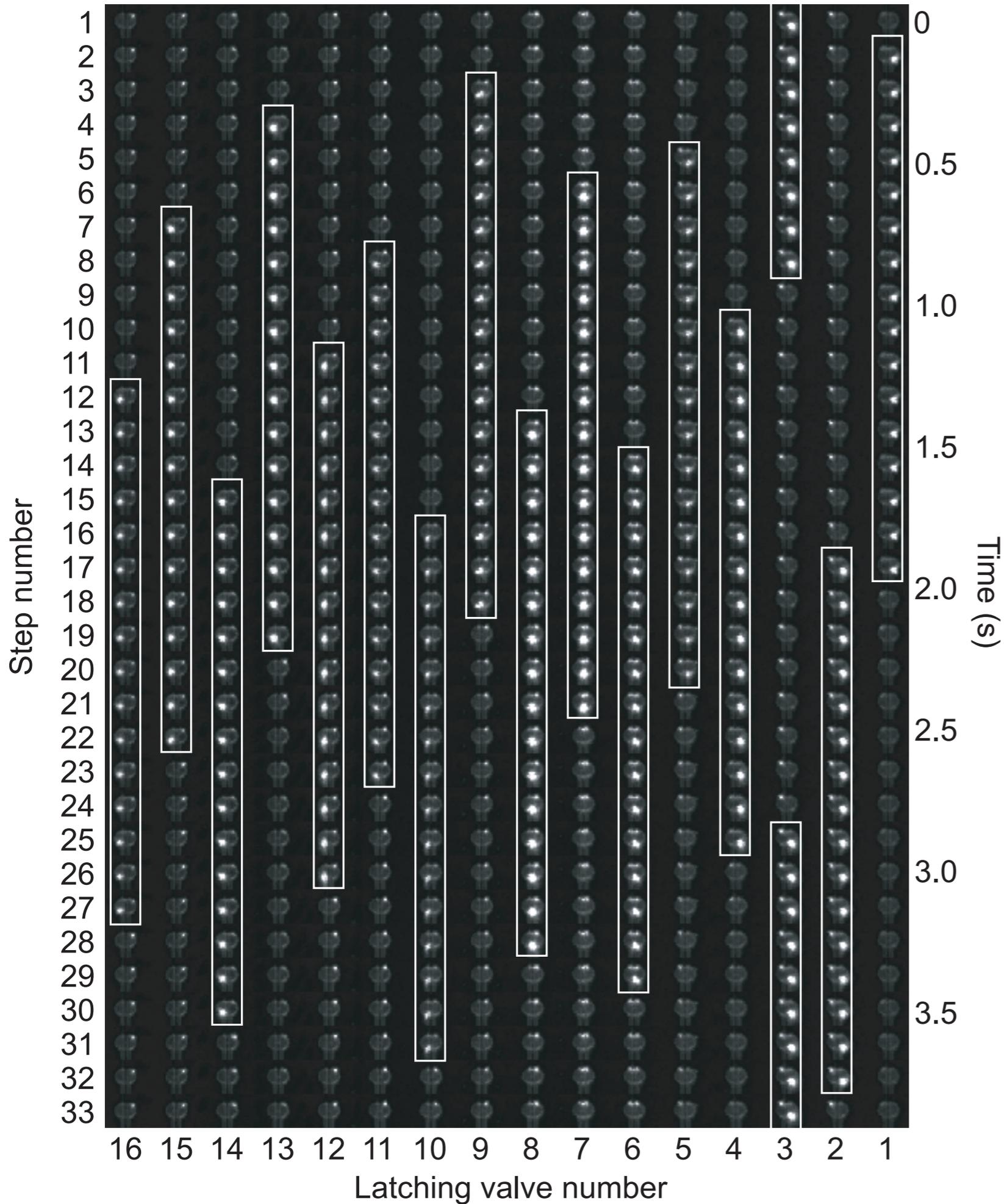


120 ms P/V pulses, **Gray** code addressing



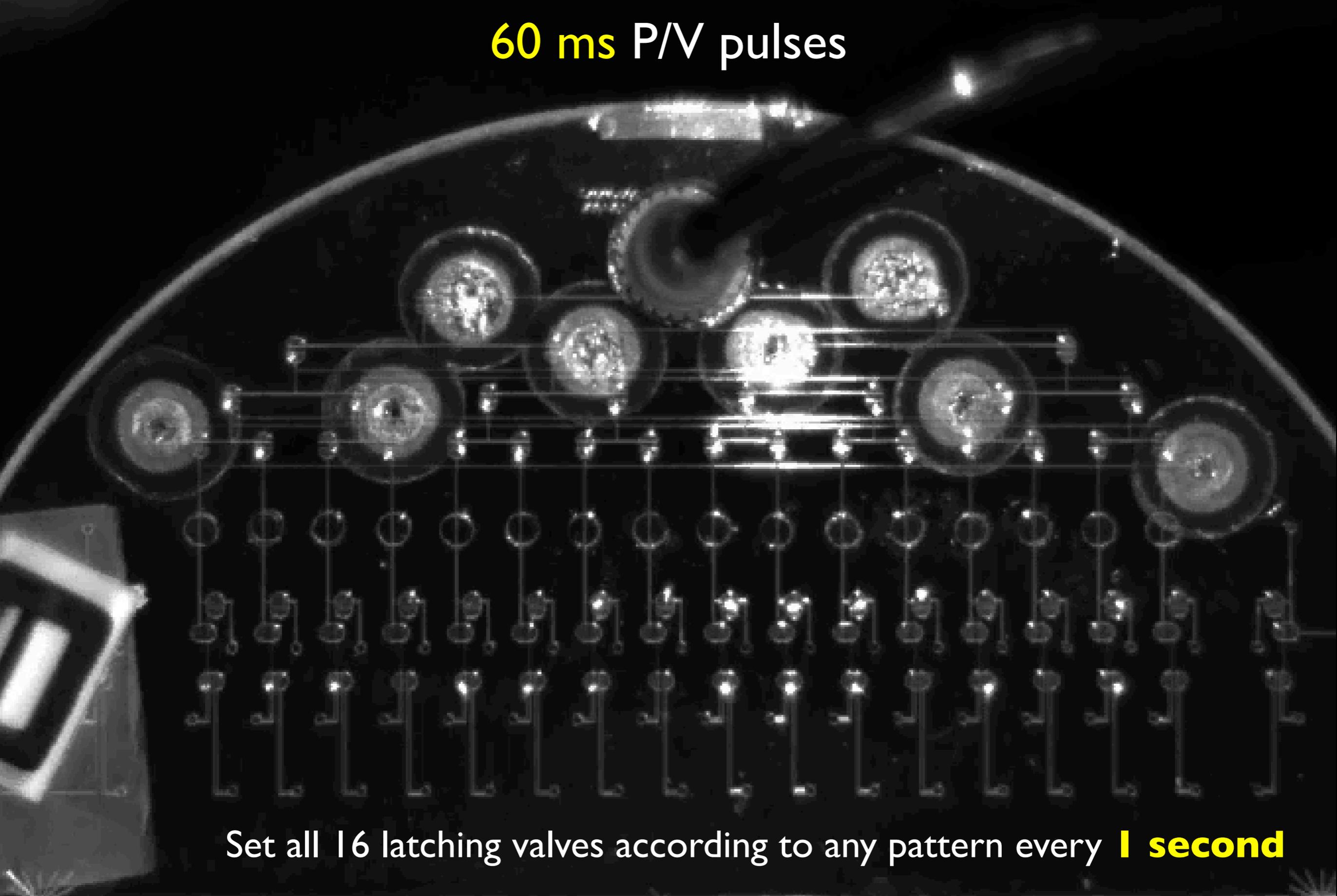
Set all 16 latching valves according to any pattern every **2 seconds**

