Programmable Microfluidics

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Harvard Medical School

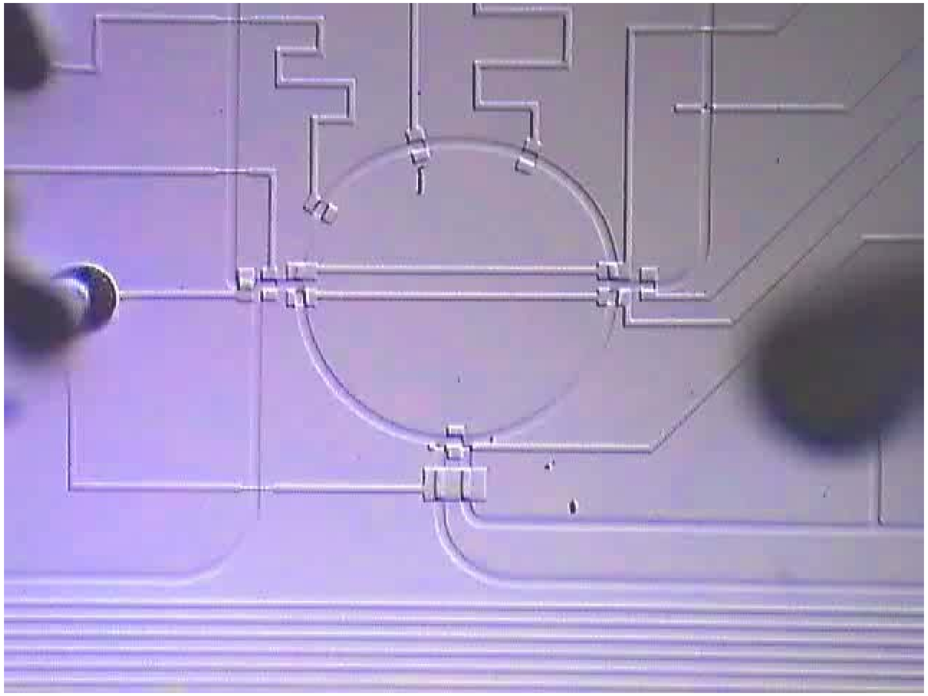
Prof. Mark Johnson

David Potter

Colorado Center for Reproductive Medicine

Microfluidic Chips

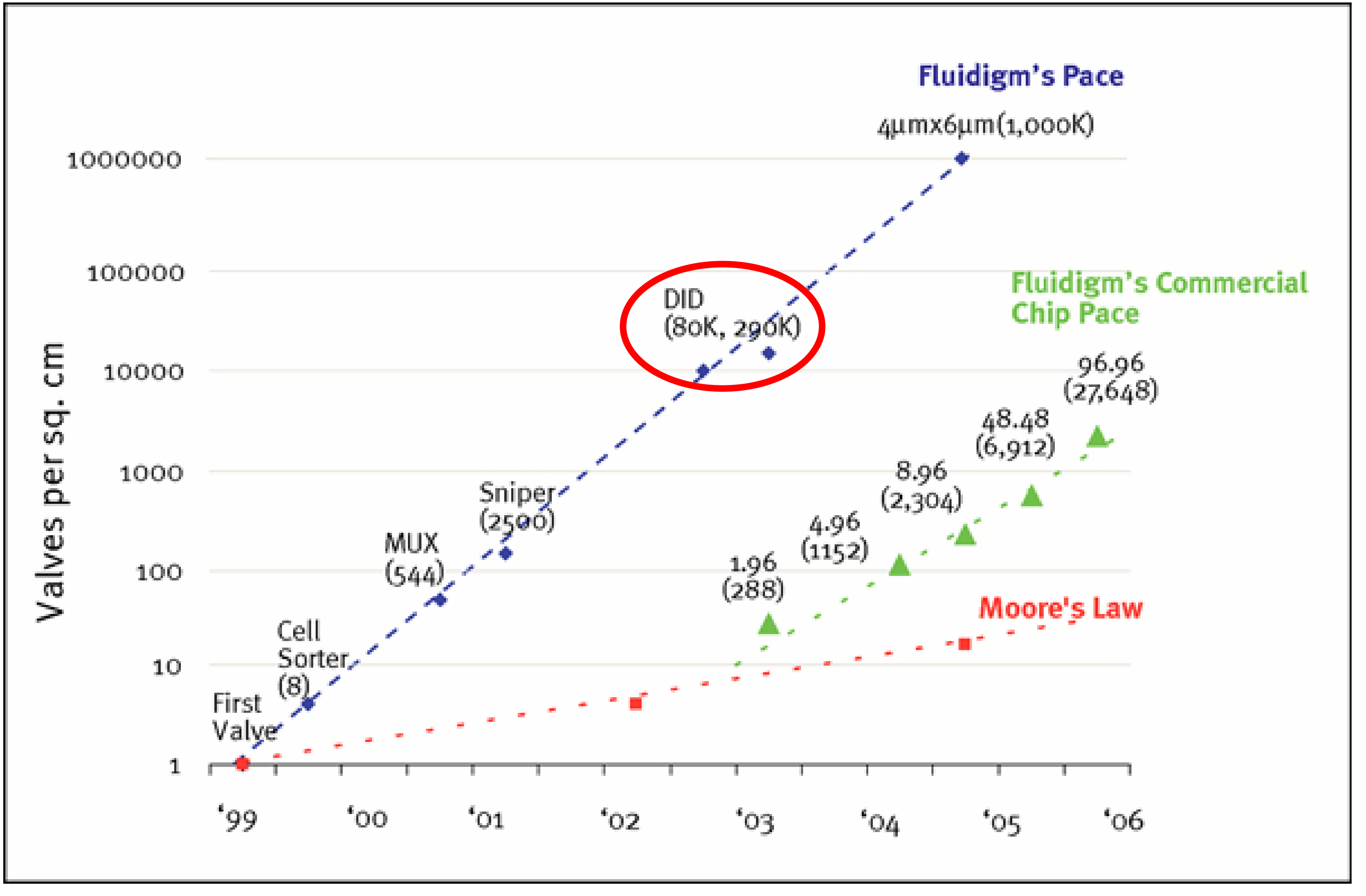
- **Idea: a whole biology lab on a single chip**
  - Input/output
  - **Sensors**: pH, glucose, temperature, etc.
  - **Actuators**: mixing, PCR, electrophoresis, cell lysis, etc.



- **Benefits:**
  - Small sample volumes
  - High throughput
  - Geometrical manipulation
- **Applications:**
  - Biochemistry - Cell biology
  - Biological computing

[Livstone/Landweber] [van Noort] [Grover/Mathies] [McCaskill] [Gehani/Reif] [Farfel/Stefanovic] [Somei/Kaneda/Fujii/Murata]

Moore's Law of Microfluidics: Valve Density Doubles Every 4 Months



Source: Fluidigm Corporation (http://www.fluidigm.com/images/mlaw_lg.jpg)

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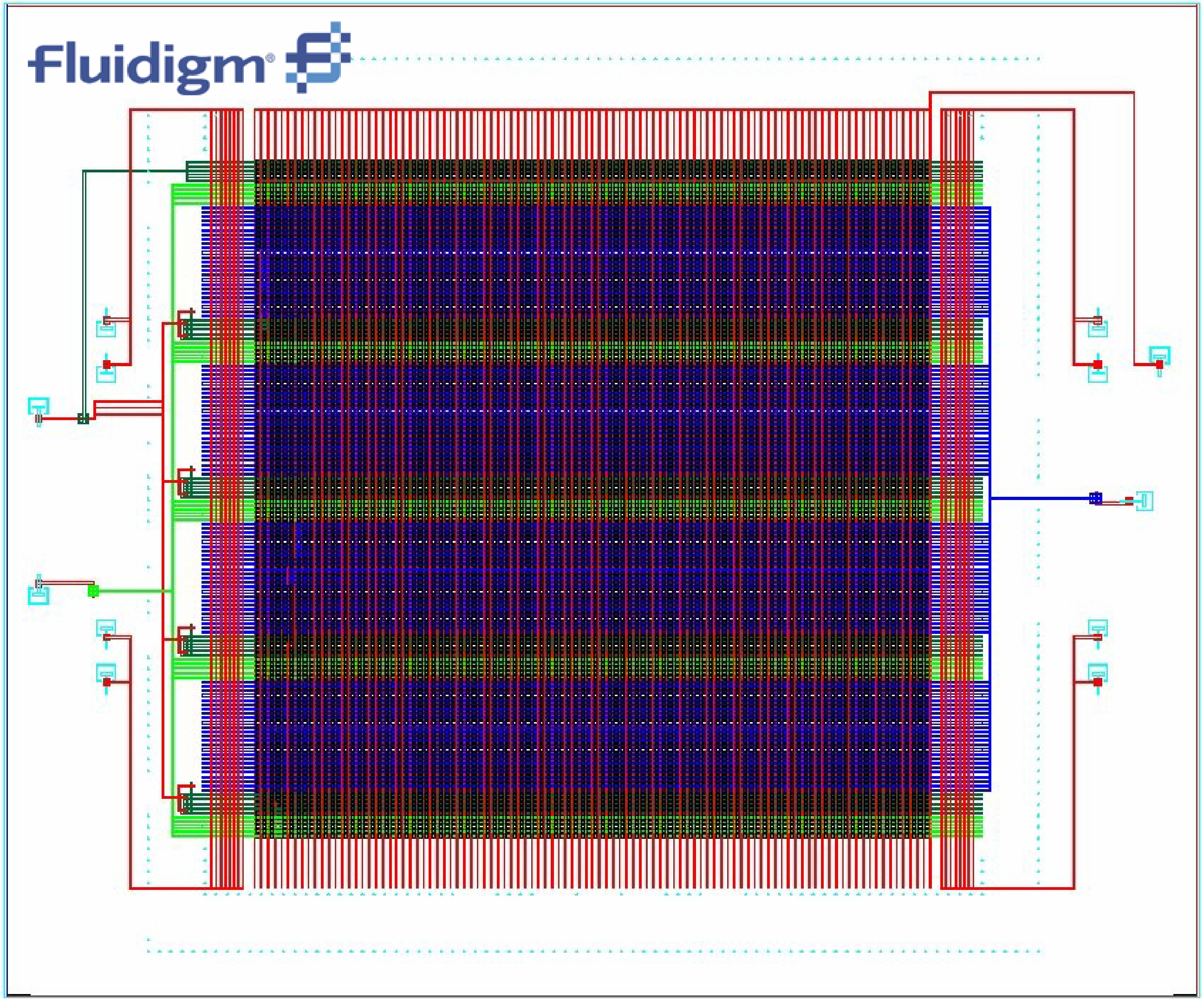
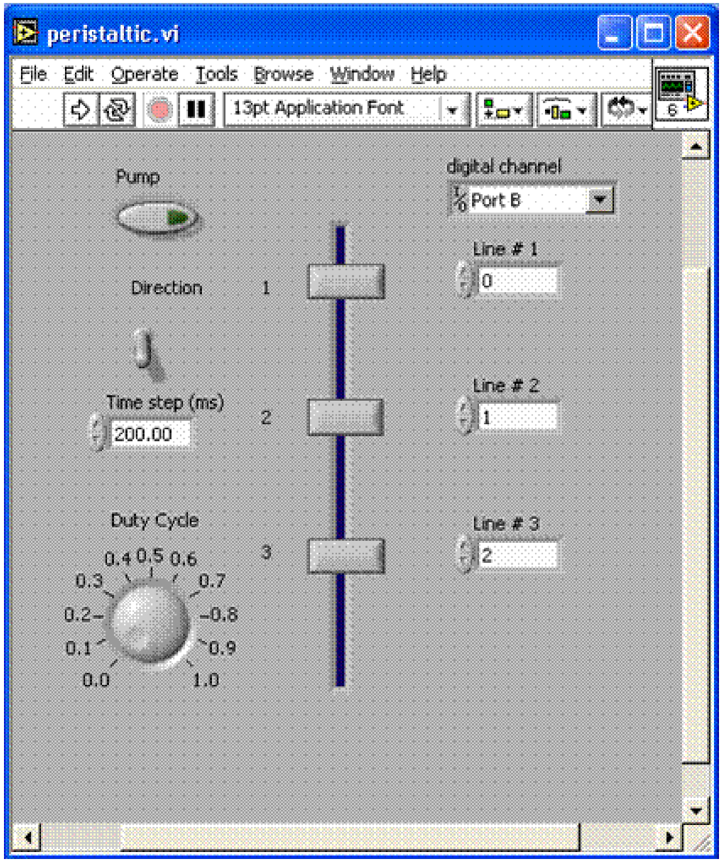
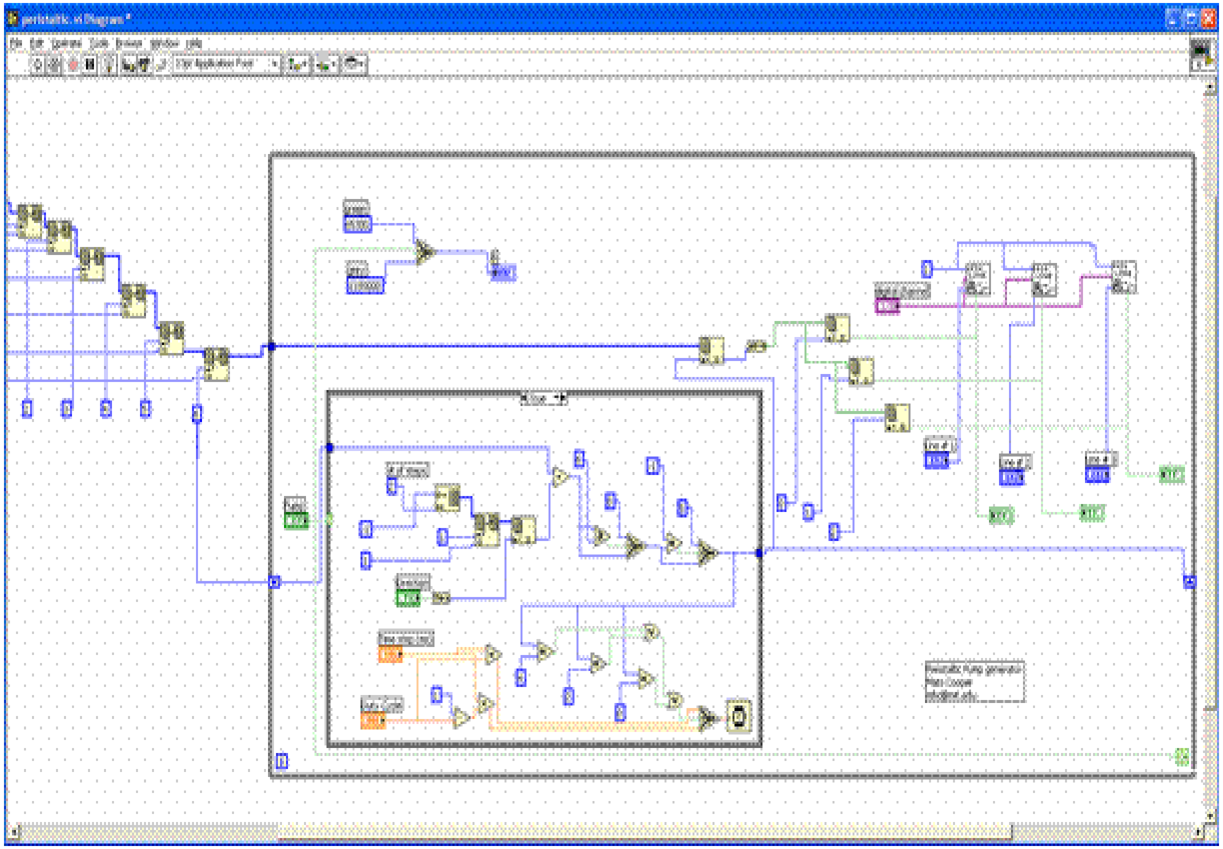