120 ms P/V pulses, inverted Valve 3



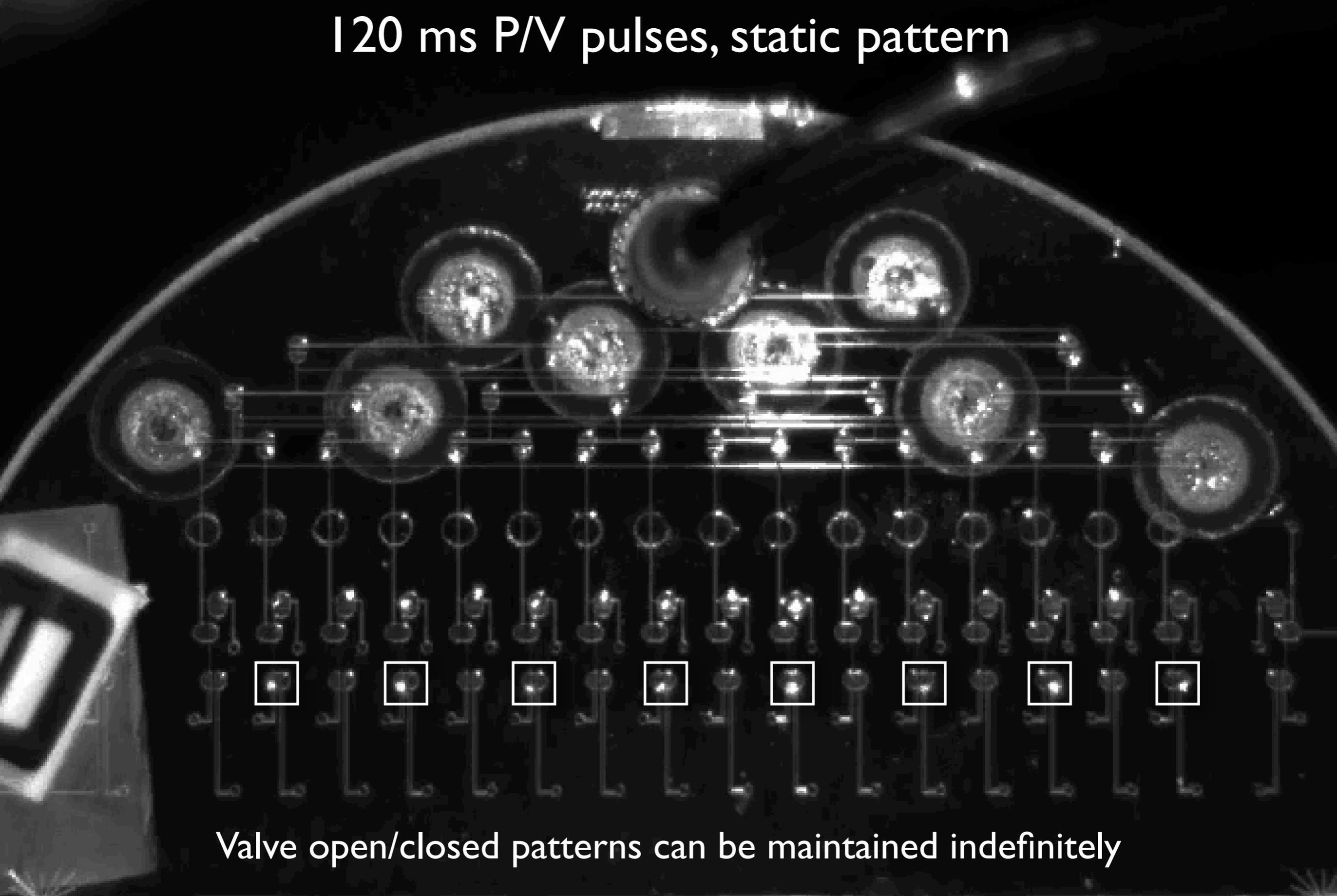
No errors

60 ms P/V pulses



Set all 16 latching valves according to any pattern every **1 second**

120 ms P/V pulses, static pattern

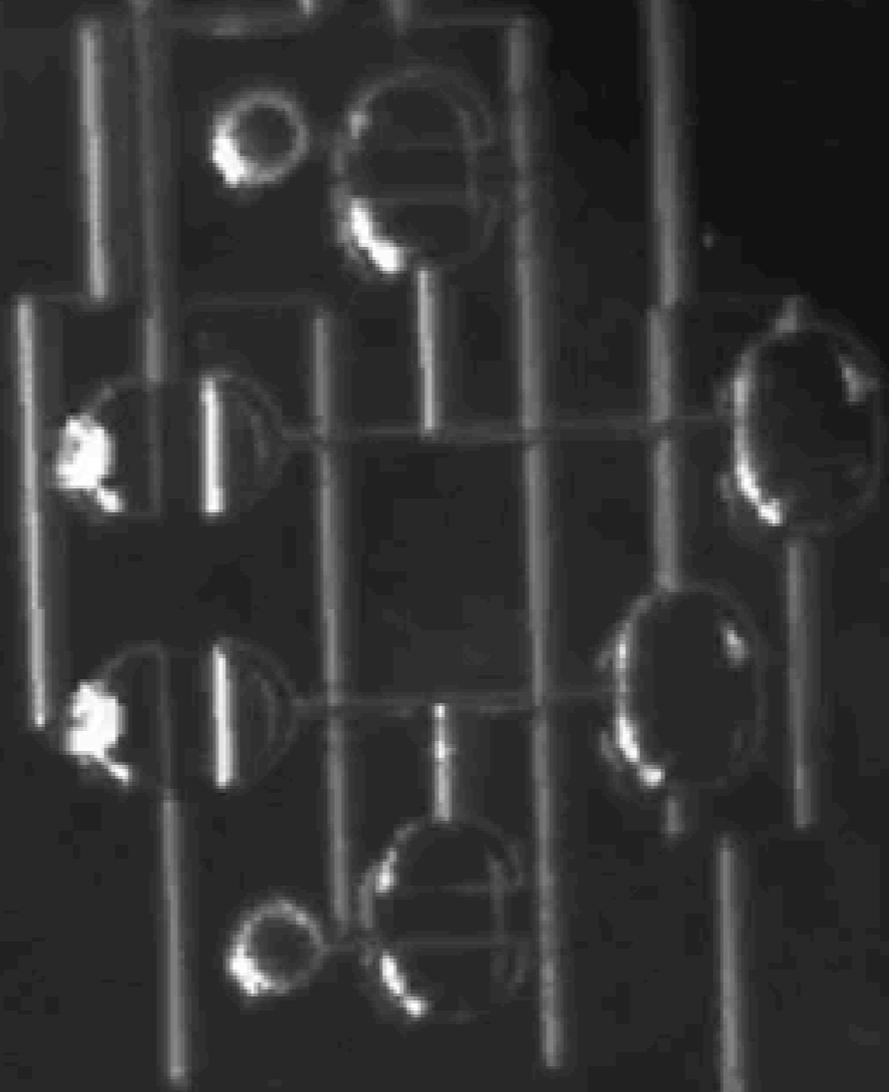


Valve open/closed patterns can be maintained indefinitely

$0 \text{ XOR } 0 = 0$

Input A

Input B

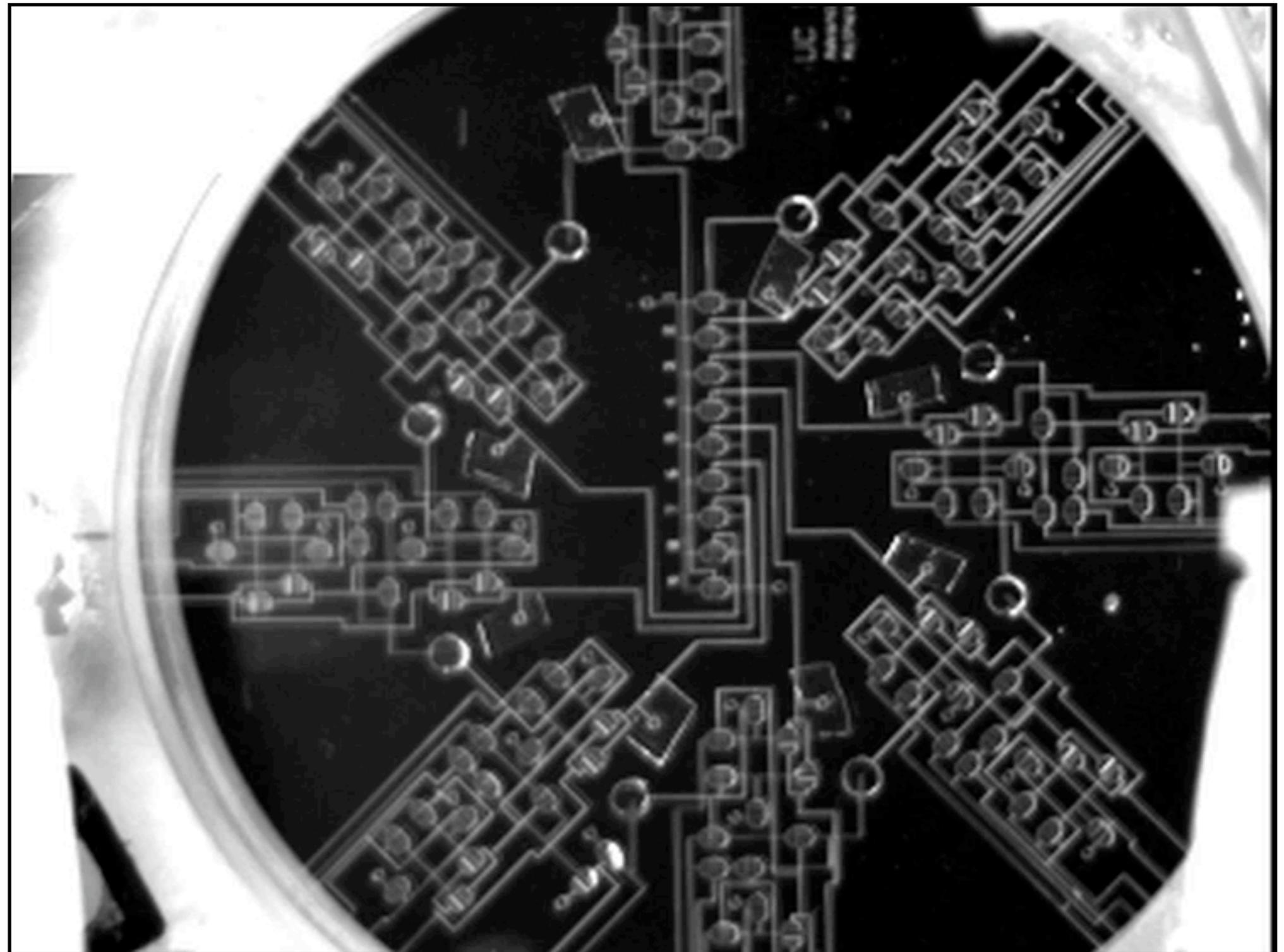


Output

Vacuum = 1 or TRUE
Pressure = 0 or FALSE

Eight-bit valve-based pneumatic adder

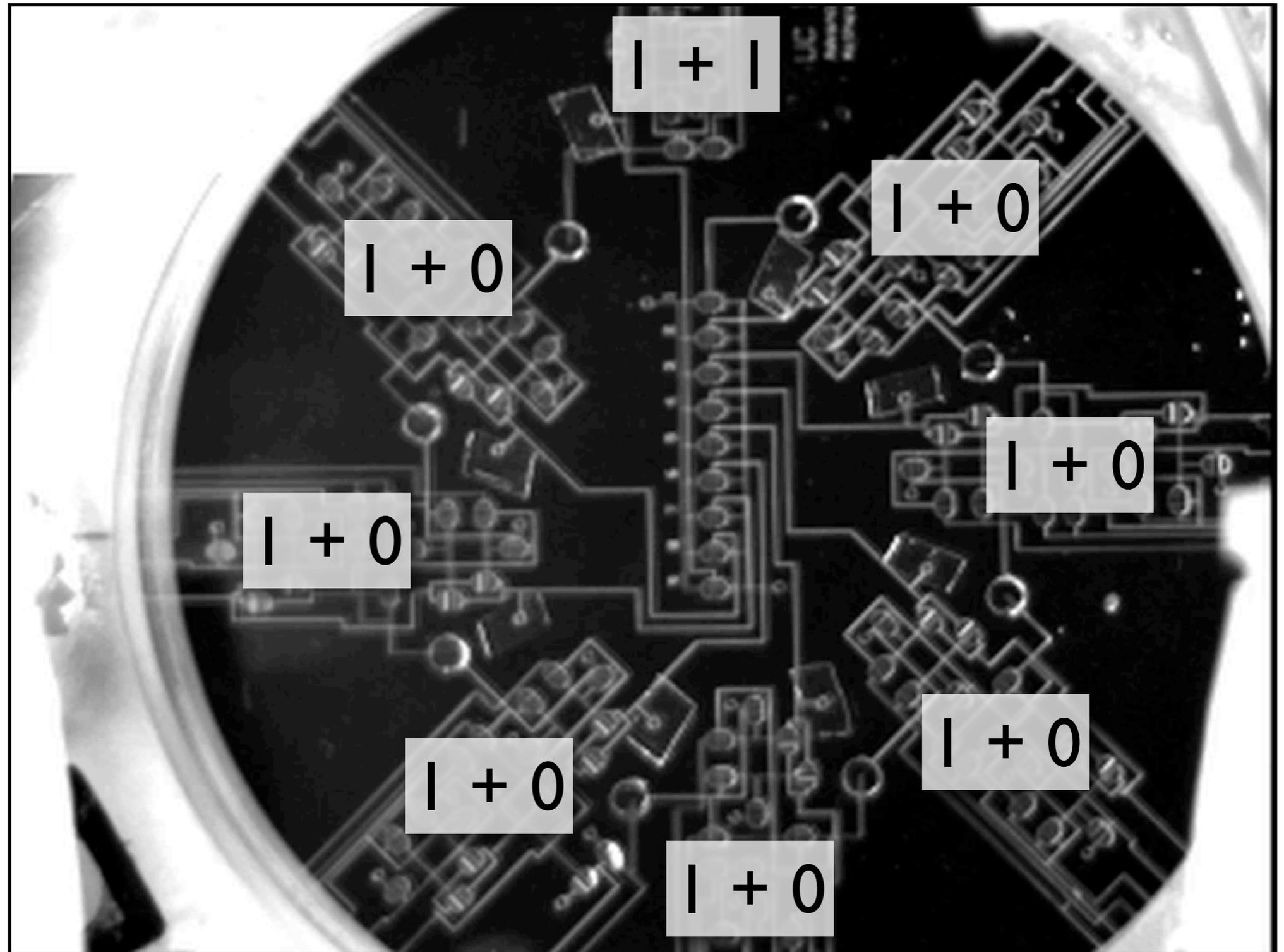
Eight **binary adders** linked in series to form an **eight-bit ripple carry adder**

$$\begin{array}{r} | | | | | | | | \\ + 00000001 \\ \hline \end{array}$$


Eight-bit valve-based pneumatic adder

Eight **binary adders** linked in series to form an **eight-bit ripple carry adder**

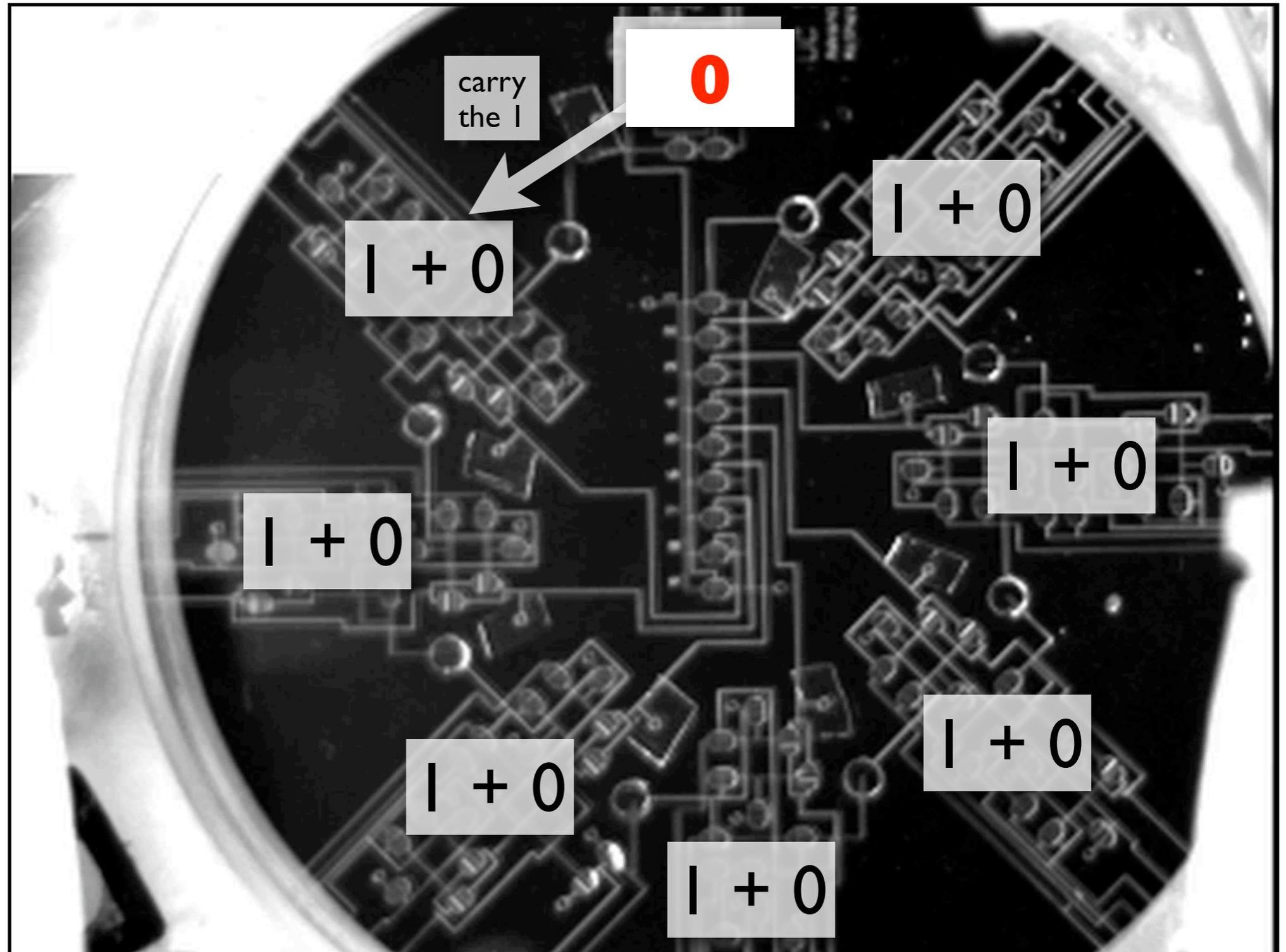
$$\begin{array}{r} | | | | | | | | \\ + 0000000 | \\ \hline \end{array}$$



Eight-bit valve-based pneumatic adder

Eight **binary adders** linked in series to form an **eight-bit ripple carry adder**

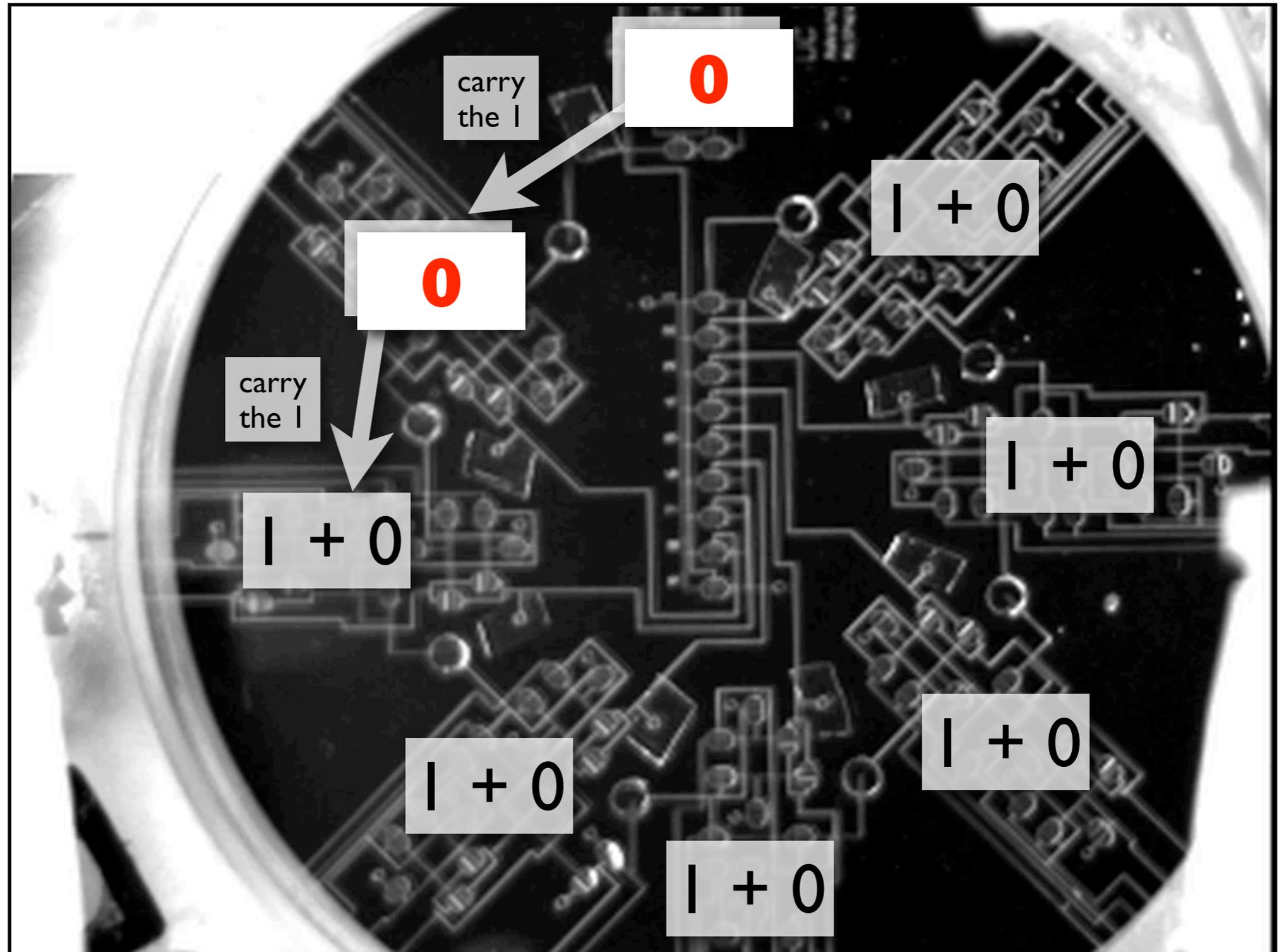
$$\begin{array}{r} | | | | | | | | \\ + 00000001 \\ \hline 0 \end{array}$$



Eight-bit valve-based pneumatic adder

Eight **binary adders** linked in series to form an **eight-bit ripple carry adder**

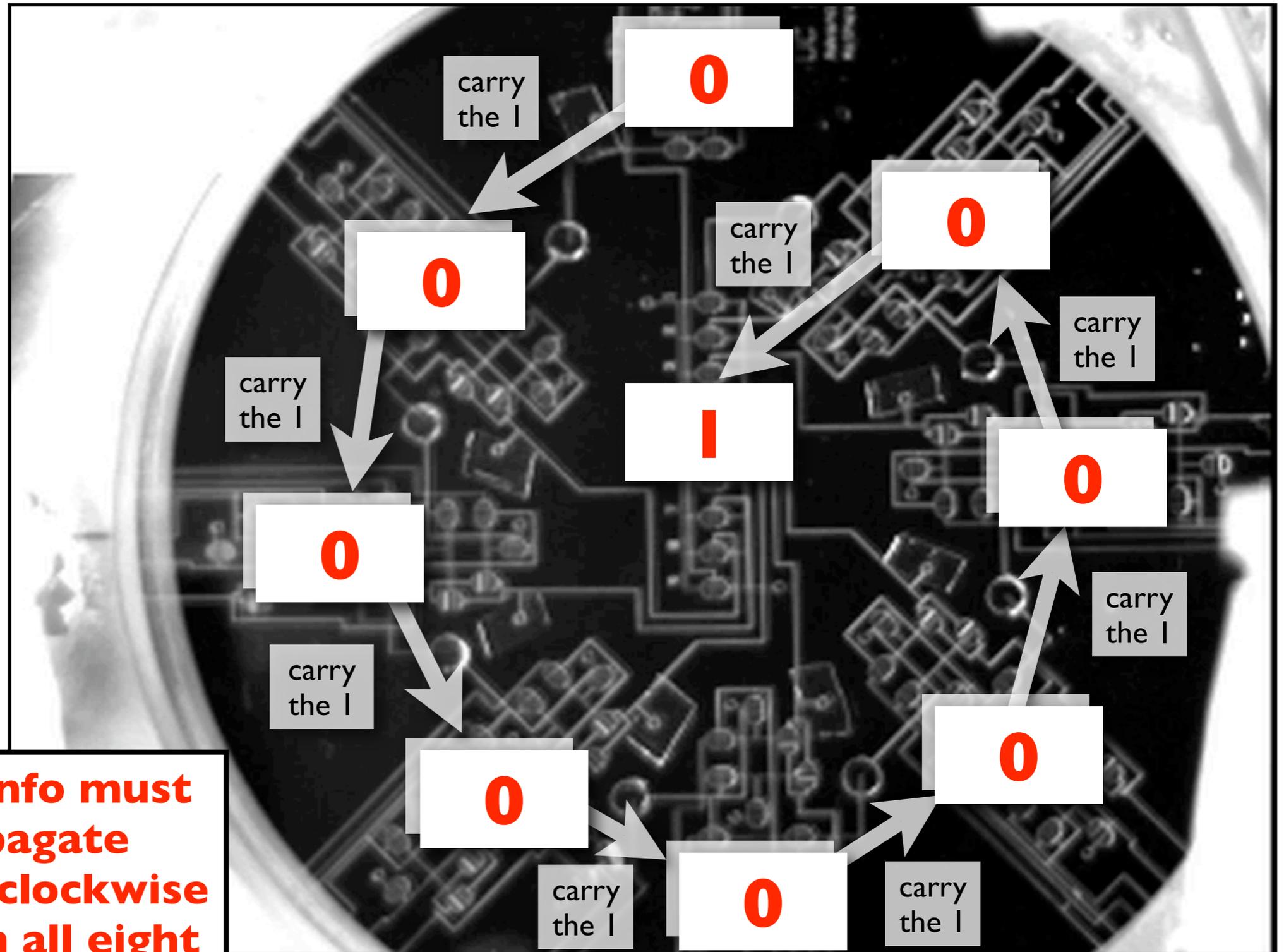
$$\begin{array}{r} \text{|||||} \\ + 00000001 \\ \hline 00 \end{array}$$



Eight-bit valve-based pneumatic adder

Eight **binary adders** linked in series to form an **eight-bit ripple carry adder**

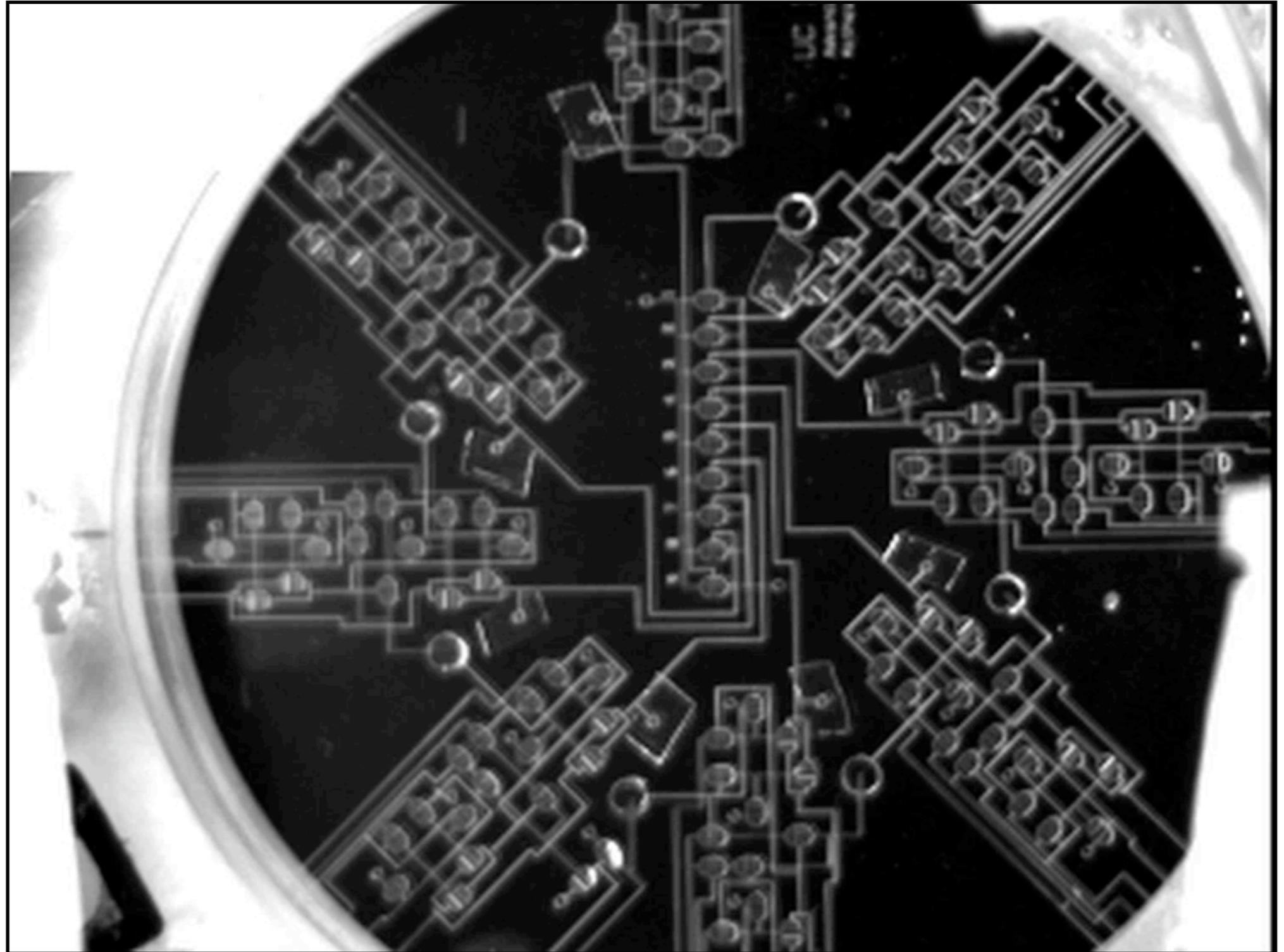
$$\begin{array}{r} \text{|||||} \\ + 00000001 \\ \hline 100000000 \end{array}$$