Source: Fluidigm Corporation (http://www.fluidigm.com/didIFC.htm)

Current Practice: Expose Gate-Level Details to Users



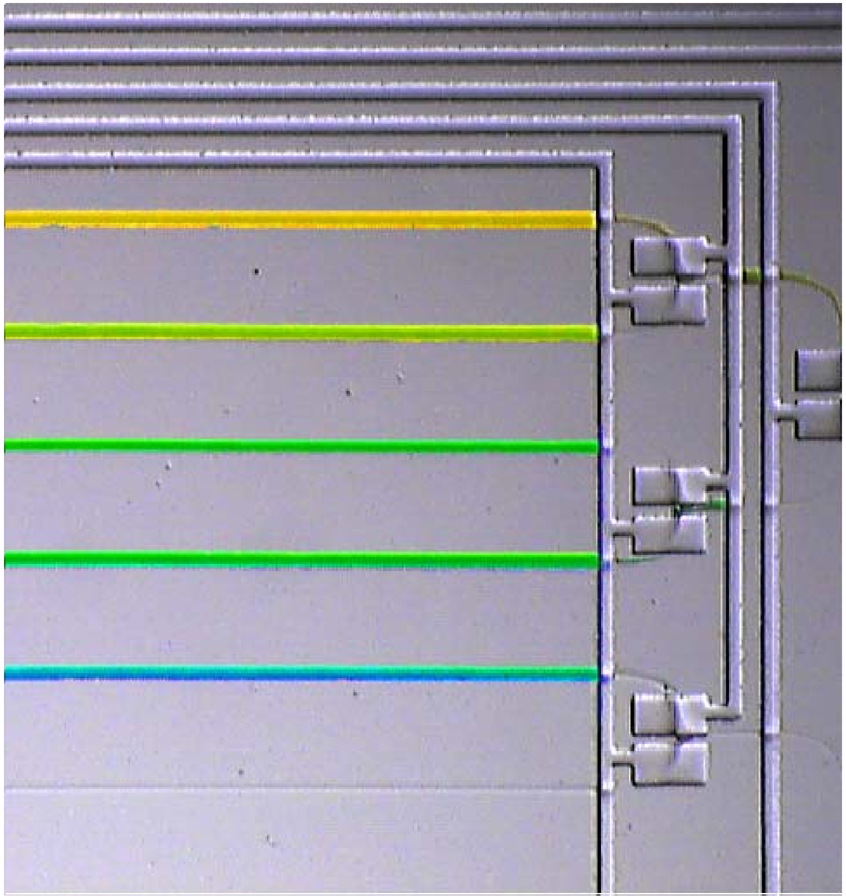


- **Manually map experiment to the valves of the device**
  - Using Labview or custom C interface
  - Given a new device, start over and do mapping again

Our Approach: "Write Once, Run Anywhere"

- **Example: Gradient generation**

```
Fluid yellow = input (0);
Fluid blue = input(1);
for (int i=0; i<=4; i++) {
   mix(yellow, 1-i/4, blue, i/4);
}
```



450 Valve Operations

- **Hidden from programmer:**
  - Location of fluids
  - Details of mixing, I/O
  - Logic of valve control
  - Timing of chip operations

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```
setValve(0, HIGH);   setValve(1, HIGH);
setValve(2, LOW);    setValve(3, HIGH);
setValve(4, LOW);    setValve(5, LOW);
setValve(6, HIGH);   setValve(7, LOW);
setValve(8, LOW);    setValve(9, HIGH);
setValve(10, LOW);   setValve(11, HIGH);
setValve(12, LOW);   setValve(13, HIGH);
setValve(14, LOW);   setValve(15, HIGH);
setValve(16, LOW);   setValve(17, LOW);
setValve(18, LOW);   setValve(19, LOW);
wait(2000);
setValve(14, HIGH);  setValve(2, LOW);
wait(1000);
setValve(4, HIGH);   setValve(12, LOW);
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setValve(19, LOW);
wait(2000);
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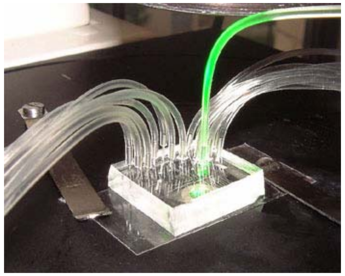
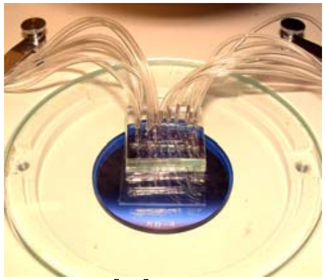
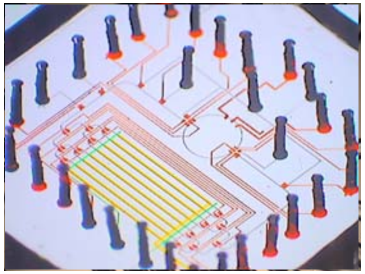
Fluidic Abstraction Layers

Protocol Description Language
- readable code with high-level mixing ops

Fluidic Instruction Set Architecture (ISA)
- primitives for I/O, storage, transport, mixing


chip 1


chip 2


chip 3

Fluidic Hardware Primitives
- valves, multiplexers, mixers, latches

Silicon Analog

C

x86

Pentium III,
Pentium IV

transistors,
registers, …

Fluidic Abstraction Layers

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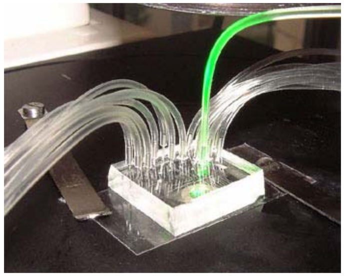
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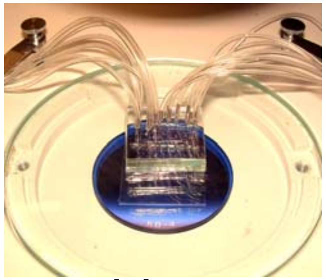
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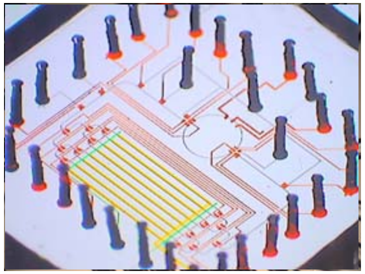
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Fluidic Hardware Primitives
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- **Benefits:**
  - Division of labor
  - Portability
  - Scalability
  - Expressivity

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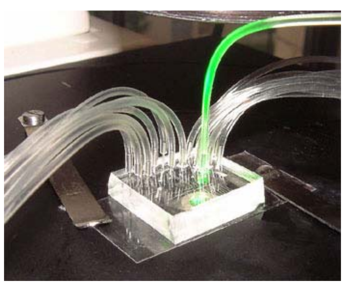
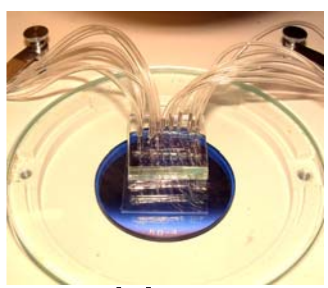

chip 1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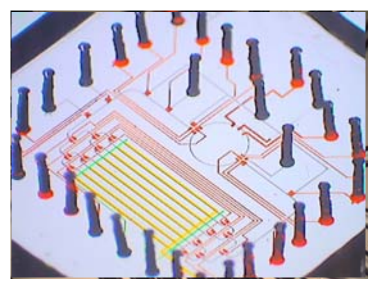
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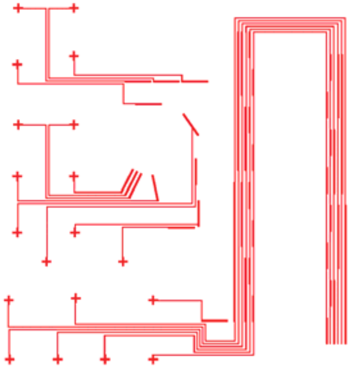
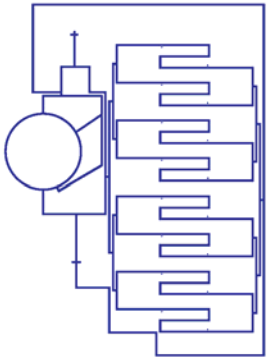
Primitive 1: A Valve (Quake et al.)



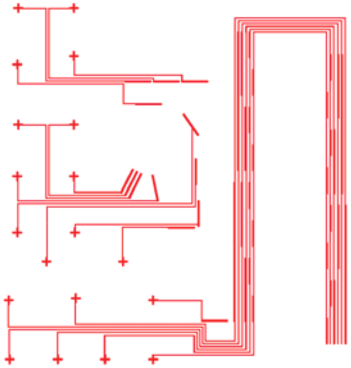
Control
Layer

0. Start with mask of channels



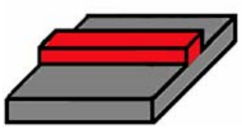
Flow
Layer

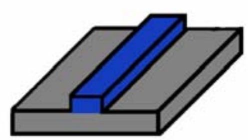
Primitive 1: A Valve (Quake et al.)

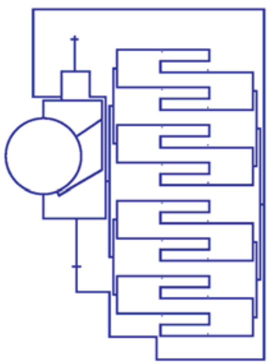


Control
Layer

1. Deposit pattern on silicon wafer







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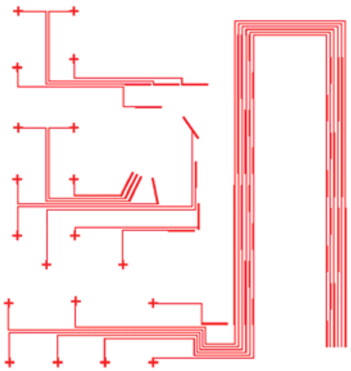
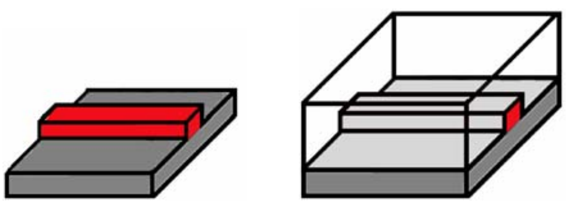
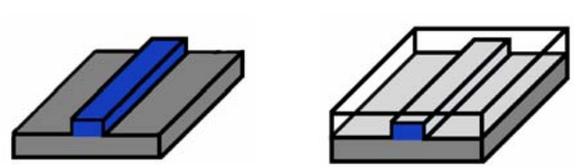


Control Layer

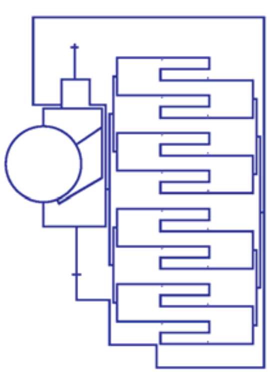
2. Pour PDMS over mold
   - polydimexylsiloxane: “soft lithography”



Thick layer (poured)



Thin layer (spin-coated)



Flow Layer

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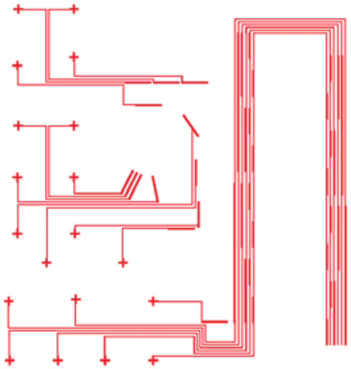
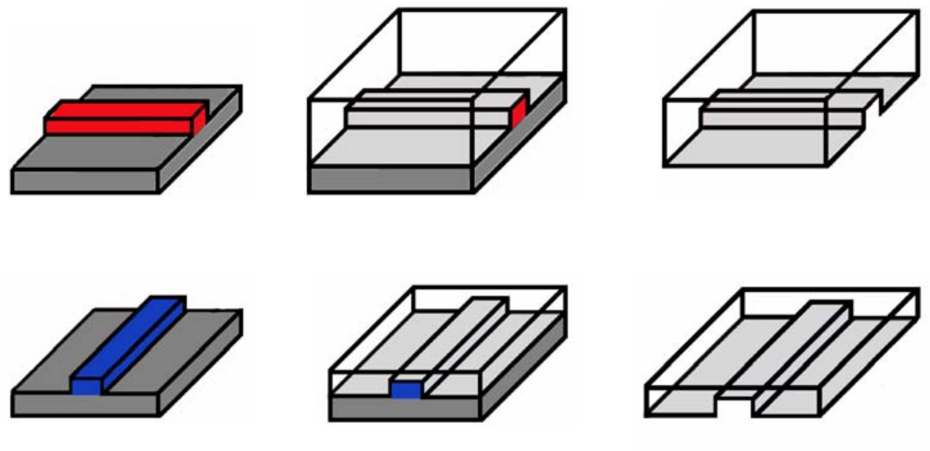
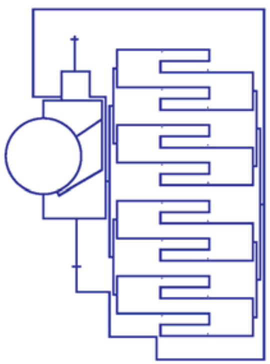