Carry info must propagate counterclockwise through all eight adders

Eight-bit valve-based pneumatic adder

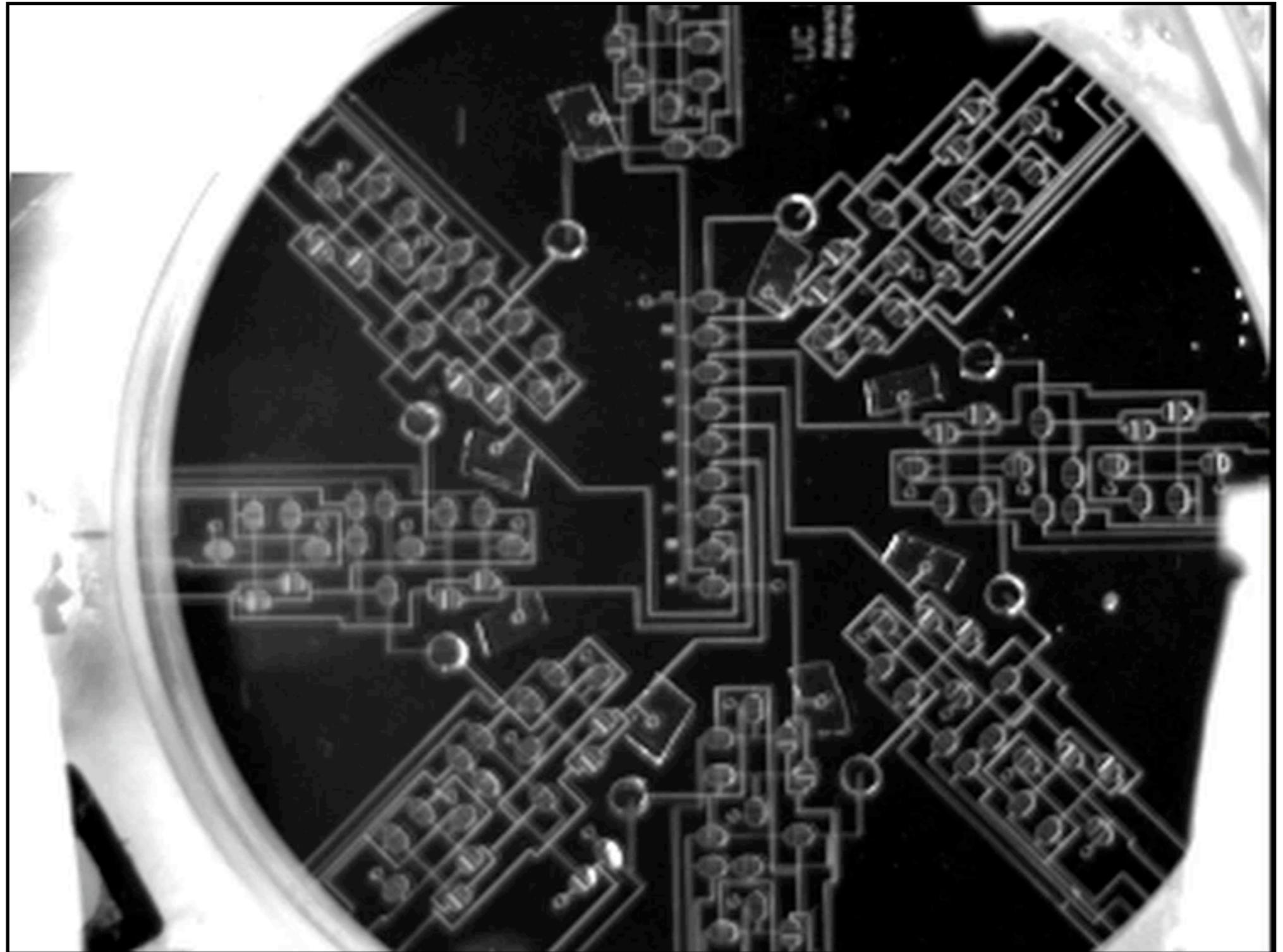
|||||||
+ 00000001



Eight-bit valve-based pneumatic adder

|||||||
+ 00000001

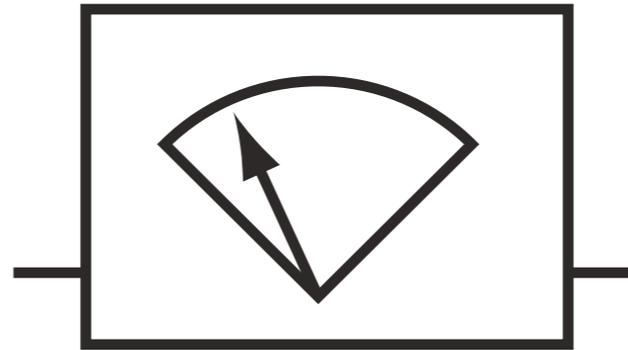
100000000



100 sums

	+	11111111	00000001	00000000	10101010	01010101
11111111						
01111111						
00111111						
01000001						
00100011						
00000001						
11001010						
11000010						
01010101						
10111100						
11100011						
11111110						
00111110						
10111011						
10110011						
00011010						
11100110						
01000101						
11010101						
00000101						

What do you want in a microfluidic readout component?



Readout

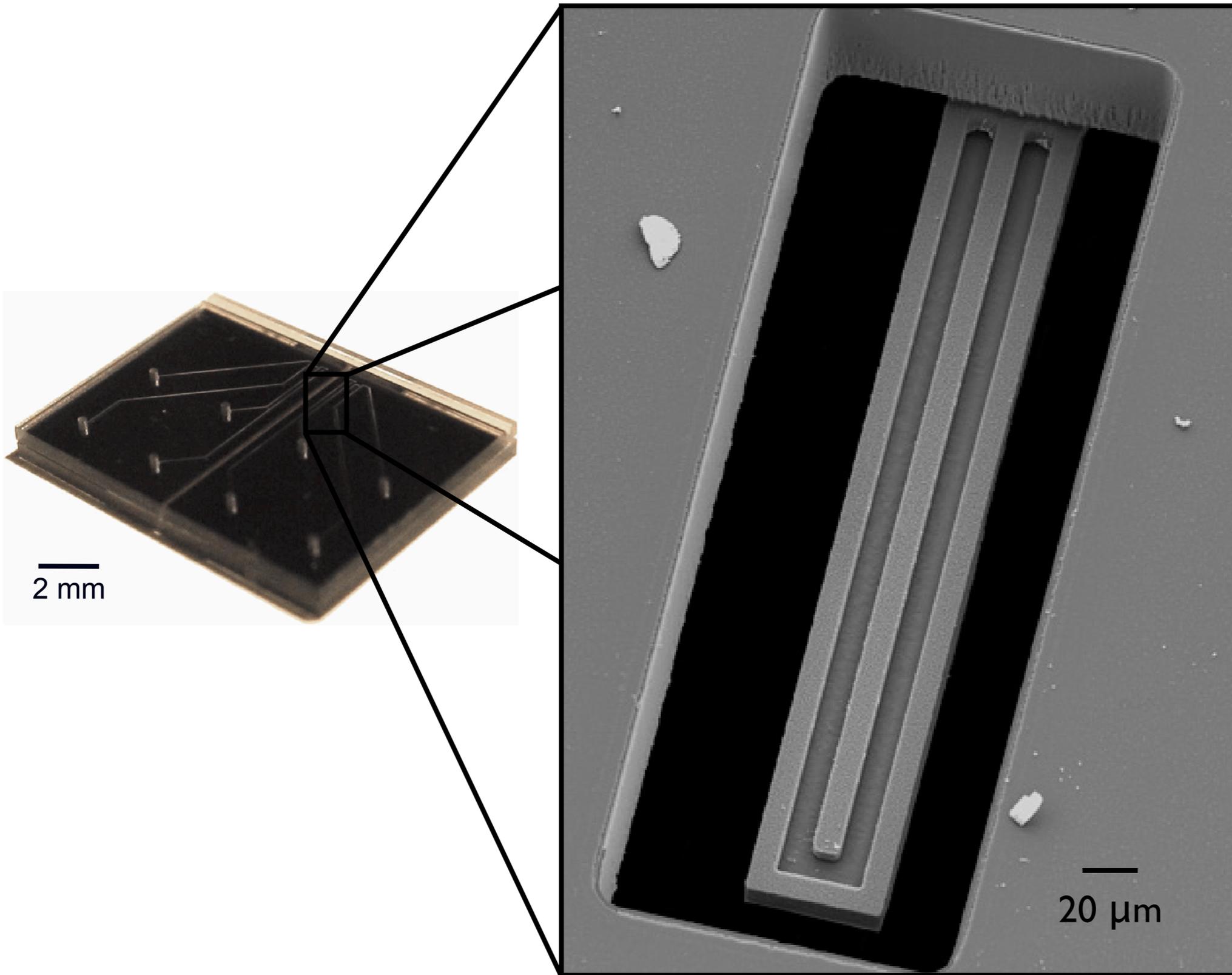
Doesn't require specific chemical properties like color, fluorescence, electrochemistry...

Doesn't change the fluid - just a passive "flow through"

Cleanable and reusable without cross-contamination

Many different modes of operation

The Suspended Microchannel Resonator (SMR)

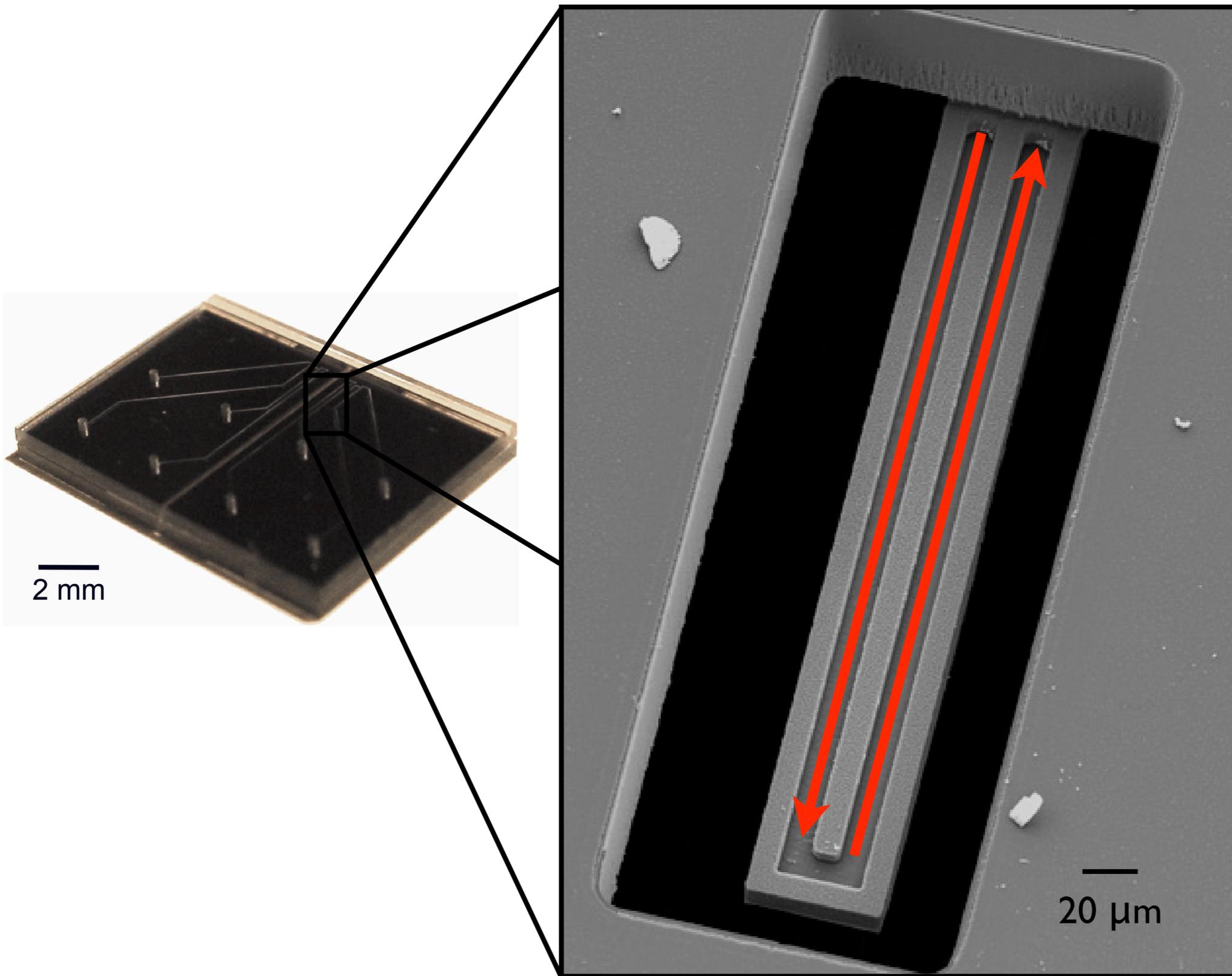


10 pL channel inside
a suspended silicon
cantilever

Resonant frequency
~200 kHz

Density of fluid
contents affects
resonant frequency

The Suspended Microchannel Resonator (SMR)



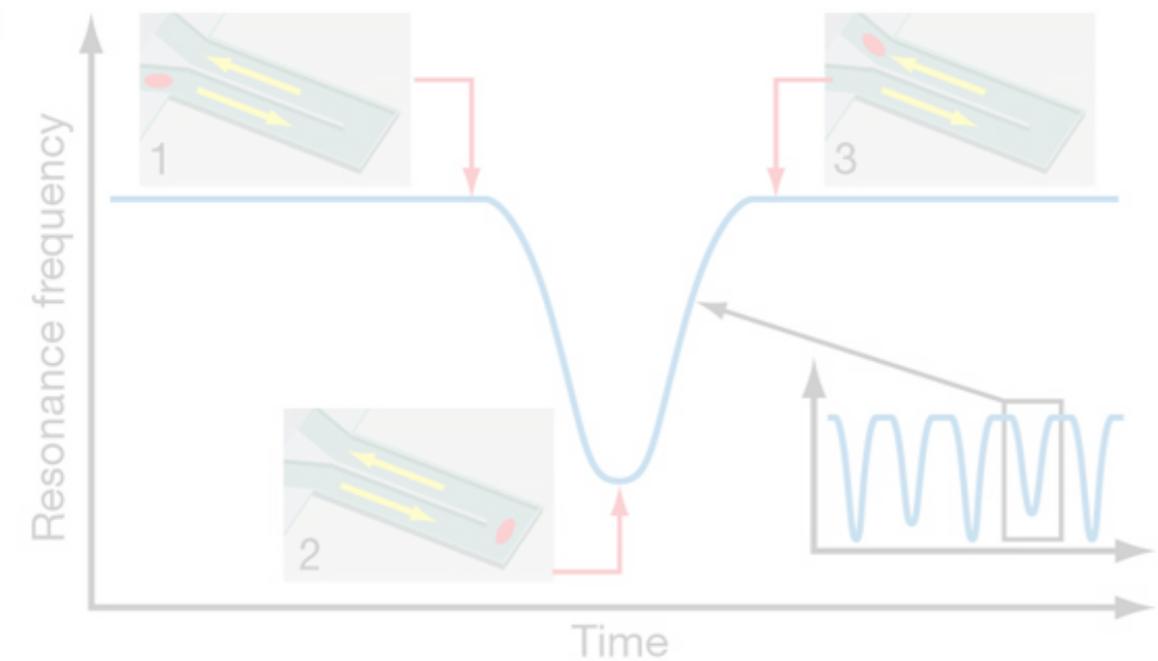
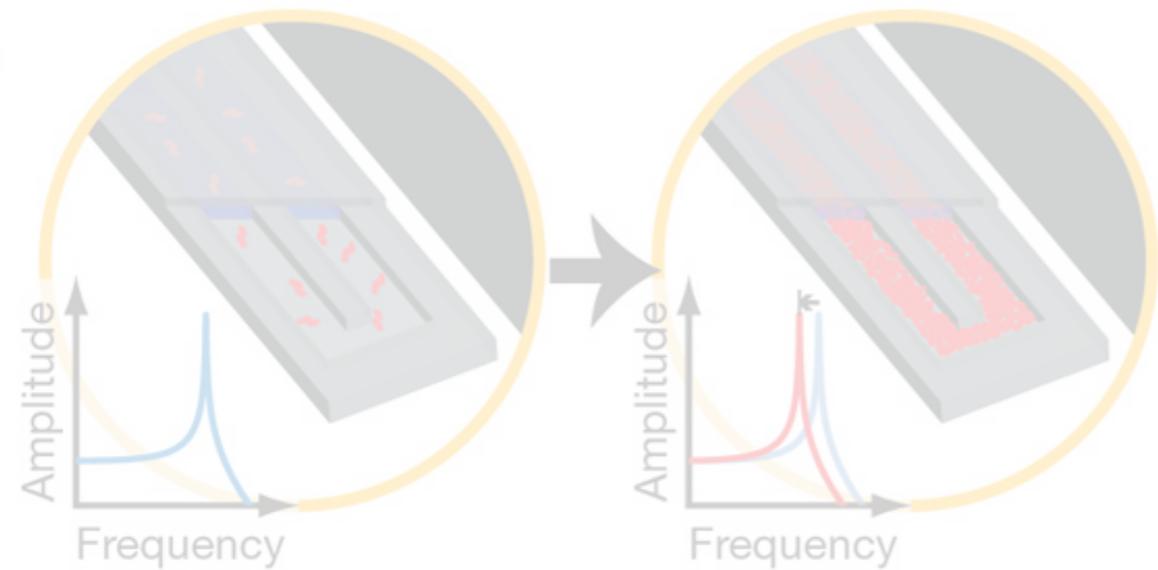
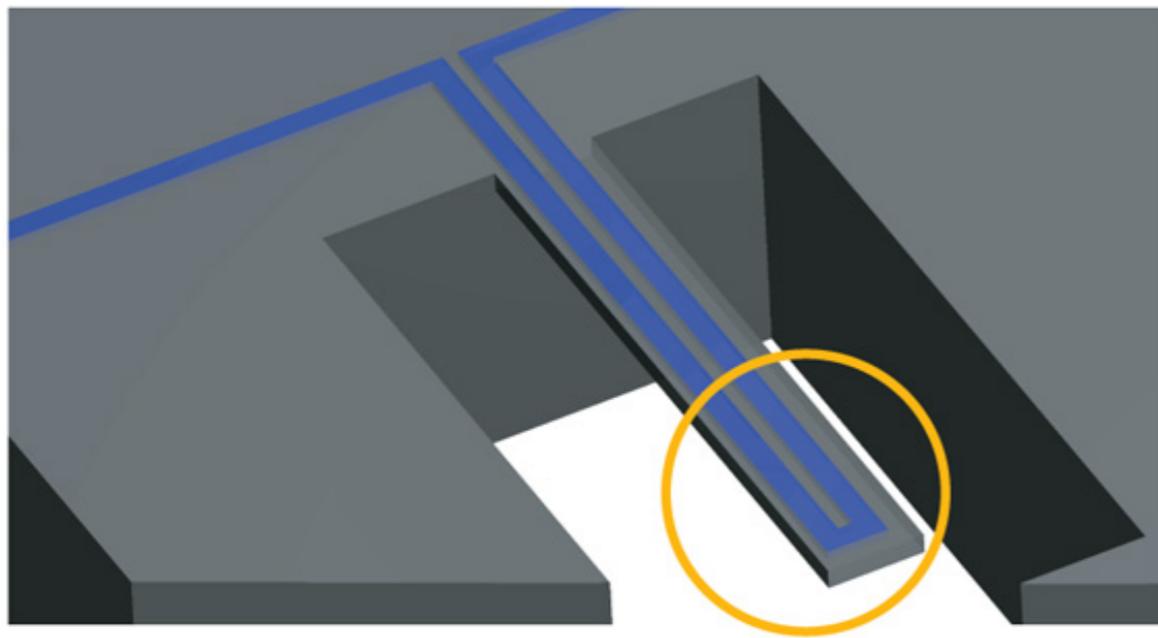
10 pL channel inside
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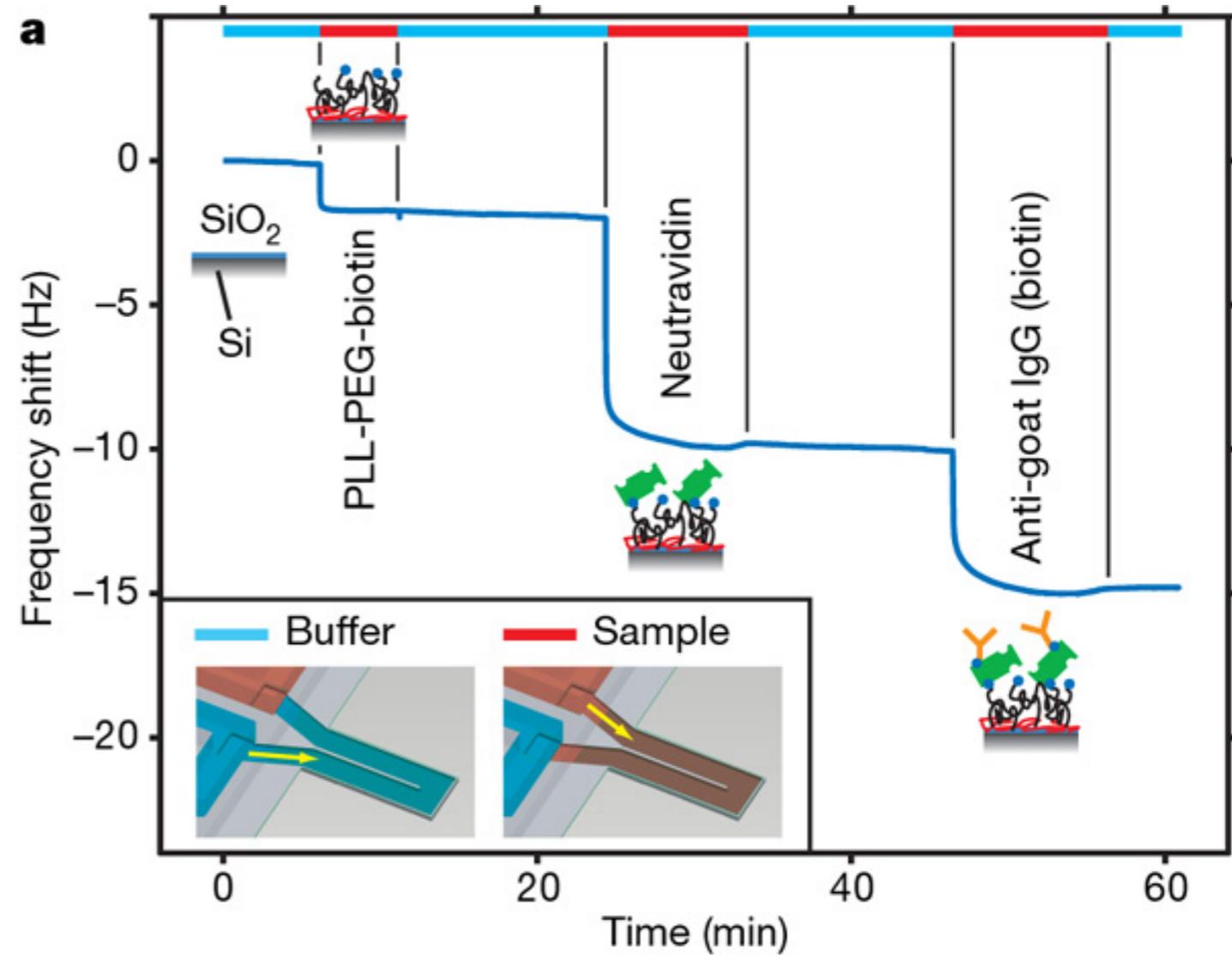
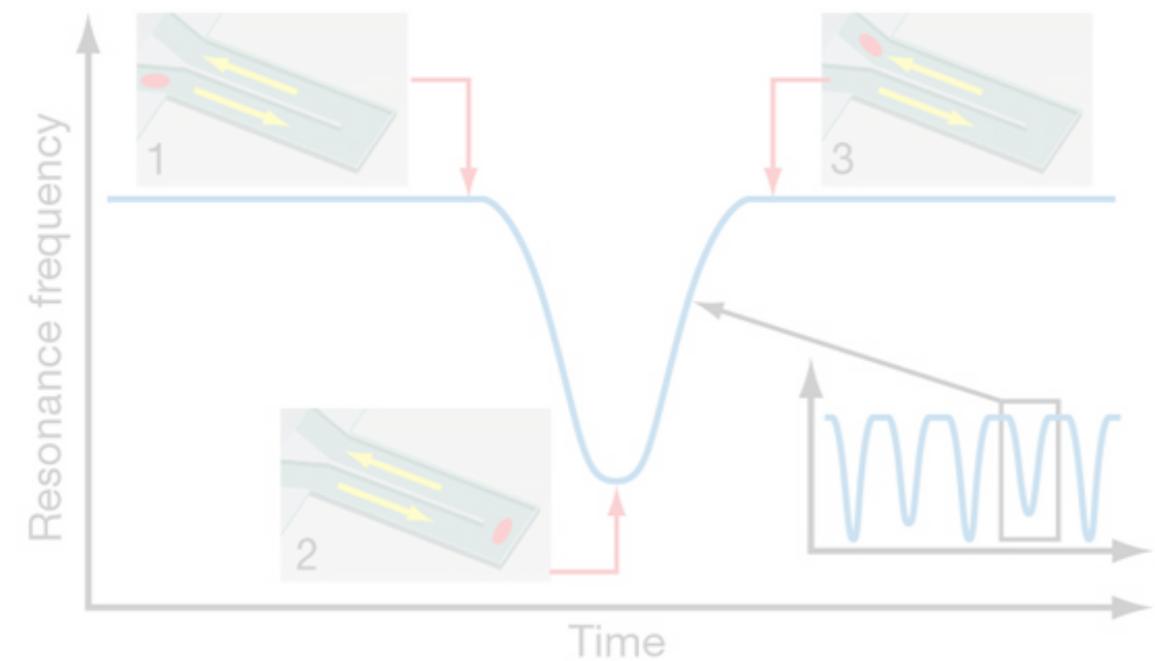
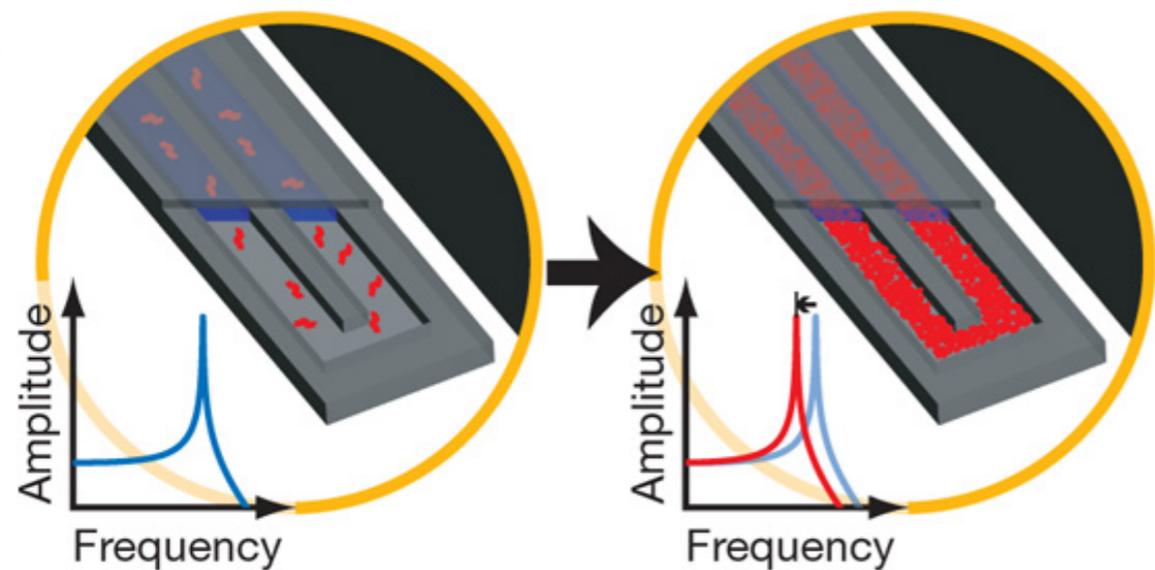
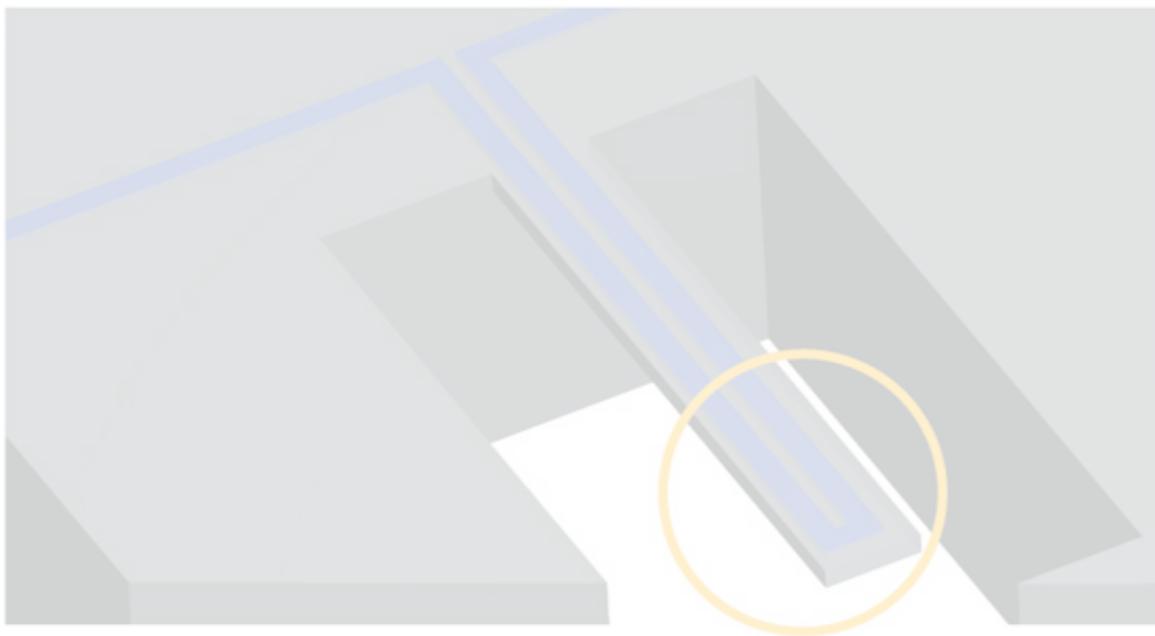
One SMR, many “programs”