Control Layer

3. Bake at 80° C (primary cure), then release PDMS from mold





Flow Layer

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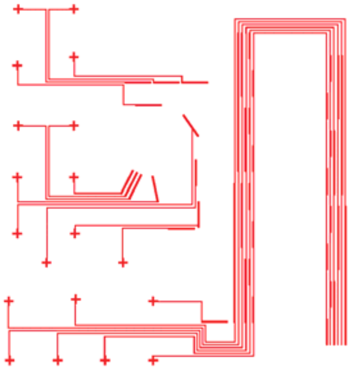
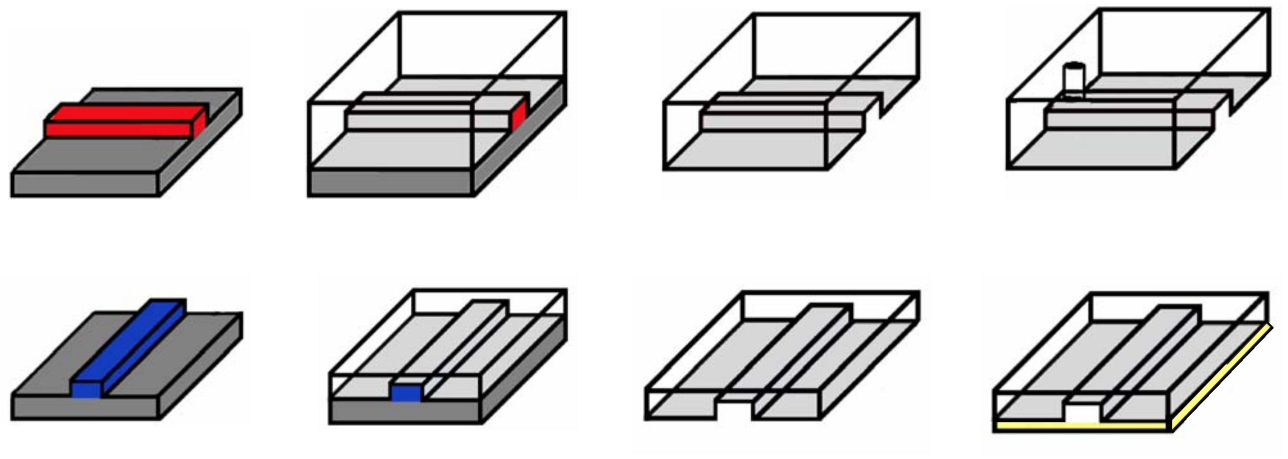
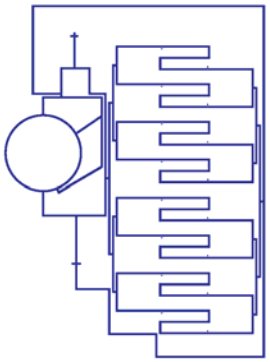


Control
Layer

4a. Punch hole in control channel
4b. Attach flow layer to glass slide





Flow
Layer

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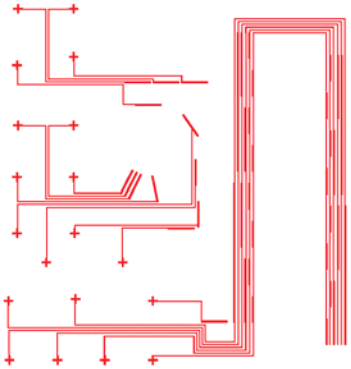
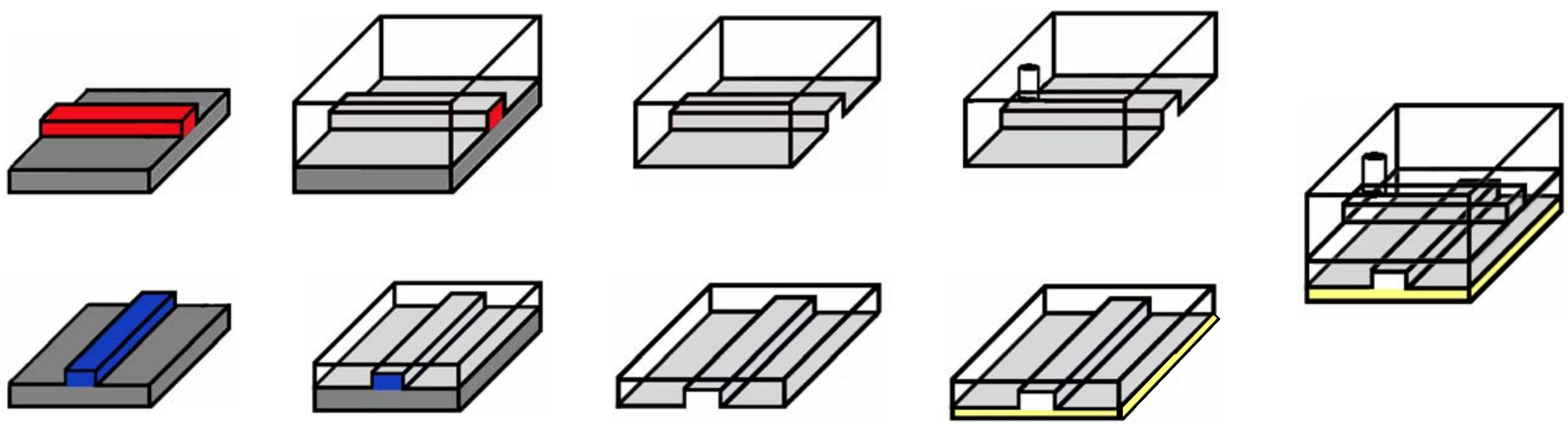
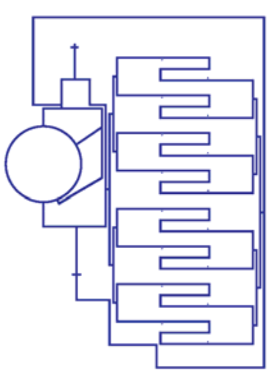


Control Layer

5. Align flow layer over control layer





Flow Layer

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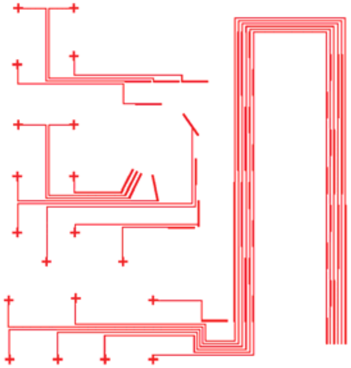
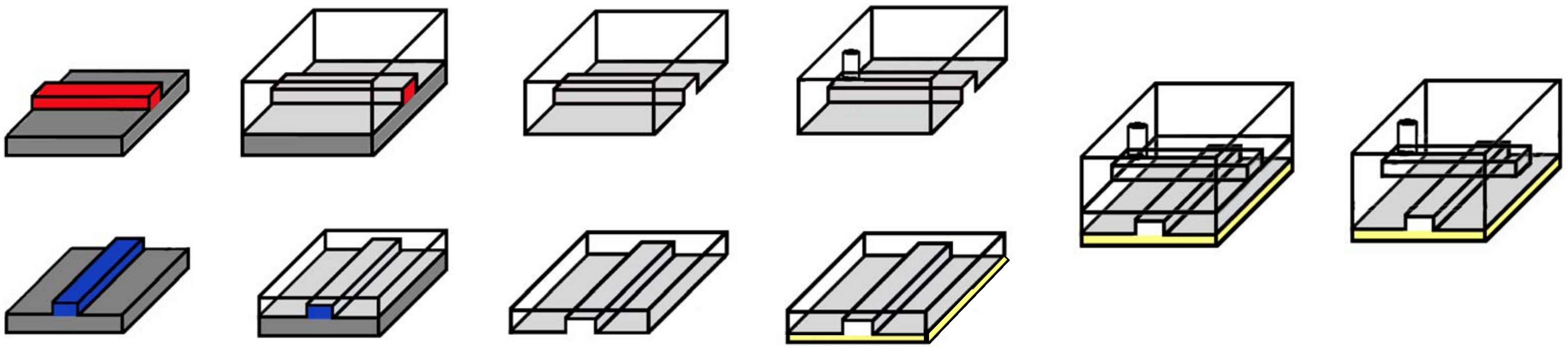
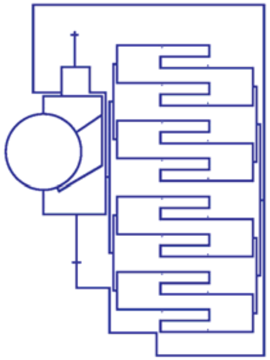


Control Layer

6. Bake at 80° C (secondary cure)





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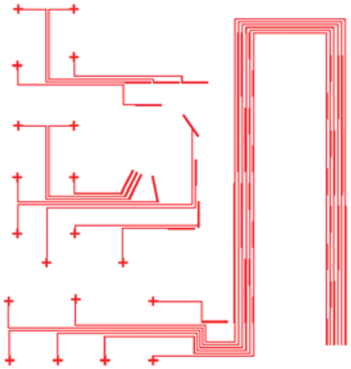
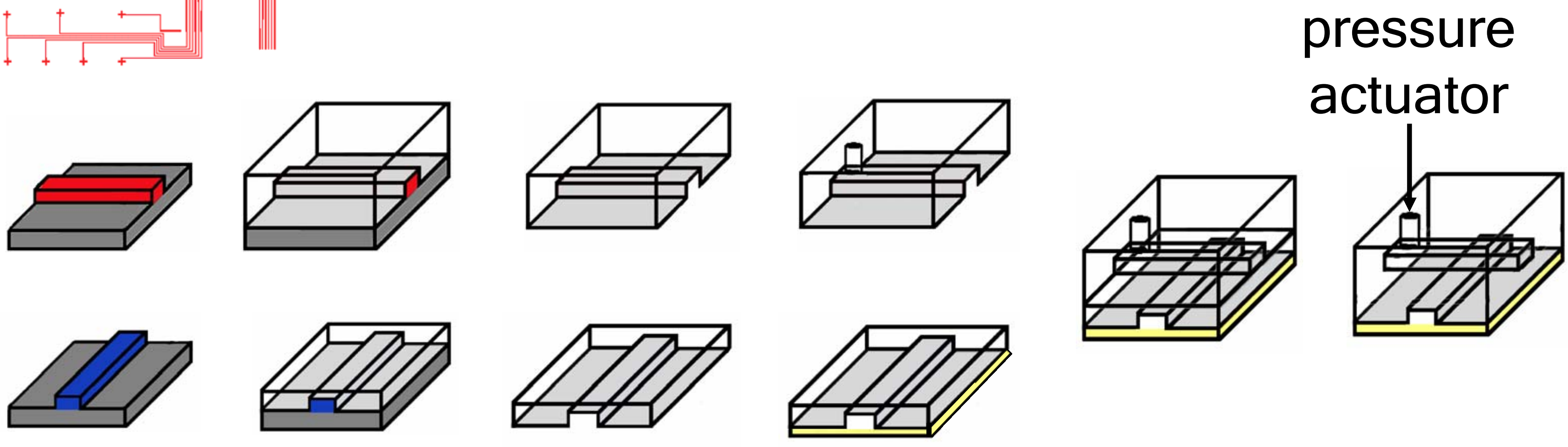
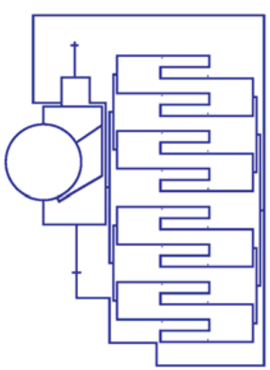


Control Layer

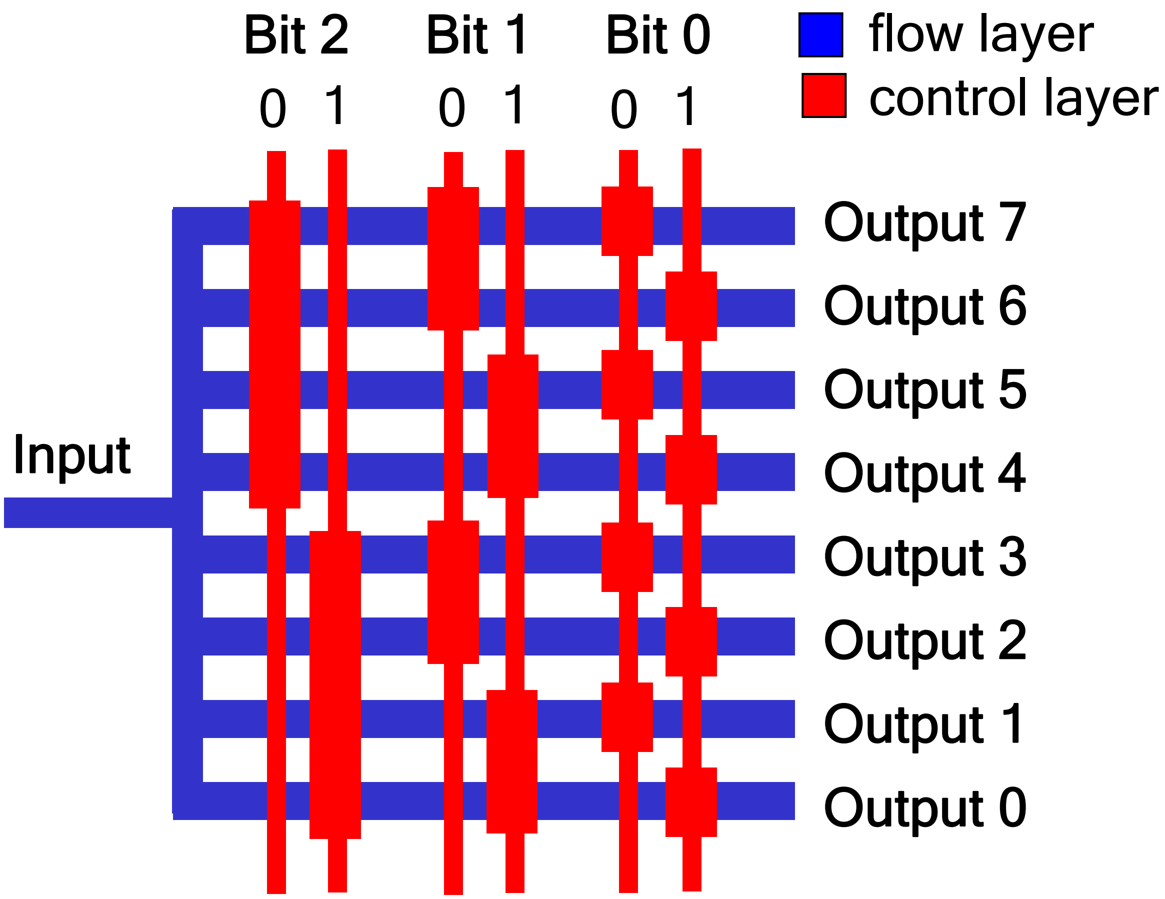
7. When pressure is high, control channel pinches flow channel to form a valve





Flow Layer

Primitive 2: A Multiplexer (Thorsen et al.)