- Bulk solution density measurement



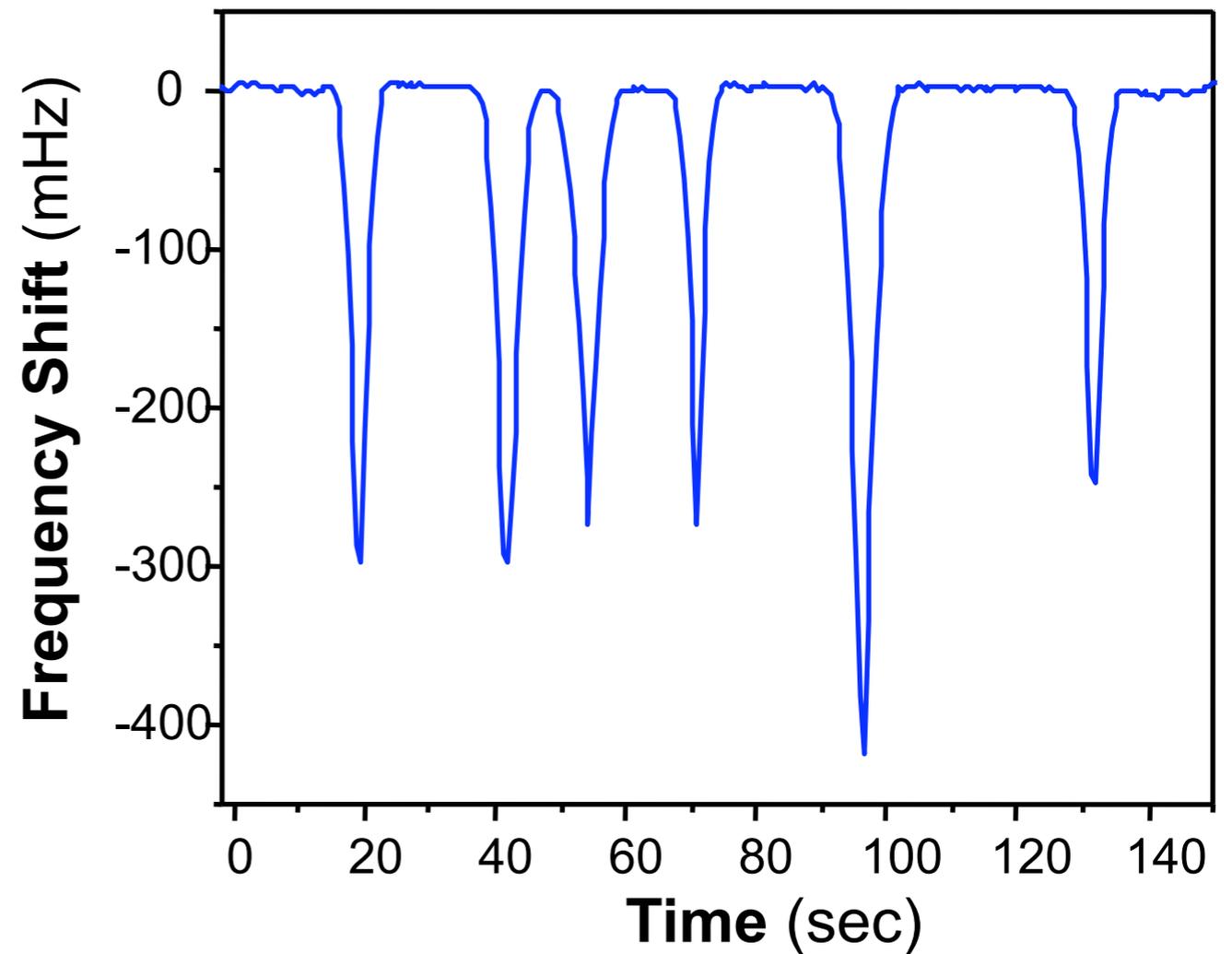
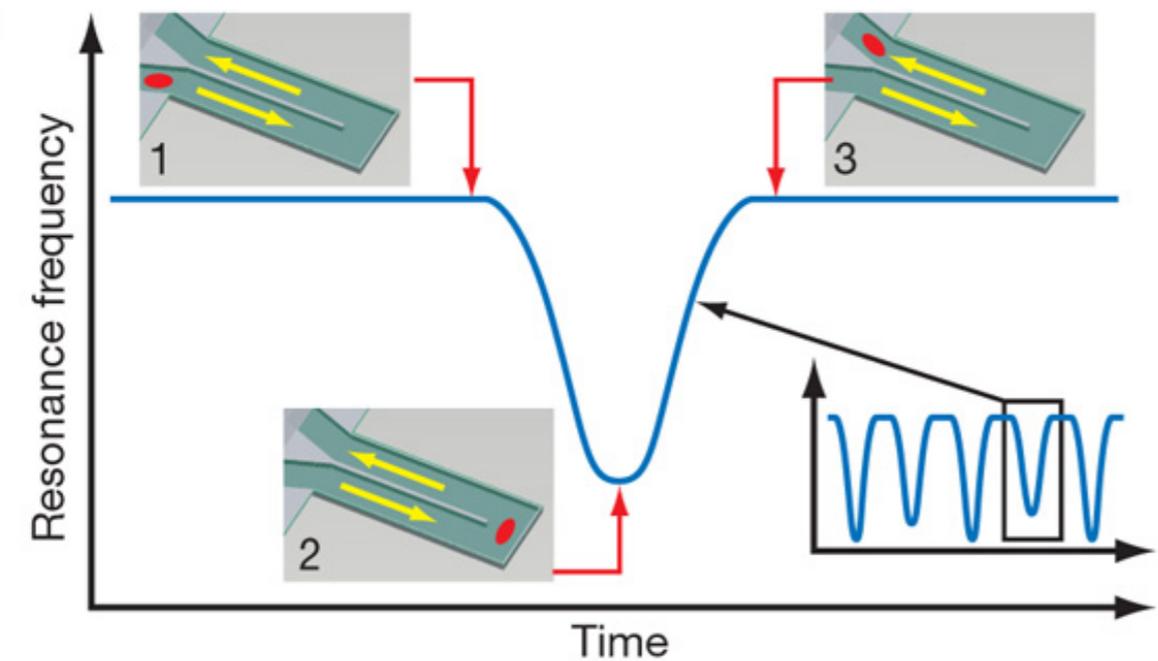
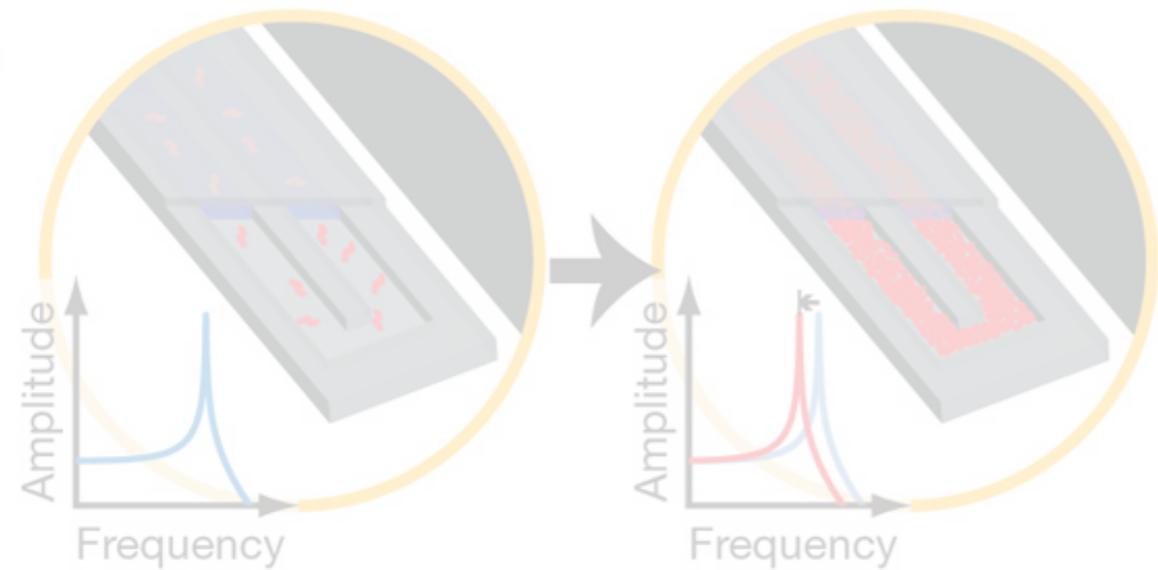
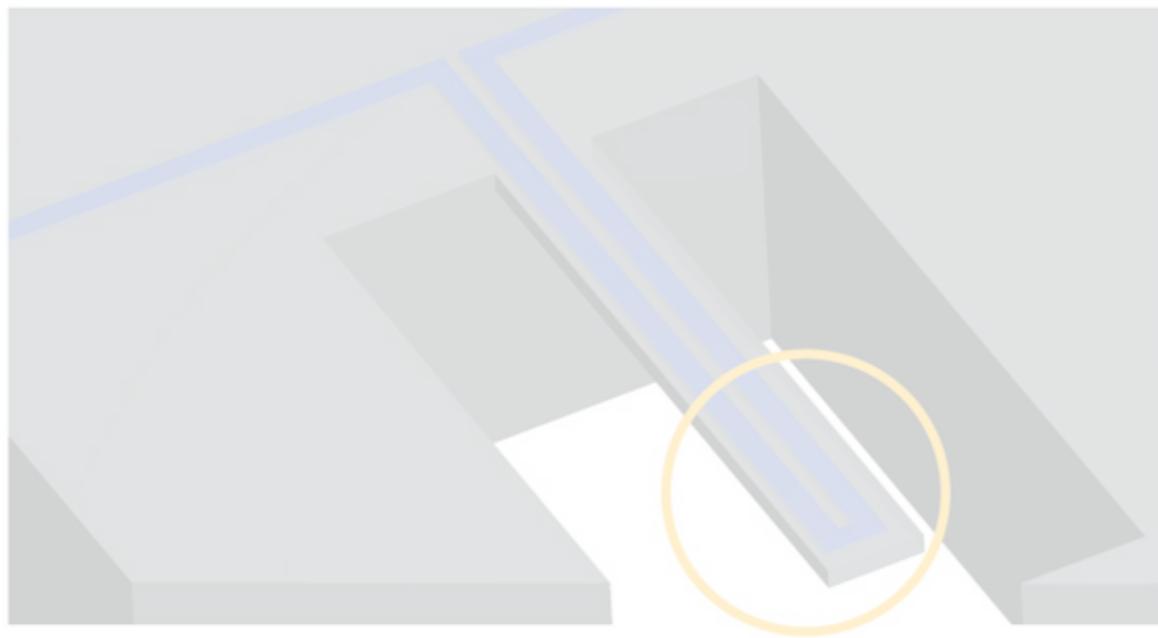
One SMR, many “programs”

- Bulk solution density measurement
- **Surface binding measurement**



One SMR, many “programs”

- Bulk solution density measurement
- Surface binding measurement
- **Particle counting and measurement**



T.P. Burg, M. Godin, S.M. Knudsen, W. Shen, G. Carlson, J.S. Foster, K. Babcock and S.R. Manalis, *Nature* **446**, 1066 (2007)

Conventional autosampler instrument

Internal volumes can take hundreds of microliters to prime and rinse

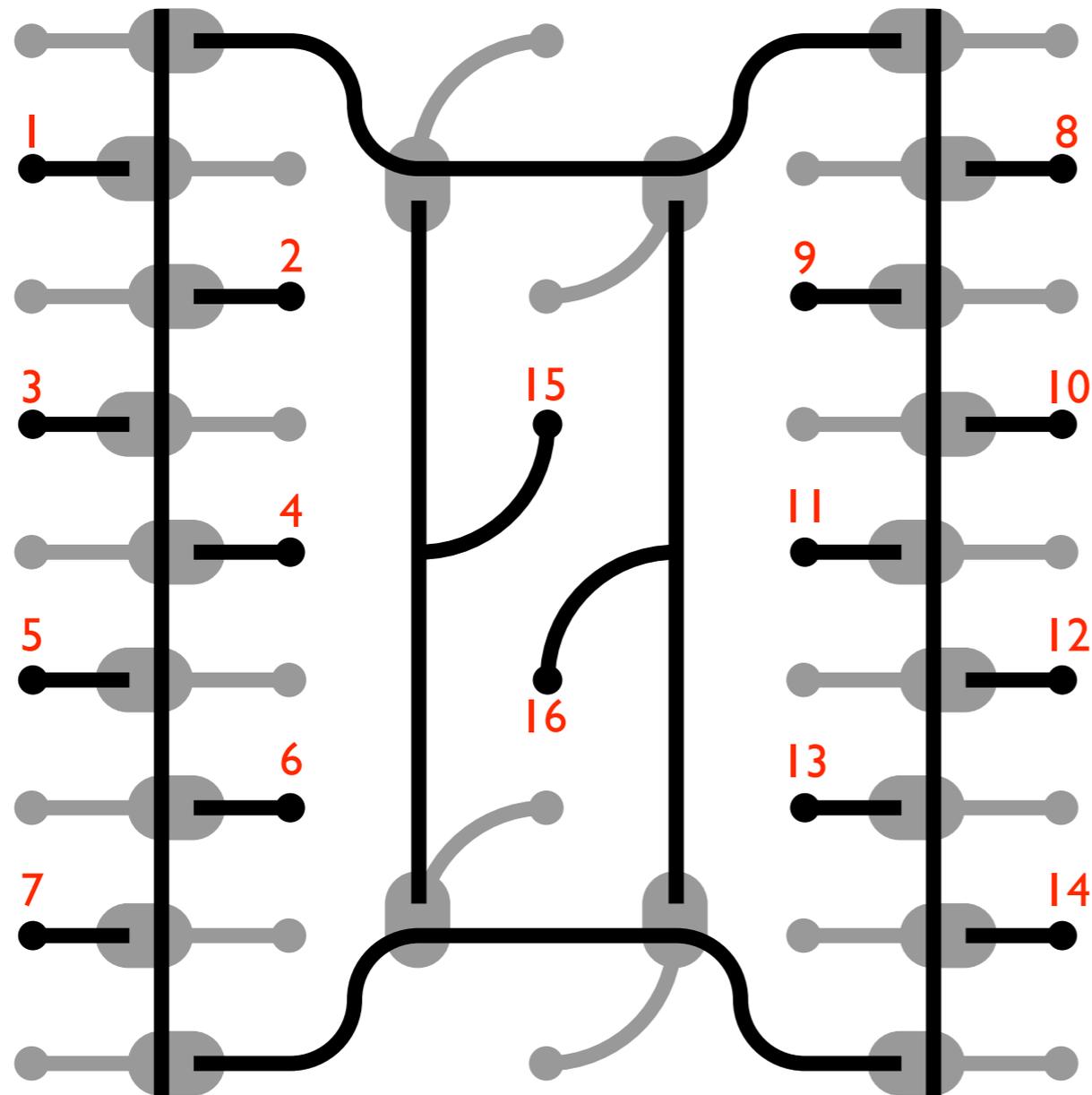
Cost, size, and power consumption precludes use in third-world or point-of-care applications



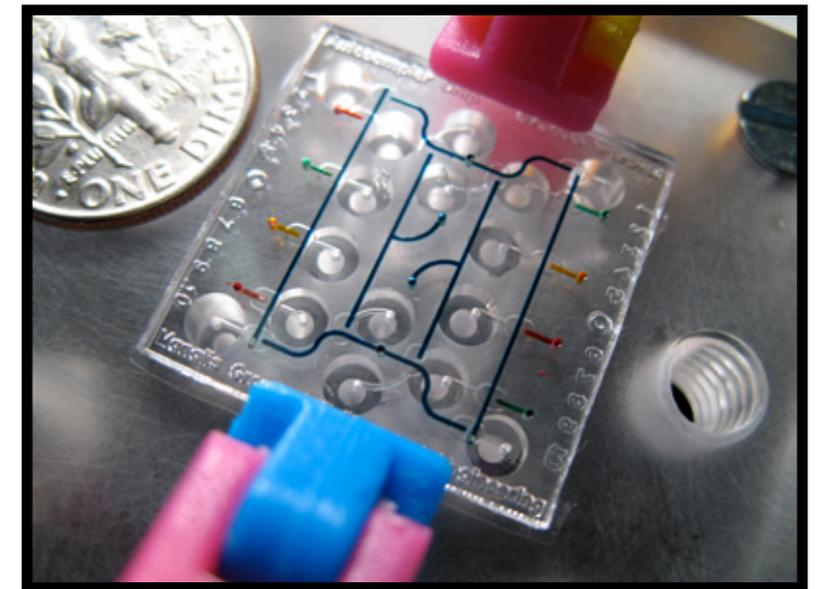
The autosampler chip

Autosampler Chip

070405 wgrover



Manalis Group, MIT Biological Engineering



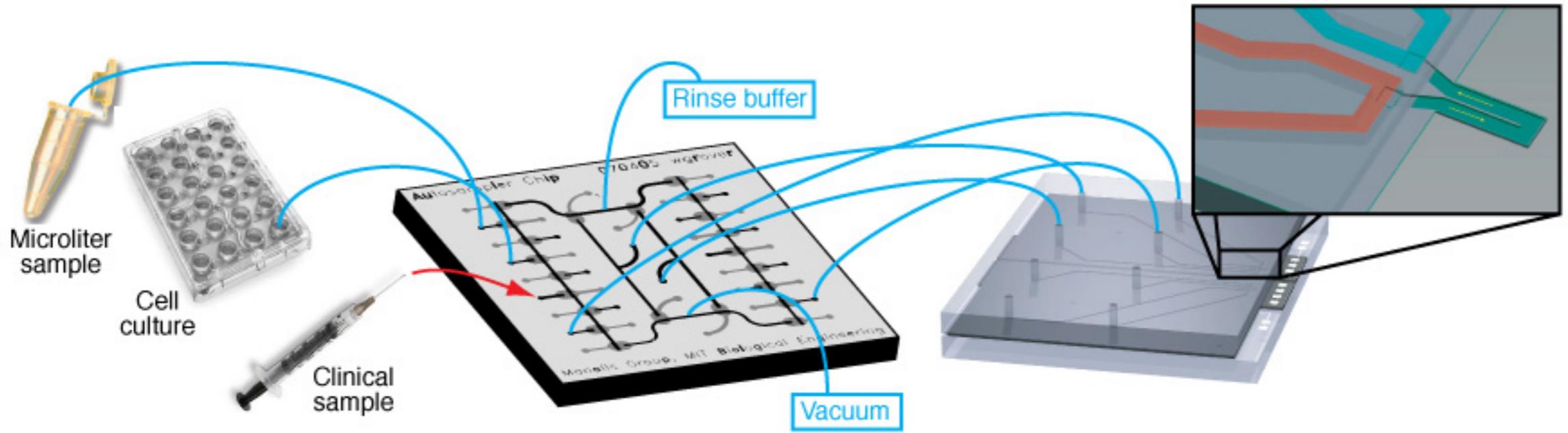
Glass-Teflon-glass valve structure for chemical inertness

Microfluidic switchboard: Fluid from any of 16 connections can be sent to any other connection

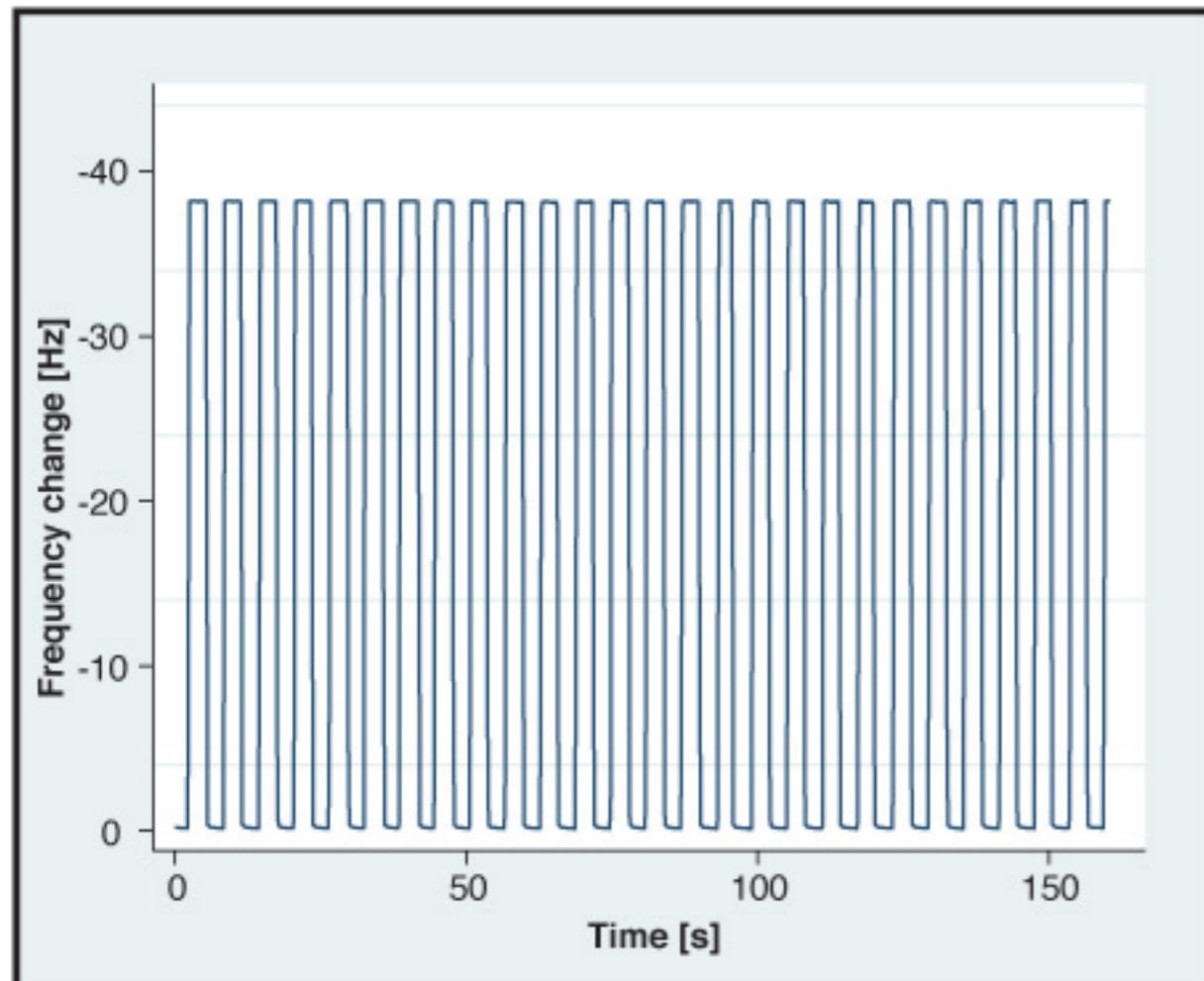
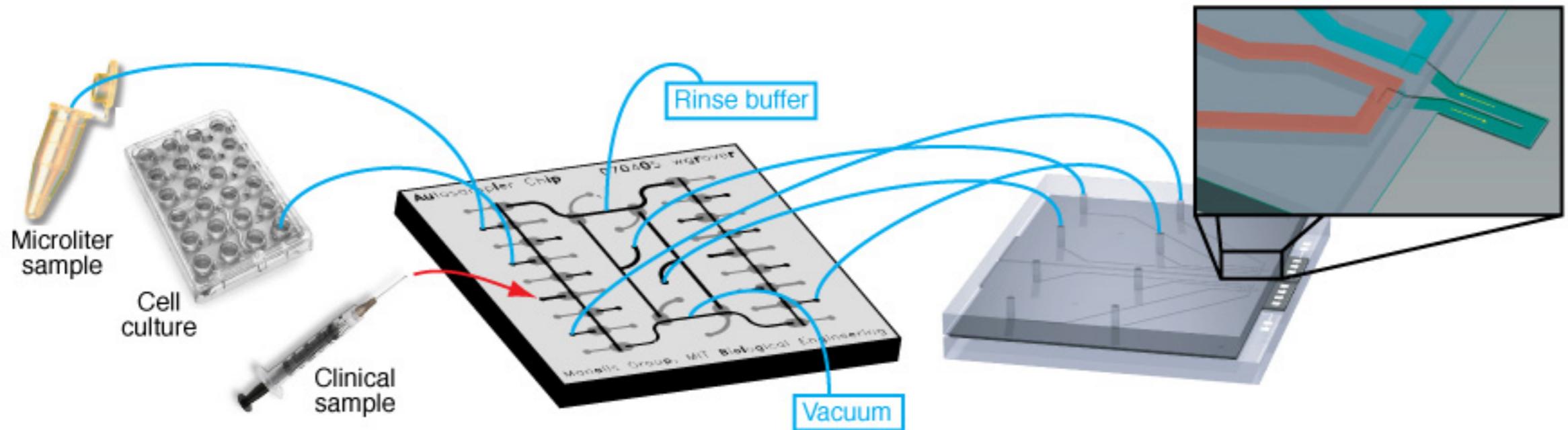
Internal volume is rinsable between operations