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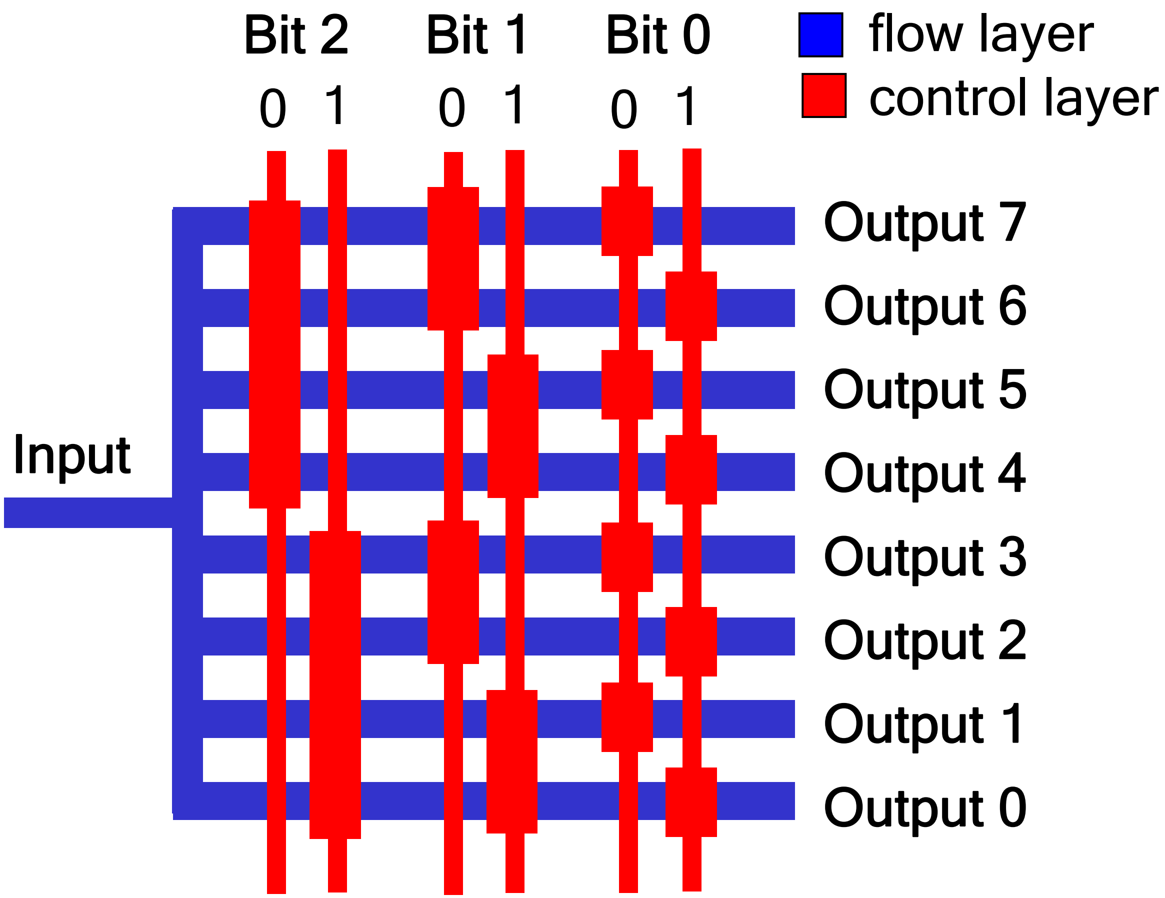

Example: select 3 = 011

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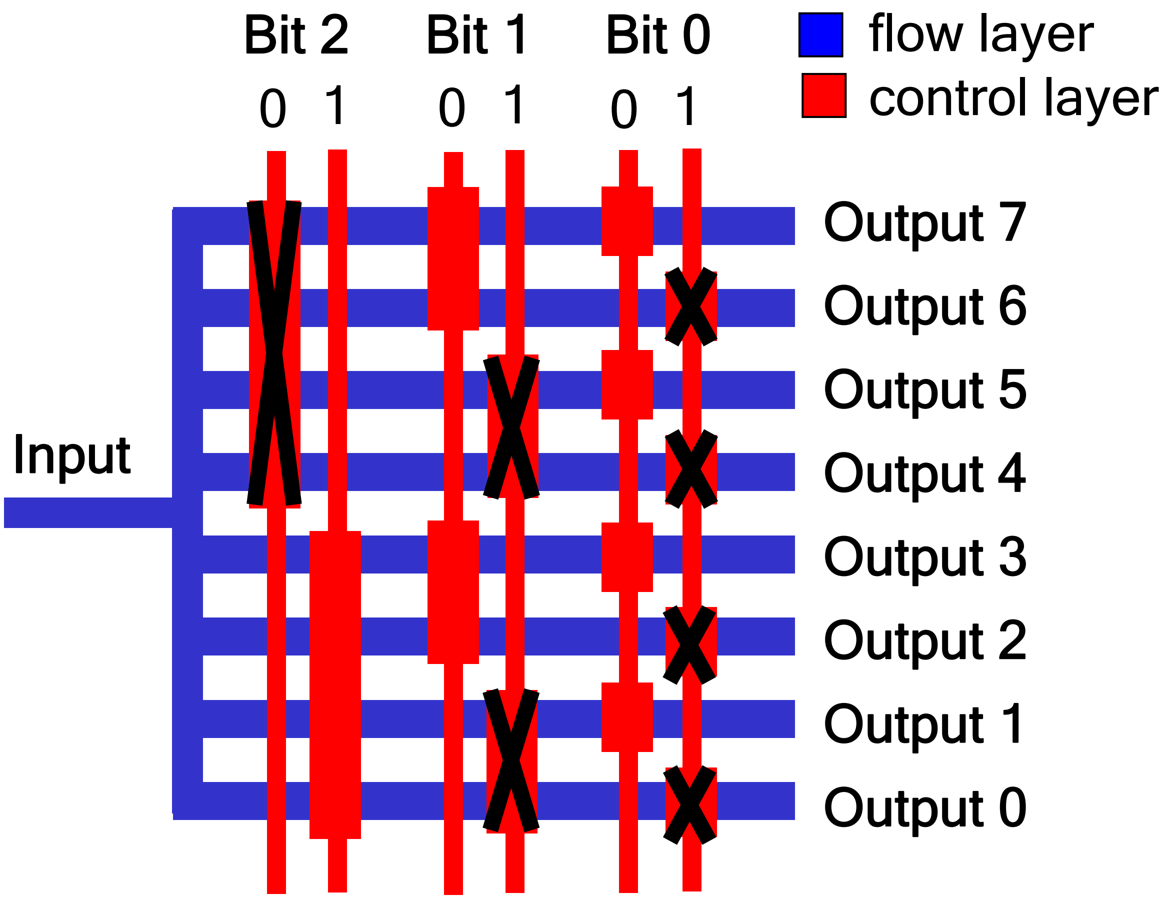

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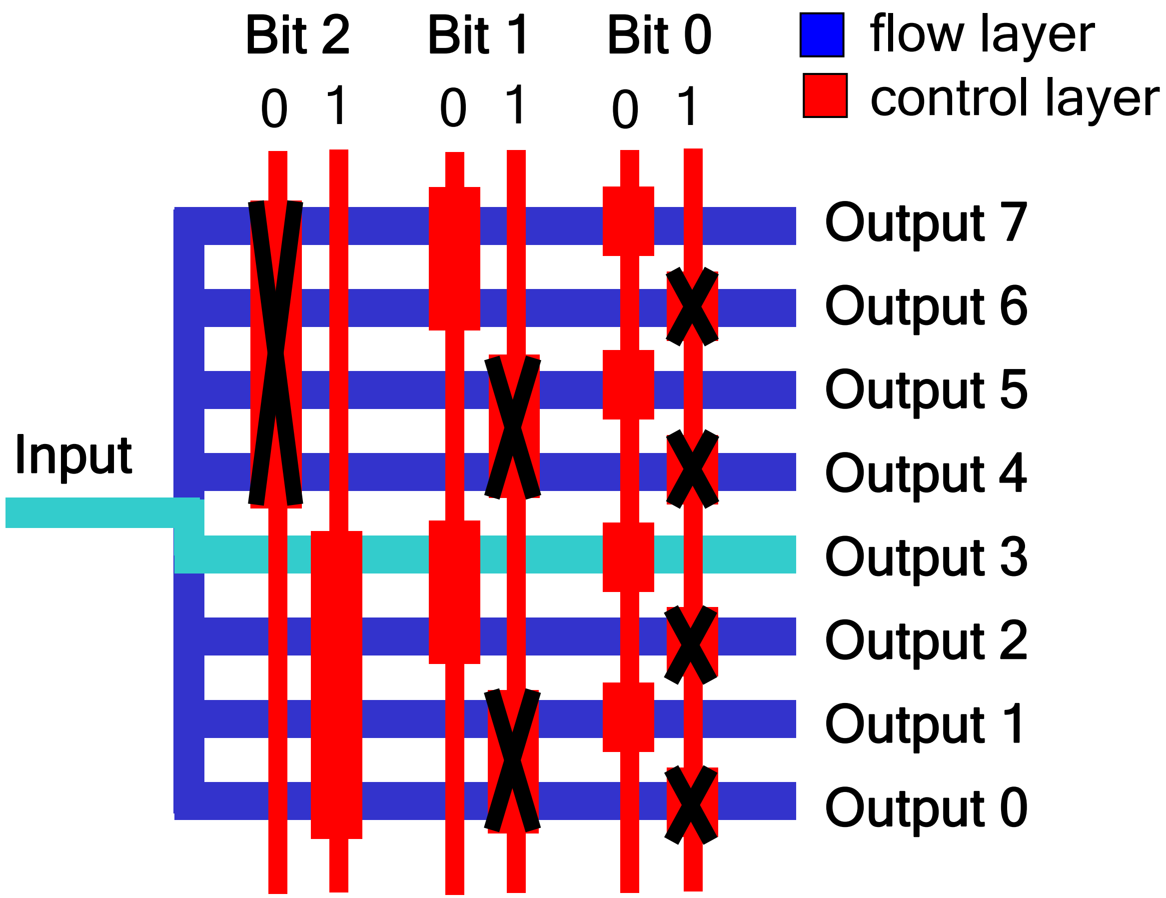

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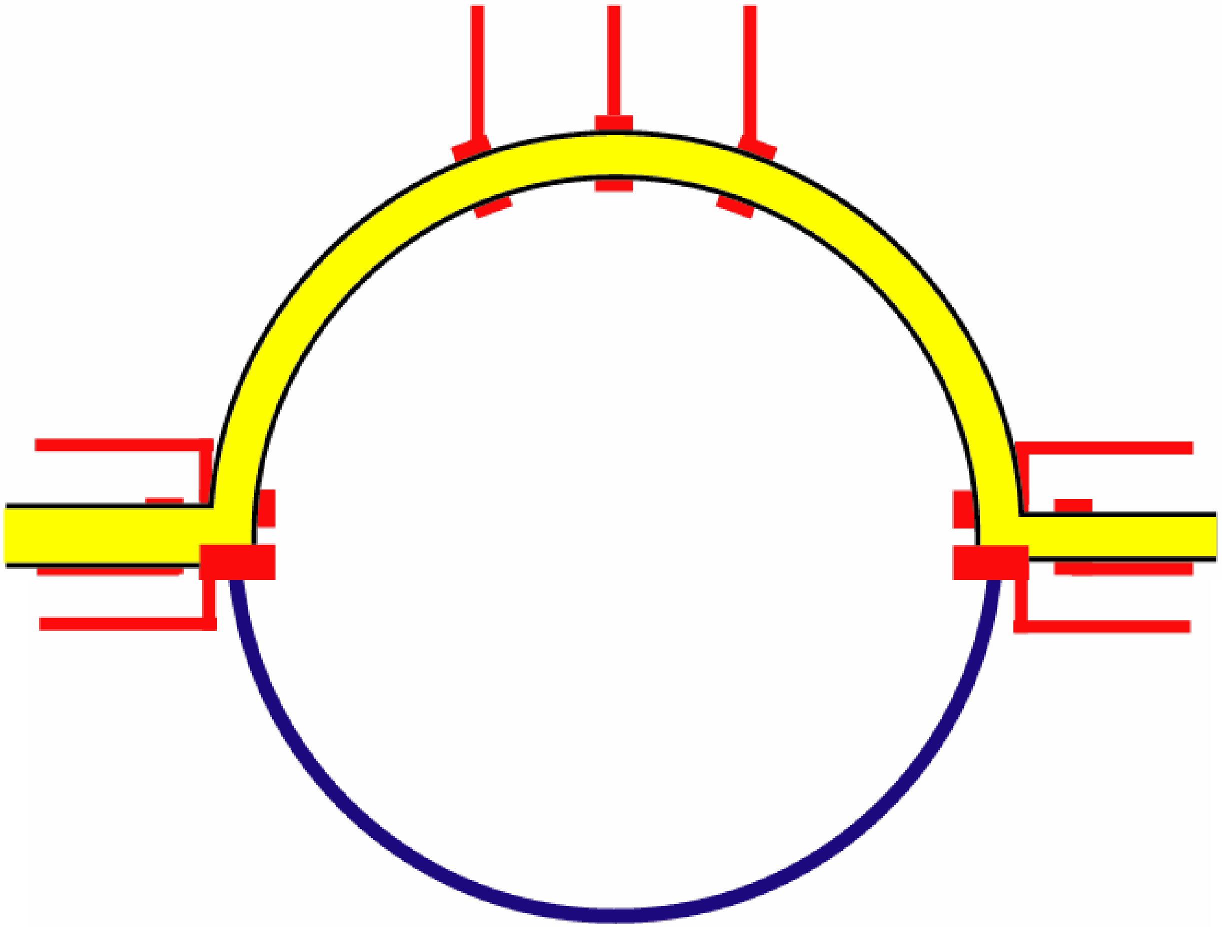