Instruction set: 240 different generic, useful operations to combine into an infinite variety of programs

Autosampler chip + SMR



Autosampler chip + SMR

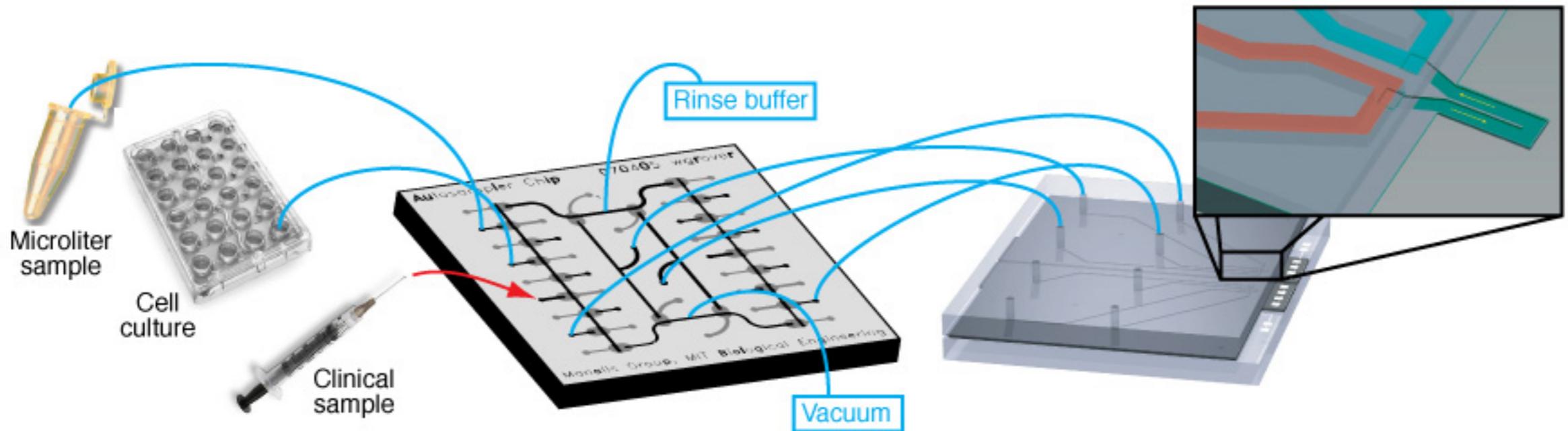


Rapid switching of fluid through SMR

Autosampler chip alternates between flowing water and 0.5x PBS (mostly 70 mM NaCl) across cantilever.

10 pL contents of cantilever replaced every **3 seconds**, requiring only **300 ms** per switch.

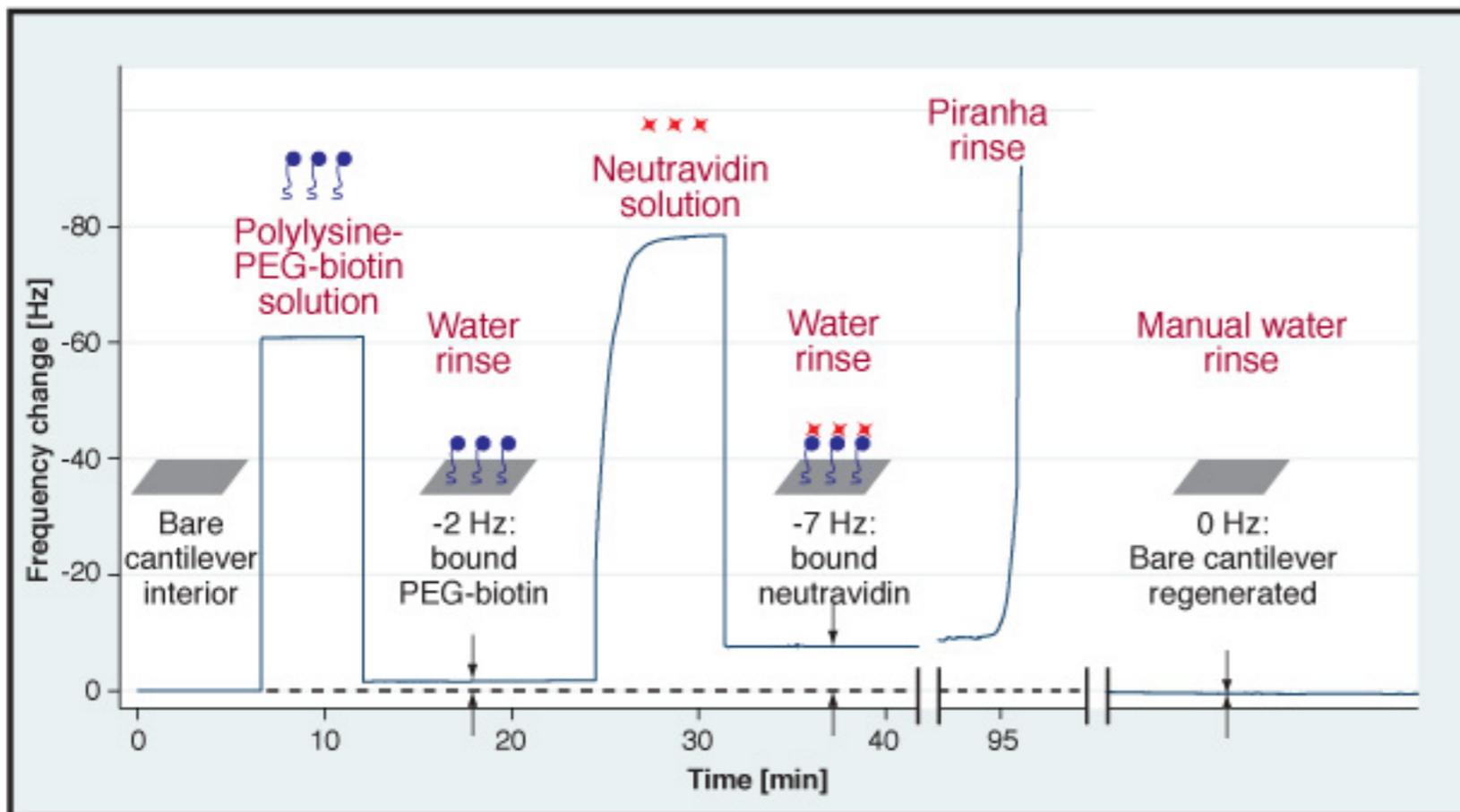
Autosampler chip + SMR



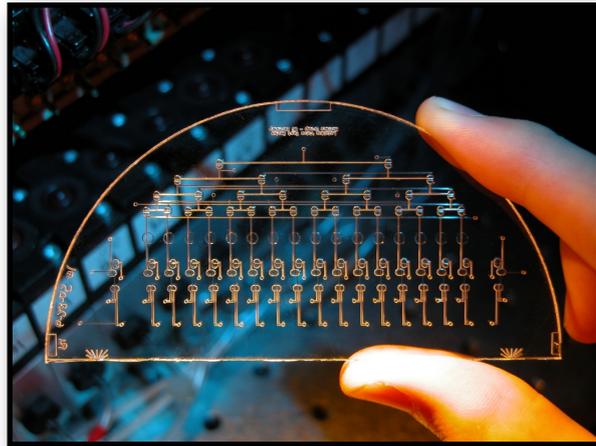
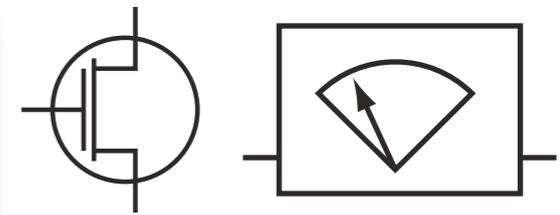
Automated building and removal of surface-bound multilayer

Frequency shifts after polylysine-PEG-biotin and neutravidin solutions confirm binding.

Return to 0 Hz baseline after autosampler chip delivers piranha (concentrated sulfuric acid and hydrogen peroxide)

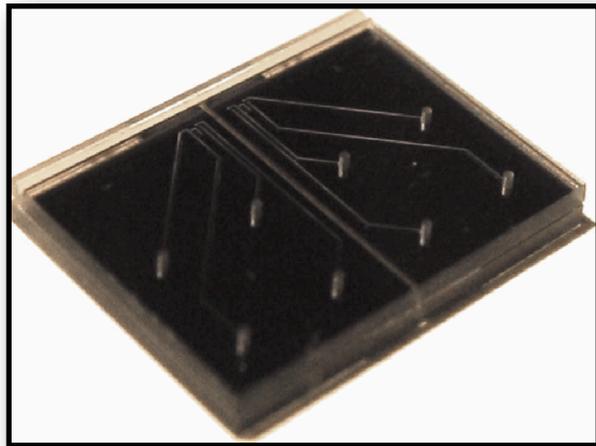


Standard toolkit of components (control, readout, etc.) that can be assembled into any useful circuit according to logical rules



Valve-based on-chip pneumatic logic

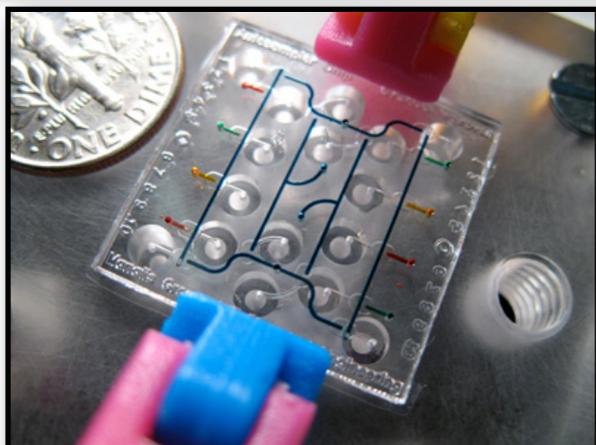
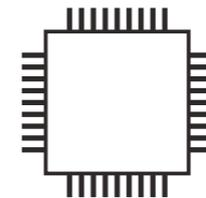
- n off-chip controllers: 2^{n-1} independent on-chip valves
- **1000** independent valves: only **11** off-chip controllers
- Possible because of normally-closed nature of valves
- \log_2 reduction in **\$, power, space** wasted by off-chip controllers
- 8-bit adder suggests any digital logic circuit is possible



Suspended Microchannel Resonator sensor

- Single component, **many different modes of operation**
- 100 ng/cm^3 fluid density resolution
- 10 pg/cm^2 surface mass resolution
- 0.25 fg particle mass resolution

Processors that can run many different programs using the same generic hardware



Autosampler chip

- Fraction of cost, size, power of conventional autosampler
- Chemically generic
- 240 instructions, infinite programs

Acknowledgments



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Teris Liu

Dr. Alison Skelley (now at Massachusetts Institute of Technology)

Robin Ivester

Erik Jensen

Prof. Richard Mathies

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Berkeley Center for Analytical Biotechnology



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Massachusetts Institute of Technology

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Dr. Scott Knudsen

Dr. Thomas Burg

Marcio von Muhlen

Prof. Scott Manalis

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