1. Load sample on top

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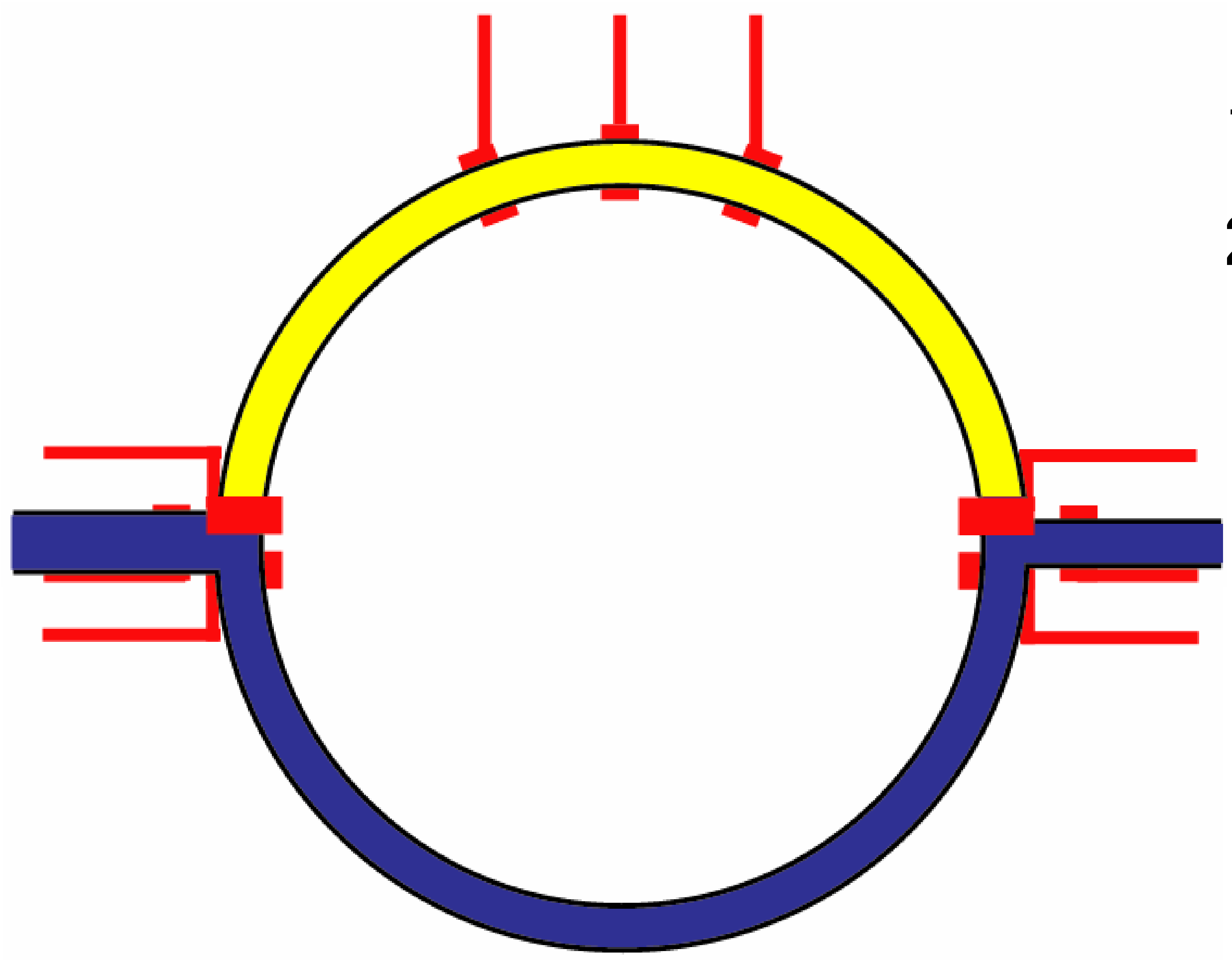
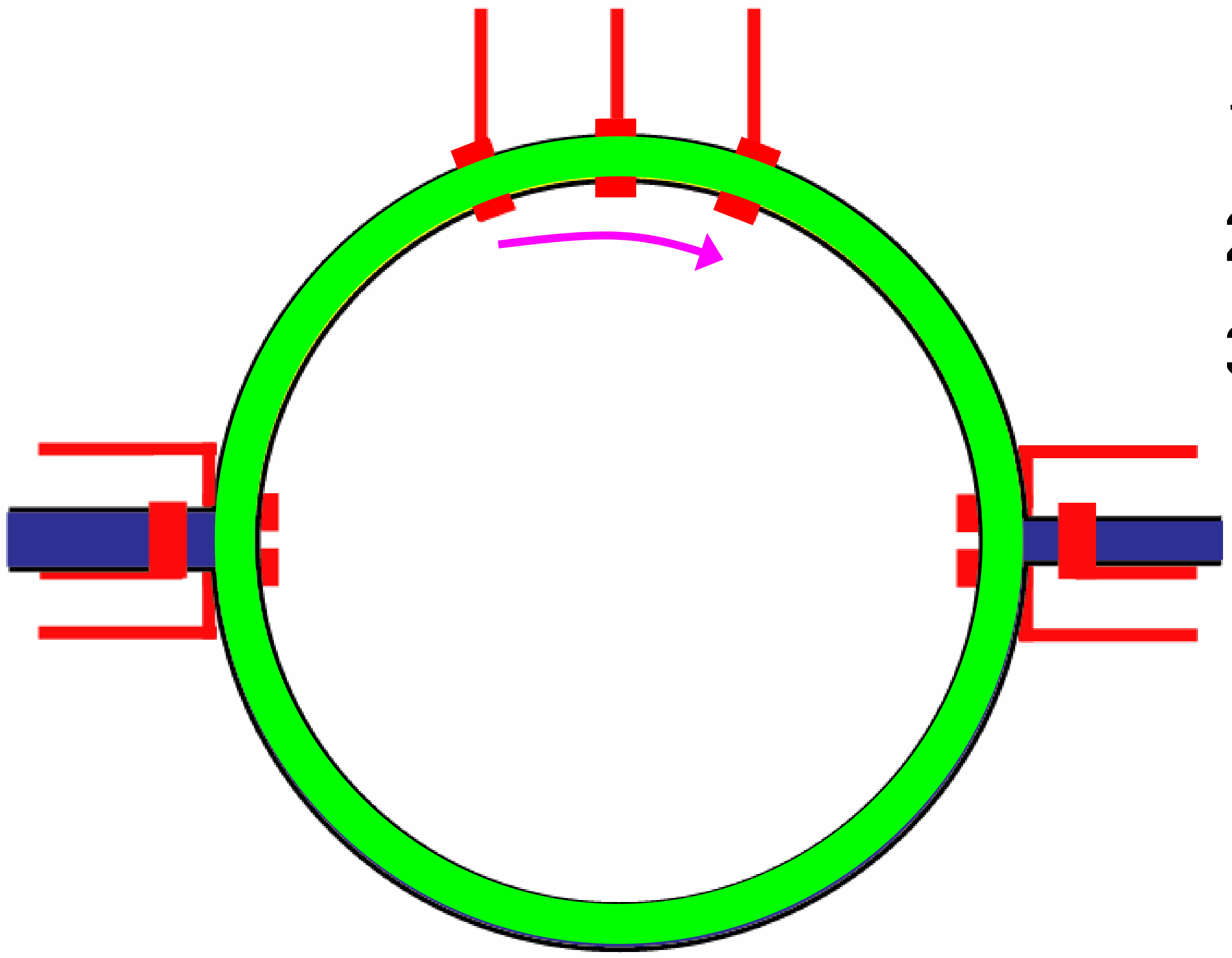


1. Load sample on top
2. Load sample on bottom

Primitive 3: A Mixer (Quake et al.)

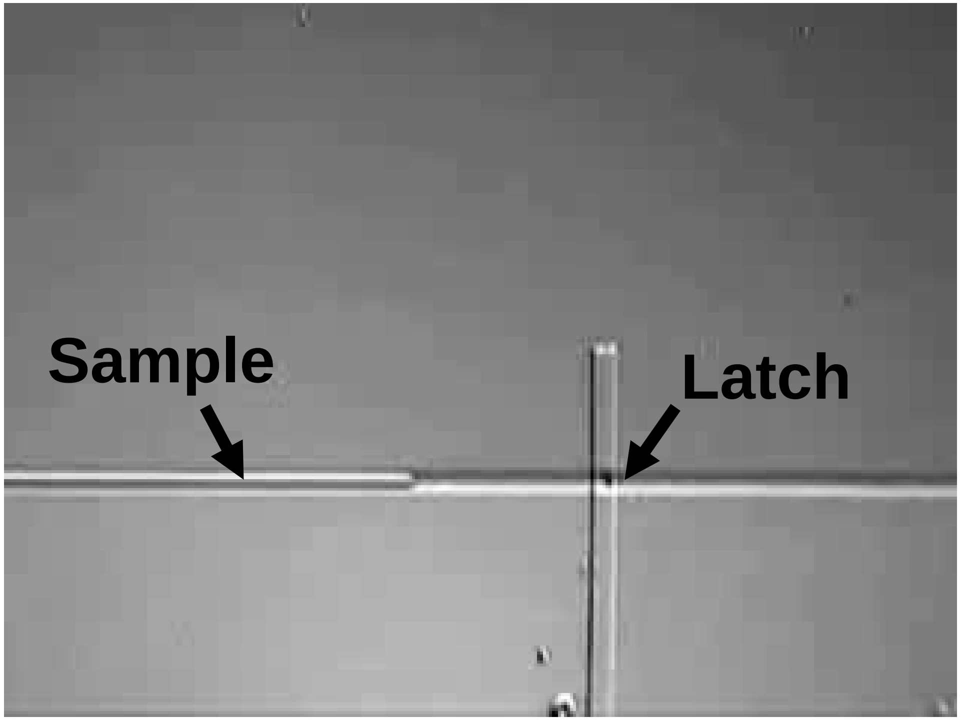


1. Load sample on top
2. Load sample on bottom
3. Peristaltic pumping

Rotary Mixing

Primitive 4: A Latch (Our contribution)

- **Purpose: align sample with specific location on device**
  - Examples: end of storage cell, end of mixer, middle of sensor

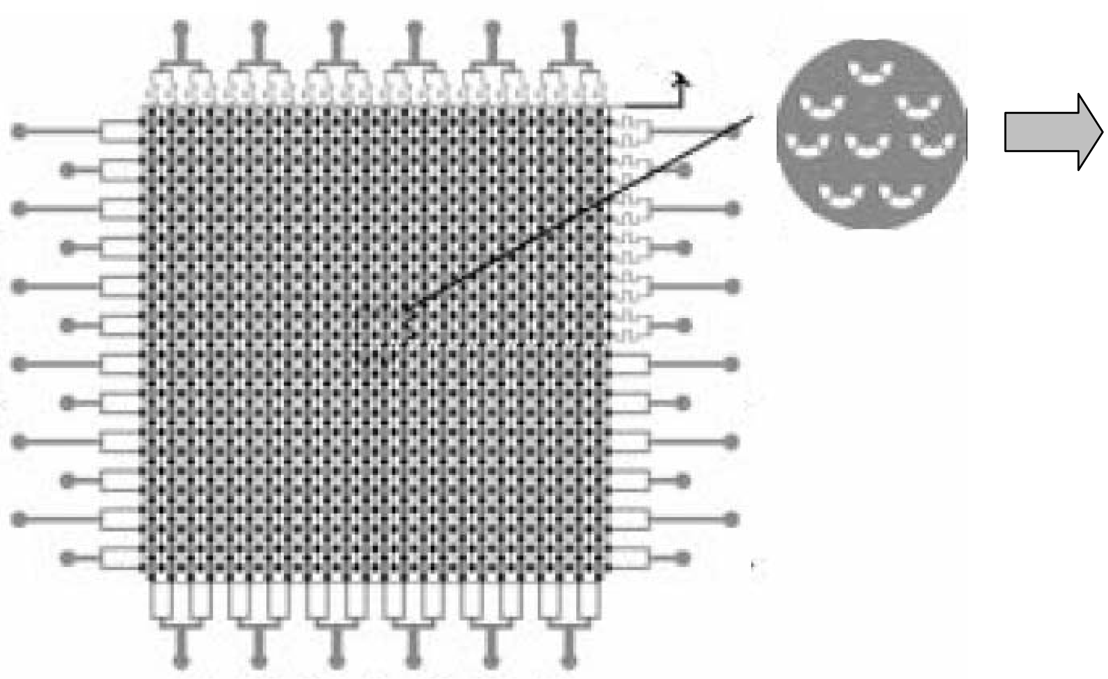


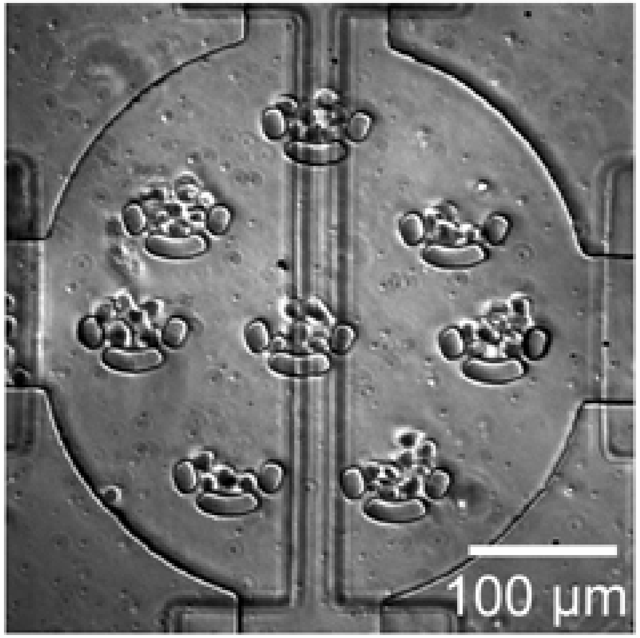
- **Latches are implemented as a partially closed valve**
  - Background flow passes freely
  - Aqueous samples are caught

Primitive 5: Cell Trap

- **Several methods for confining cells in microfluidic chips**
  - U-shaped weirs
  - Holographic optical traps
  - C-shaped rings / microseives
  - Dialectrophoresis

- **In our chips: U-Shaped Microseives in PDMS Chambers**

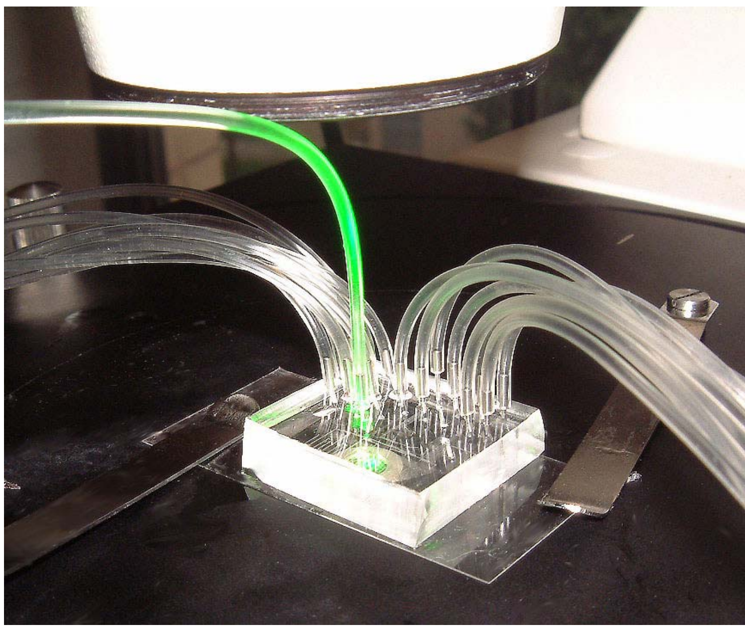




Source: *Wang, Kim, Marquez, and Thorsen, Lab on a Chip 2007*

Primitive 6: Imaging and Detection

- **As PDMS chips are translucent, contents can be imaged directly**
  - Fluorescence, color, opacity, etc.



- **Feedback can be used to drive the experiment**

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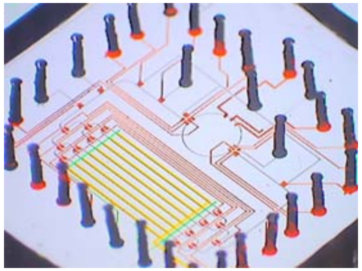
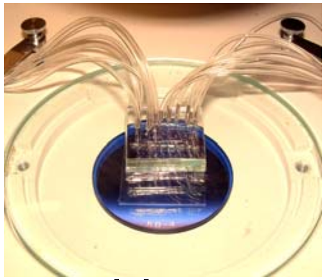
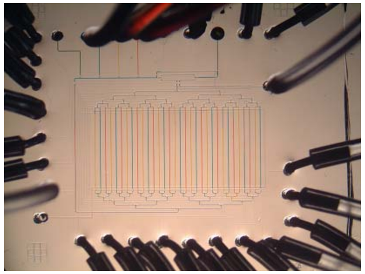
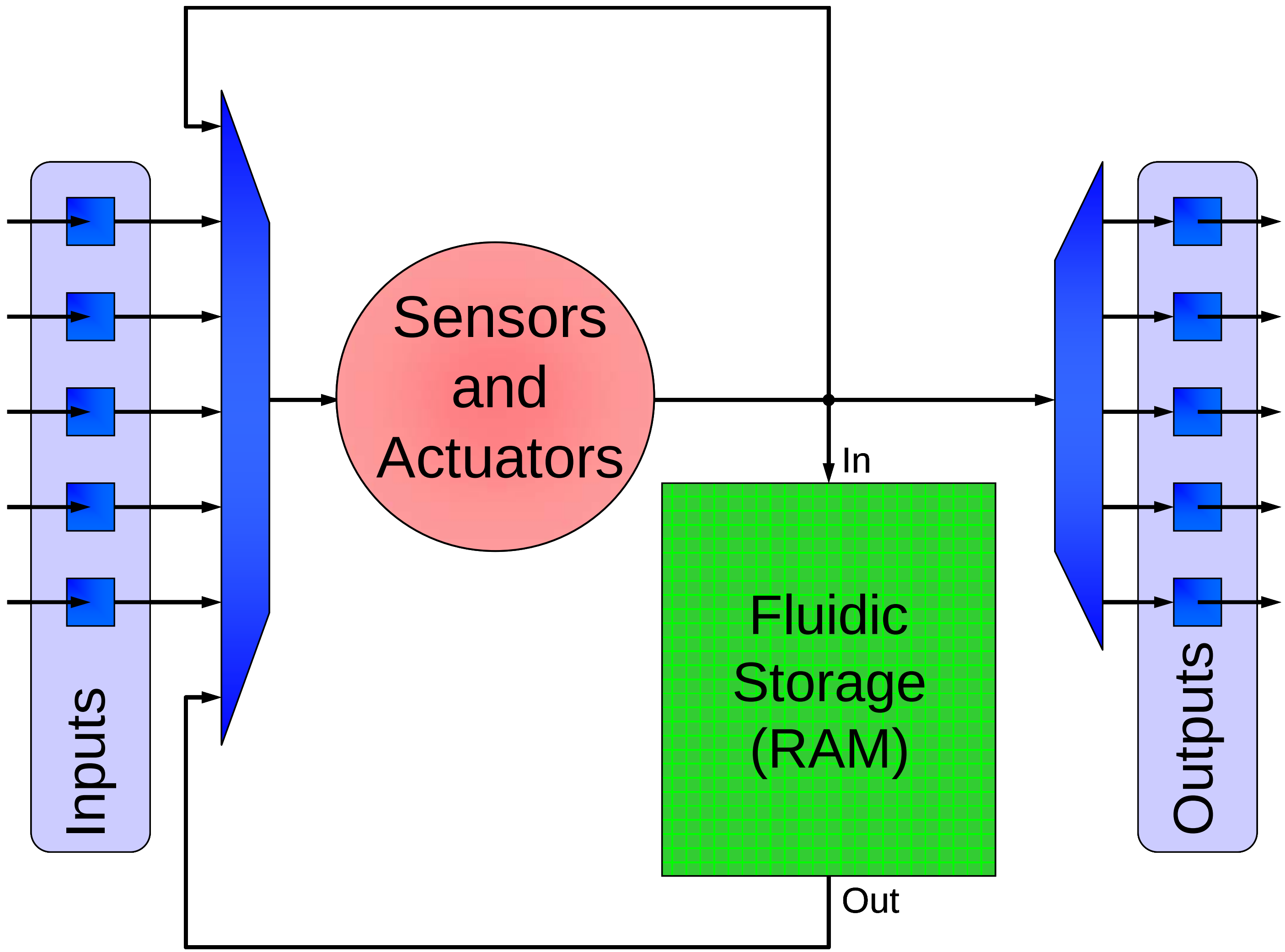

chip 1


chip 2


chip 3

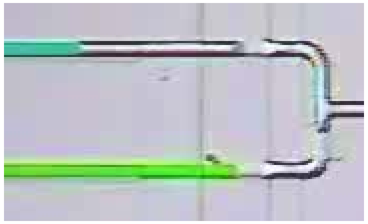
Fluidic Hardware Primitives
- valves, multiplexers, mixers, latches

Toward "General Purpose" Microfluidic Chips

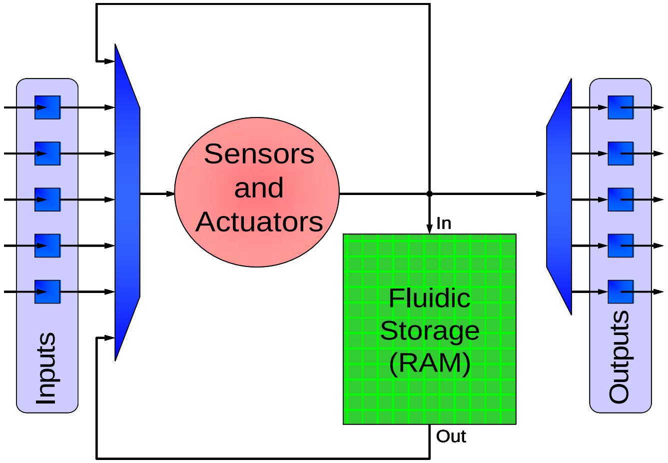


Abstraction 1: Digital Architecture

- **Recent techniques can control independent samples**
  - Droplet-based samples [Fair et al.]
  - Continuous-flow samples [Our contribution]
  - Microfluidic latches [Our contribution]



- **In abstract machine, all samples have unit volume**
  - Input/output a sample
  - Store a sample
  - Operate on a sample



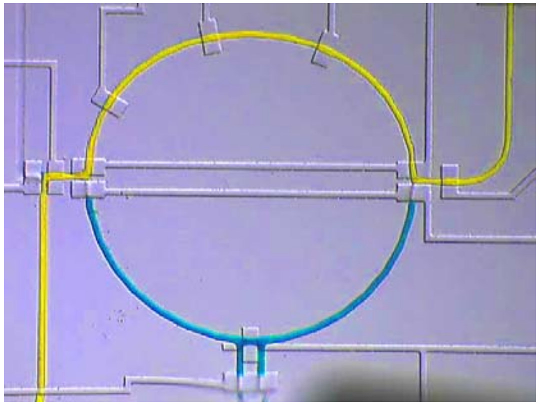
- **Challenge for a digital architecture: fluid loss**
  - No chip is perfect – will lose some volume over time
  - Causes: imprecise valves, adhesion to channels, evaporation, ...
  - How to maintain digital abstraction?

Maintaining a Digital Abstraction

Electronics		Microfluidics
Soft error Handling?	**High-Level Language**	Expose loss in language ✓ - User deals with it
? ? ?		
Randomized Gates [Palem]	**Instruction Set Architecture (ISA)**	Expose loss in ISA ✓ - Compiler deals with it
? ? ?		
Replenish charge (GAIN)	**Hardware**	Replenish fluids? - Maybe (e.g., with water) - But may affect chemistry
Loss of charge		Loss of fluids

Abstraction 2: Mix Instruction

- **Microfluidic chips have various mixing technologies**
  - Electrokinetic mixing [Levitan et al.]
  - Droplet mixing [Fair et al.]
  - Rotary mixing [Quake et al.]



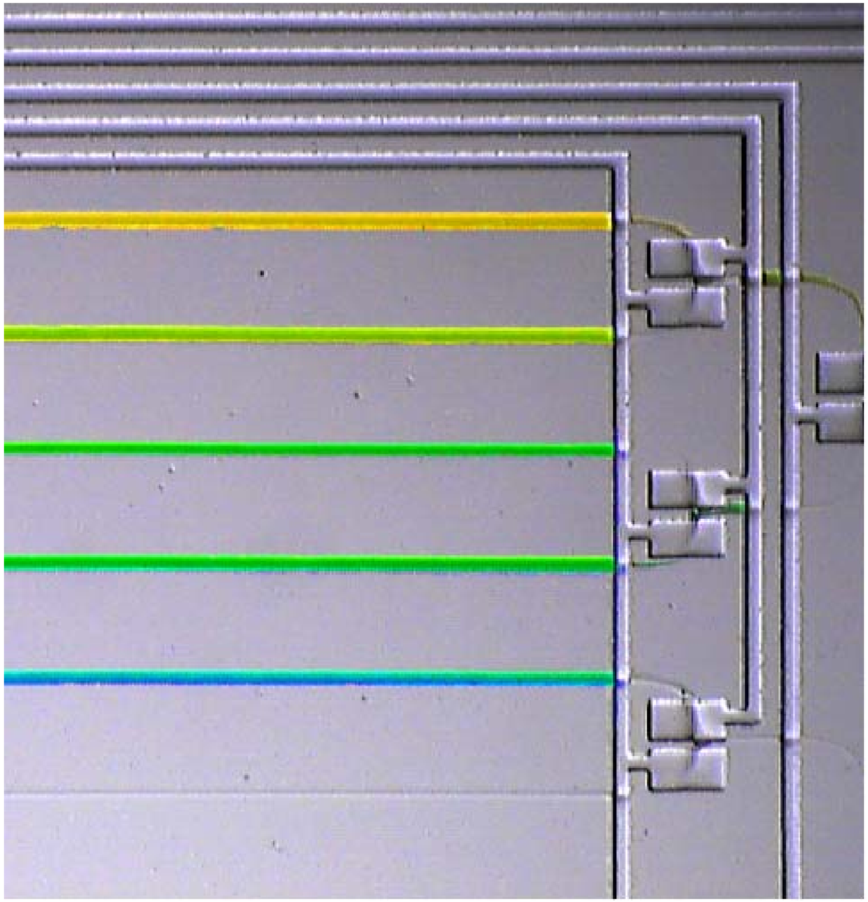
- **Common attributes:**
  - Ability to mix two samples in equal proportions, store result
- **Fluidic ISA:** **mix** (int src_1, int src_2, int dst)
  - Ex: mix(1, 2, 3)

Storage Cells	
1	
2	
3	
4	

Mixer

  - To allow for lossy transport, only 1 unit of mixture retained

Gradient Generation in Fluidic ISA



Gradient Generation in Fluidic ISA

```
wait(2000);
setValve(14, HIGH); setValve(2, LOW);
wait(1000);
setValve(4, HIGH);   setValve(12, LOW);
setValve(16, HIGH); setValve(18, HIGH);
setValve(19, LOW);
wait(2000);
setValve(0, LOW);    setValve(1, LOW);
setValve(2, LOW);    setValve(3, HIGH);
setValve(4, LOW);    setValve(5, HIGH);
setValve(6, HIGH);   setValve(7, LOW);
setValve(8, LOW);    setValve(9, HIGH);
setValve(10, HIGH); setValve(11, LOW);
setValve(12, LOW);  setValve(13, LOW);
setValve(14, LOW);  setValve(15, HIGH);
setValve(16, HIGH); setValve(17, LOW);
setValve(18, HIGH); setValve(19, LOW);
```

abstraction

```
input(0, 0);
input(1, 1);
input(0, 2);
mix(1, 2, 3);
input(0, 2);
mix(2, 3, 1);
input(1, 3);
input(0, 4);
mix(3, 4, 2);
input(1, 3);
input(0, 4);
mix(3, 4, 5);
input(1, 4);
mix(4, 5, 3);
mix(0, 4);
```

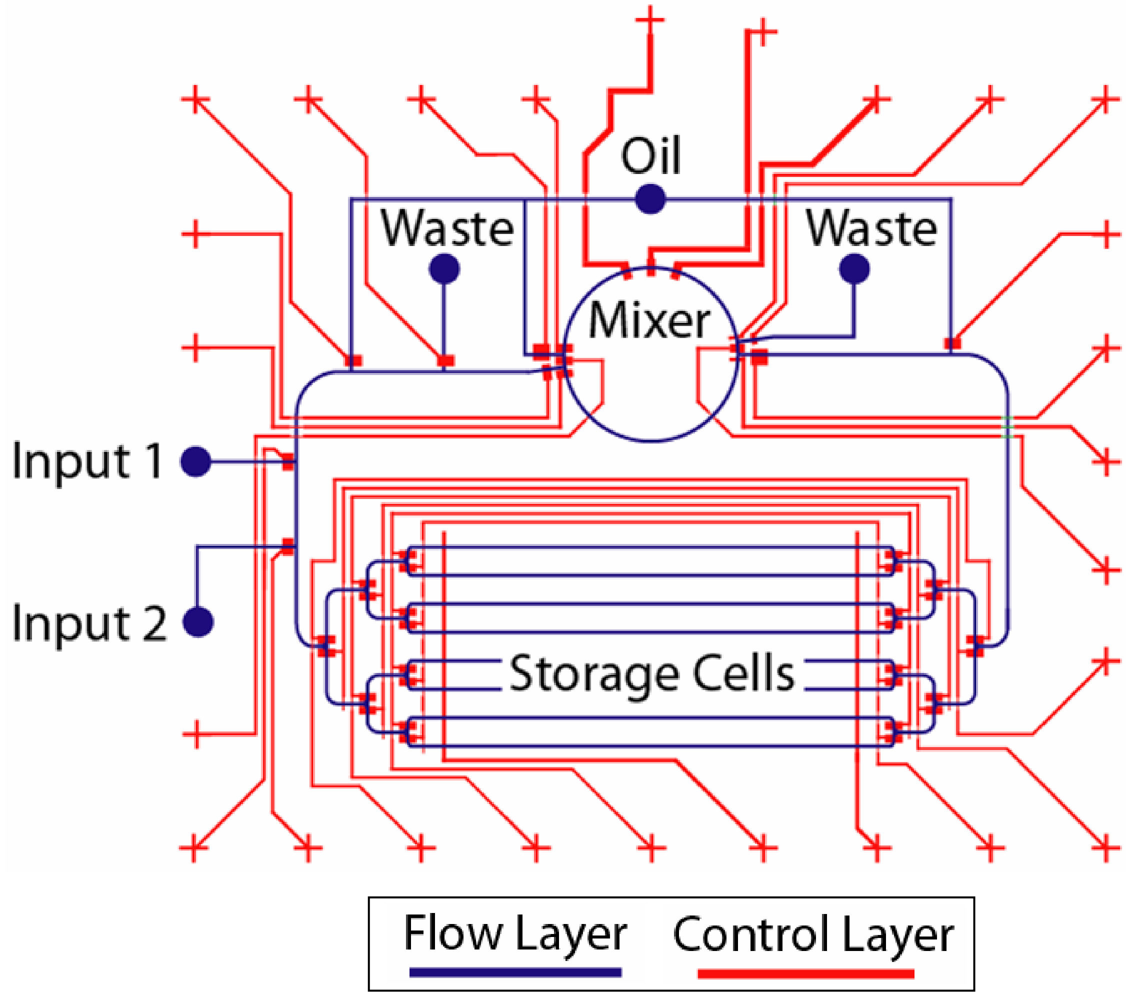
Direct Control

- 450 valve actuations
- only works on 1 chip

Fluidic ISA

- 15 instructions
- portable across chips

Implementation: Oil-Driven Chip



	Inputs	Storage Cells	Background Phase	Wash Phase	Mixing
Chip 1	2	8	Oil	—	Rotary

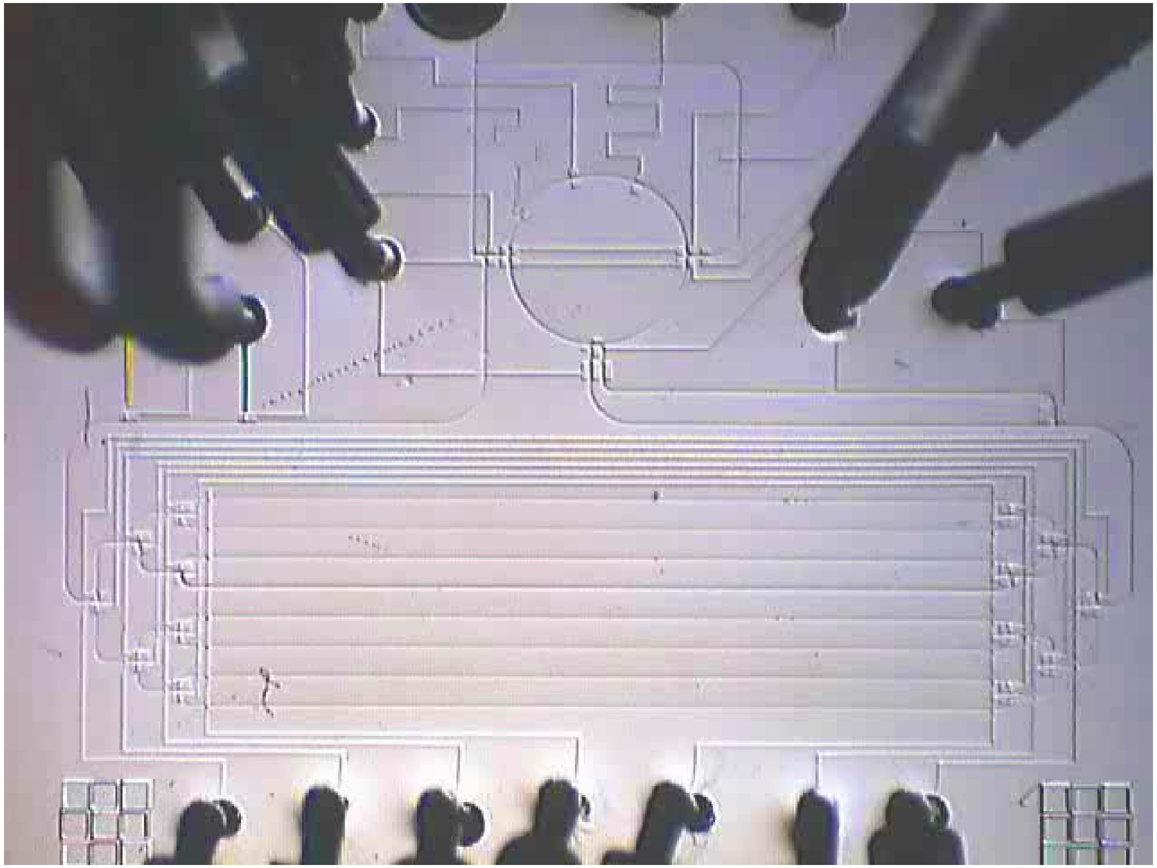
Implementation: Oil-Driven Chip

mix (S_1, S_2, D) {

1. Load S_1
2. Load S_2
3. Rotary mixing
4. Store into D

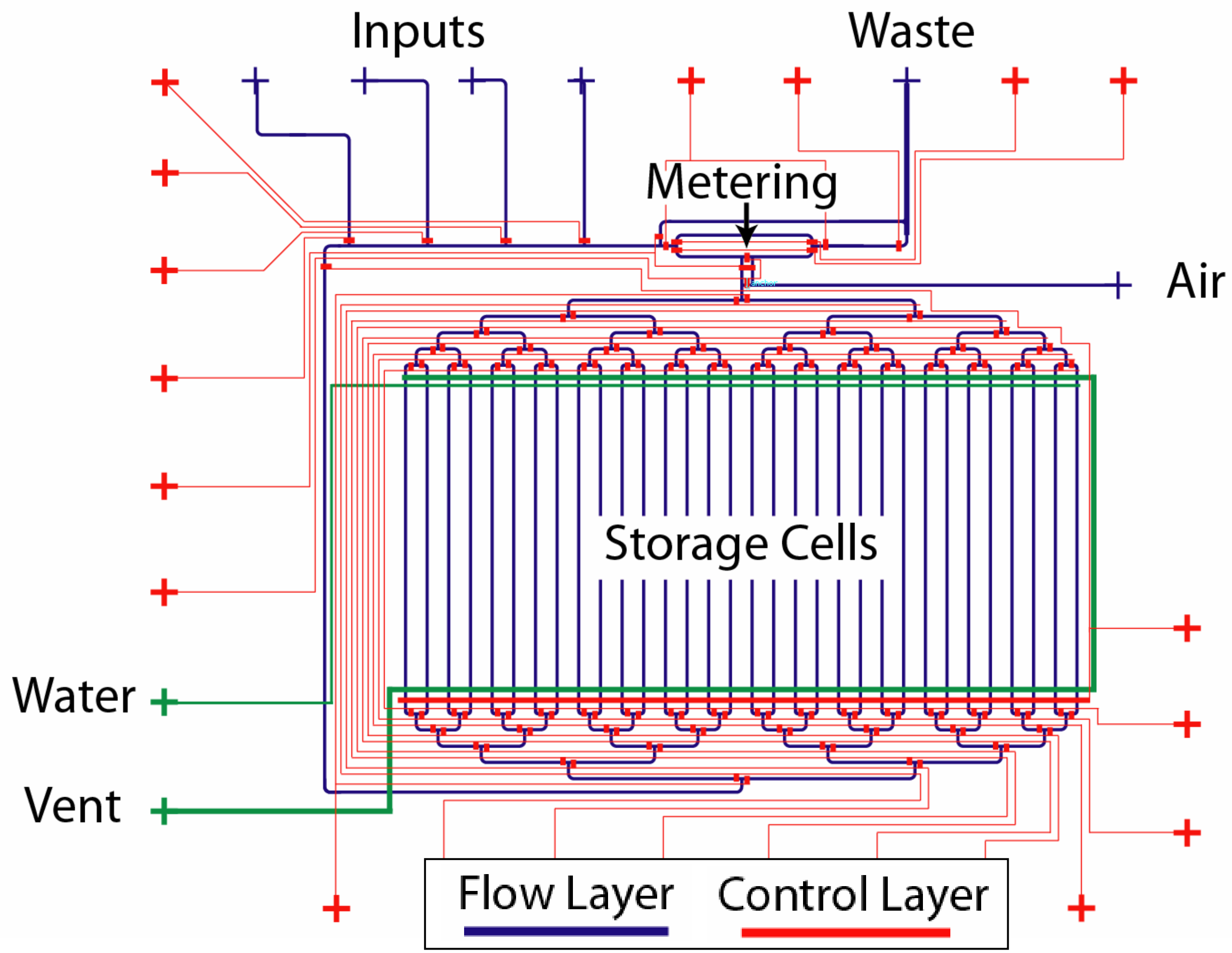
}

50x real-time



	Inputs	Storage Cells	Background Phase	Wash Phase	Mixing
Chip 1	2	8	Oil	—	Rotary

Implementation 2: Air-Driven Chip



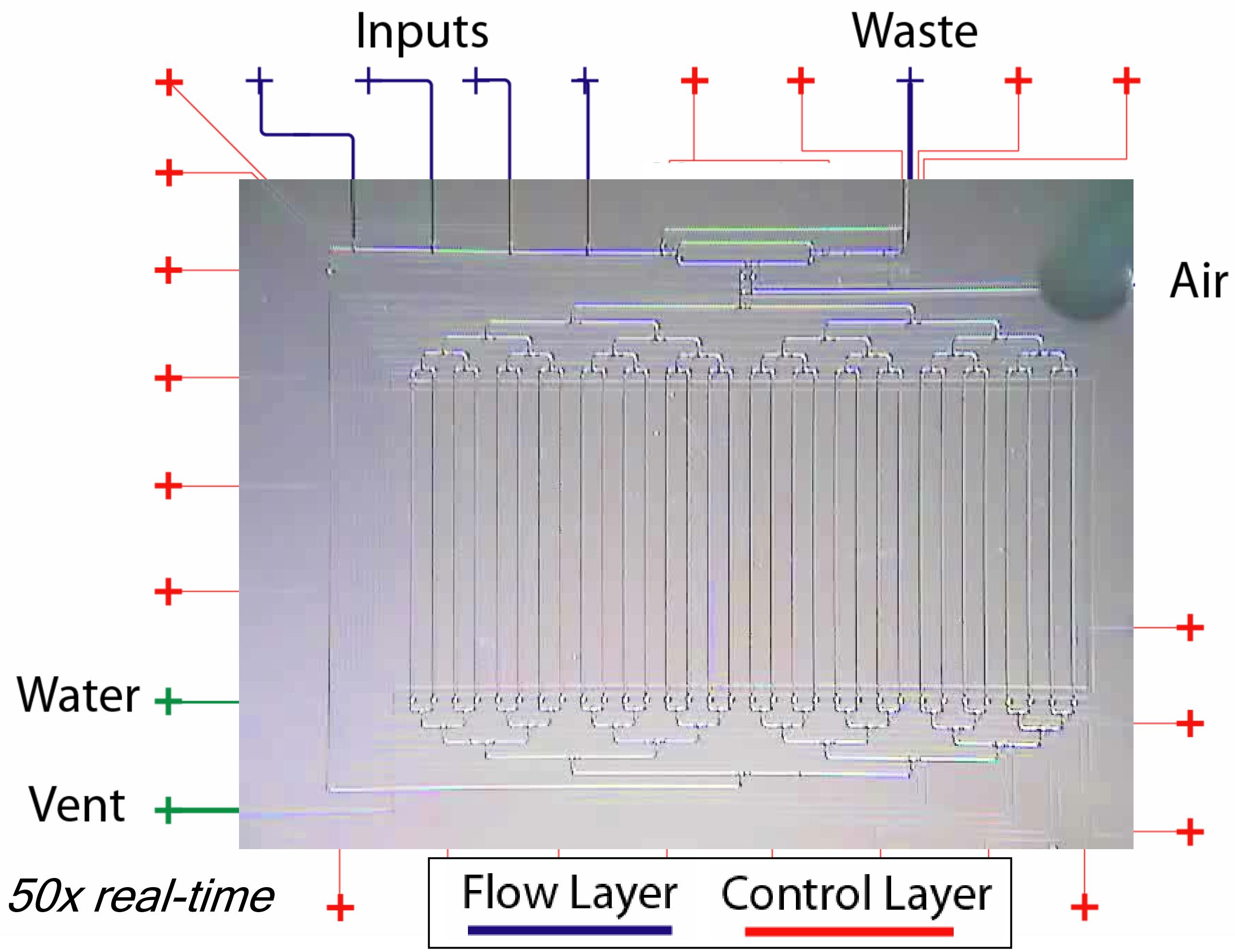
	Inputs	Storage Cells	Background Phase	Wash Phase	Mixing
Chip 1	2	8	Oil	—	Rotary
Chip 2	4	32	Air	Water	In channels

Implementation 2: Air-Driven Chip

mix (S_1, S_2, D) {

1. Load S_1
2. Load S_2
3. Mix / Store into D
4. Wash S_1
5. Wash S_2

}

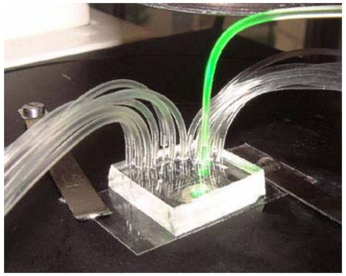


	Inputs	Storage Cells	Background Phase	Wash Phase	Mixing
Chip 1	2	8	Oil	—	Rotary
Chip 2	4	32	Air	Water	In channels

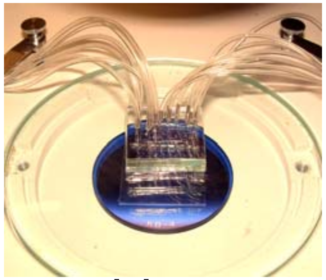
Fluidic Abstraction Layers

Protocol Description Language
- readable code with high-level mixing ops

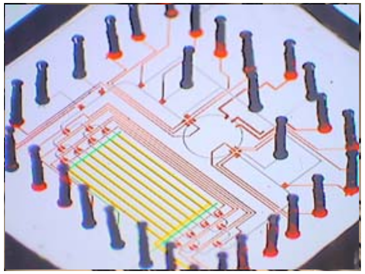
Fluidic Instruction Set Architecture (ISA)
- primitives for I/O, storage, transport, mixing



chip 1



chip 2



chip 3

Fluidic Hardware Primitives
- valves, multiplexers, mixers, latches

Abstraction 1: Managing Fluid Storage

Fluidic ISA

```
input(0, 0);
input(1, 1);
input(0, 2);
mix(1, 2, 3);
input(0, 2);
mix(2, 3, 1);
input(1, 3);
input(0, 4);
mix(3, 4, 2);
input(1, 3);
input(0, 4);
mix(3, 4, 5);
input(1, 4);
mix(4, 5, 3);
mix(0, 4);
```

```
Fluid[] out = new Fluid[8];
Fluid yellow, blue, green;
out[0] = input(0);
yellow = input(0);
blue = input(1);
green = mix(yellow, blue);
yellow = input(0);
out[1] = mix(yellow, green);
yellow = input(0);
blue = input(1);
out[2] = mix(yellow, blue);
yellow = input(0);
blue = input(1);
green = mix(yellow, blue);
blue = input(1);
out[3] = mix(blue, green);
out[4] = input(1);
```

1. Storage Management

- **Programmer uses location-independent Fluid variables**
  - Runtime system assigns & tracks location of each Fluid
  - Comparable to automatic memory management (e.g., Java)

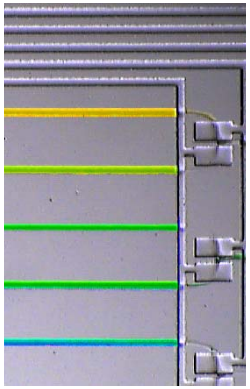
Abstraction 2: Fluid Re-Generation

```
Fluid[] out = new Fluid[8];
Fluid yellow, blue, green;
out[0] = input(0);
yellow = input(0);
blue = input(1);
green = mix(yellow, blue);
yellow = input(0);
out[1] = mix(yellow, green);
yellow = input(0);
blue = input(1);
out[2] = mix(yellow, blue);
yellow = input(0);
blue = input(1);
green = mix(yellow, blue);
blue = input(1);
out[3] = mix(blue, green);
out[4] = input(1);
```

```
Fluid[] out = new Fluid[8];
Fluid yellow = input(0);
Fluid blue = input(1);
Fluid green = mix(yellow, blue);

out[0] = yellow;
out[1] = mix(yellow, green);
out[2] = green;
out[3] = mix(blue, green);
out[4] = blue;
```

2. Fluid Re-Generation



- **Programmer may use a Fluid variable multiple times**
  - Each time, a physical Fluid is consumed on-chip
  - Runtime system re-generates Fluids from computation history

Custom Re-Generation

- **Some species cannot be regenerated by repeating history**
  - e.g., if selective mutagenesis has evolved unique sequence
- **Users can extend Fluid class, specify how to regenerate**
  - e.g., run PCR to amplify sequence of interest

```
class DNASample extends Fluid {

    // Return array of fluids that are equivalent to this fluid
    Fluid[] regenerate() {
        Fluid amplified = performPCR(this, cycles, primer1, primer2, …);
        Fluid[] diluted = dilute(amplified, Math.pow(2, cycles));
        return diluted;
    }

    // Return minimum quantity of this fluid needed to generate others
    int minQuantity() {
        return 1;
    }
}
```

Unique Fluids Prohibit Re-Generation

- **Some Fluids may be unique, with no way to amplify**
  - E.g., products of cell lysis
- **Users can express this constraint using a UniqueFluid:**

```
class UniqueFluid extends Fluid {
    Fluid[] regenerate() {
        throw new EmptyFluidException();
    }
}
```

```
UniqueFluid f = lysisProduct();
UniqueFluid[] diluted = dilute(f);
for (int i=0; i<diluted.length; i++) {
    analyze(diluted[i]);
}
```

- **Can compiler verify that unique fluids used only once?**
  - Unique (linear) types is a rich research area in prog. languages
    [Wadler] [Hogg] [Baker] [Minsky] [Boyland] [Fahndrich & DeLine]
  - But solutions often require annotations & do not handle arrays
  - Practical approach: verify in simple cases, warn about others

→Opportunity for programming language research

Abstraction 3: Arbitrary Mixing

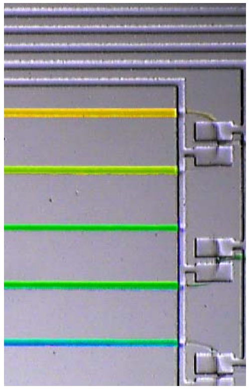
```
Fluid[] out = new Fluid[8];
Fluid yellow = input(0);
Fluid blue = input(1);
Fluid green = mix(yellow, blue);

out[0] = yellow;
out[1] = mix(yellow, green);
out[2] = green;
out[3] = mix(blue, green);
out[4] = blue;
```

2. Fluid Re-Generation

```
Fluid[] out = new Fluid[8];
Fluid yellow = input (0);
Fluid blue = input (1);

out[0] = yellow;
out[1] = mix(yellow, 3/4, blue, 1/4);
out[2] = mix(yellow, 1/2, blue, 1/2);
out[3] = mix(yellow, 1/4, blue, 3/4);
out[4] = blue;
```



3. Arbitrary Mixing

- **Allows mixing fluids in any proportion, not just 50/50**
  - Fluid **mix** (Fluid F_1, float p_1, Fluid f_2, float F_2)

    → Returns Fluid that is p_1 parts $\mathbf{F_1}$ and $\mathbf{p_2}$ parts $\mathbf{F_2}$
  - Runtime system translates to 50/50 mixes in Fluidic ISA
  - Note: some mixtures only reachable within error tolerance ε

Abstraction 3: Arbitrary Mixing

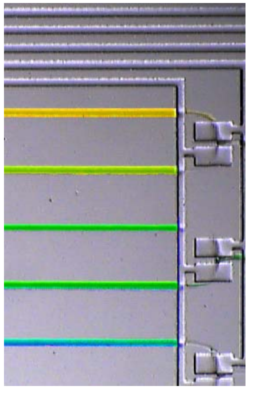
```
Fluid[] out = new Fluid[8];
Fluid yellow = input (0);
Fluid blue = input (1);

out[0] = yellow;
out[1] = mix(yellow, 3/4, blue, 1/4);
out[2] = mix(yellow, 1/2, blue, 1/2);
out[3] = mix(yellow, 1/4, blue, 3/4);
out[4] = blue;
```

3. Arbitrary Mixing

```
Fluid[] out = new Fluid[8];
Fluid yellow = input (0);
Fluid blue = input (1);

for (int i=0; i<=4; i++) {
  out[i] = mix(yellow, 1-i/4, blue, i/4);
}
```

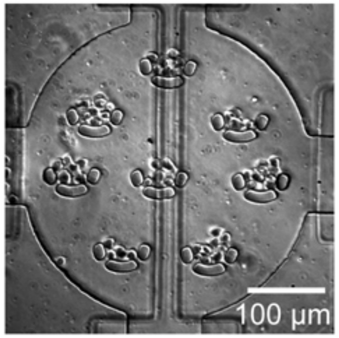


4. Parameterized Mixing

- **Allows mixing fluids in any proportion, not just 50/50**
  - Fluid **mix** (Fluid F_1, float p_1, Fluid f_2, float F_2)
    - → Returns Fluid that is p_1 parts $\mathbf{F_1}$ and $\mathbf{p_2}$ parts $\mathbf{F_2}$
  - Runtime system translates to 50/50 mixes in Fluidic ISA
  - Note: some mixtures only reachable within error tolerance ε

Abstraction 4: Cell Traps

- **Unlike fluids, cells adhere to a specific location on chip**
  - To interact with cells, need to move Fluids to their location



- **CellTrap abstraction establishes a fixed chamber on chip**
  - Fundamental capability: fill with a given fluid (incl. cell culture)

```
class CellTrap {

    // establish a new, empty location on chip
    CellTrap();

    // replace contents of cell trap with new fluid; return old contents
    UniqueFluid drainAndRefill(Fluid newContents);

    // regenerate contents of cell trap; return drained fluid as needed
    Fluid drainAndRegenerate();
}
```

Abstraction 4: Cell Traps

```
CellTrap celltrap = new CellTrap();              // setup cell culture
for (int i=0; i<N; i++)
    celltrap.drainAndRefill(cellCulture);

celltrap.drainAndRefill(distilledWater);         // analyze cell metabolites
Fluid metabolites = drainAndRegenerate();
analyzeWithIndicators(metabolites);

celltrap.drainAndRefill(antibodyStain);          // stain cells for imaging
```

→ **Must schedule all uses of metabolites before staining**

- Otherwise, runtime error
- Like unique variables, difficult to verify safety in general case
- But thanks to language, compiler can give useful warnings

Abstraction 5: Timing Constraints

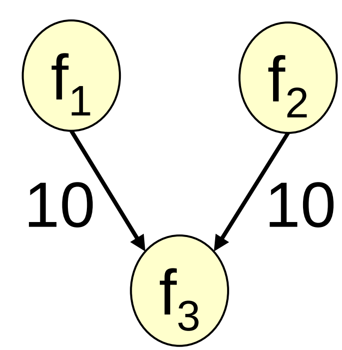
- **Precise timing is critical for many biology protocols**
  - Minimum delay: cell growth, enzyme digest, denaturing, etc.
  - Maximum delay: avoid precipitation, photobleaching, etc.
  - Exact delay: regular measurements, synchronized steps, etc.

- **Simple API for indicating timing constraints:**
  - fluid.**useBetween**(N, M)
  - celltrap.**useBetween**(N, M)

  → Schedule next use of a Fluid (or drain of a CellTrap) between N and M seconds from time of the call

  → Also becomes part of Fluid's regeneration history

- **Note: may *require* parallel execution**
  - Fluid f1 = mix(…); f1.useBetween(10, 10);
  - Fluid f2 = mix(…); f2.useBetween(10, 10);
  - Fluid f3 = mix(f1, f2);



Scheduling the Execution

- **Scheduling problem has two parts:**
  1. Given dependence graph, find a good schedule
  2. Extract dependence graph from the program

1. Finding a Schedule

Abstract scheduling problem:

– Given task graph $G = (V, E)$ with [min, max] latency per edge

– Find shortest schedule ($V \mapsto Z$) respecting latency on each edge

→ Case 1: Unbounded parallelism

- Can express as system of linear difference constraints
- Solve optimally in polynomial time

→ Case 2: Limited parallelism

- Adds constraint: only k vertices can be scheduled at once
- Can be shown to be NP-hard (reduce from PARTITION)
- Rely on greedy heuristics for now

2. Extracting Dependence Graph

- **Static analysis difficult due to aliasing, etc.**
  - Requires extracting precise producer-consumer relationships
- **Opportunity:**
  Perform scheduling at runtime, using lazy evaluation
  - Microfluidic operations are slow → computer can run ahead
  - Build dependence graph of all operations up to decision point
- **Hazard: constraints that span decision points**
  - Dynamic analysis cannot look into upcoming control flow
  - We currently prohibit such constraints – leave as open problem

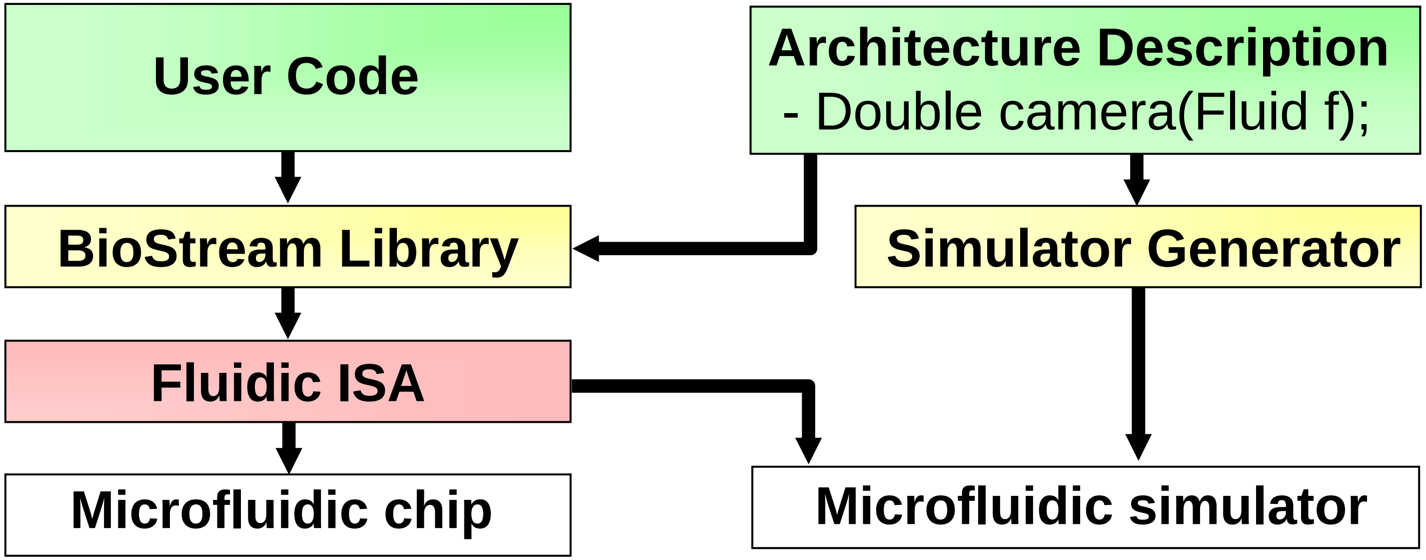
BioStream Protocol Language

- **Implements the abstractions**
  - Full support for storage management, fluid re-generation, arbitrary mixing
  - Partial support for cells, timing

```
Fluid yellow = input (0);
Fluid blue = input (1);
Fluid[] out = new Fluid[8];

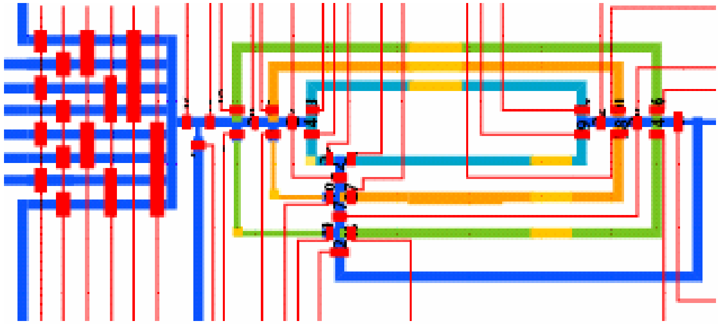
for (int i=0; i<=4; i++)
  out[i] = mix(yellow, 1-i/4,
                blue, i/4);
```

- **Implemented as a Java library**
  - Allows flexible integration with general-purpose Java code
- **Targets microfluidic chips or auto-generated simulator**

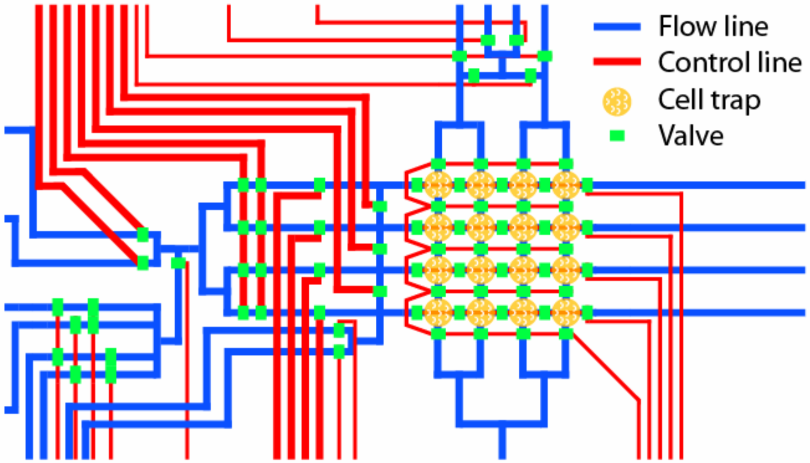


Applications in Progress

1. **What are the best indicators for oocyte viability?**
   - With Mark Johnson's and Todd Thorsen's groups
   - During in-vitro fertilization, monitor cell metabolites and select healthiest embryo for implantation



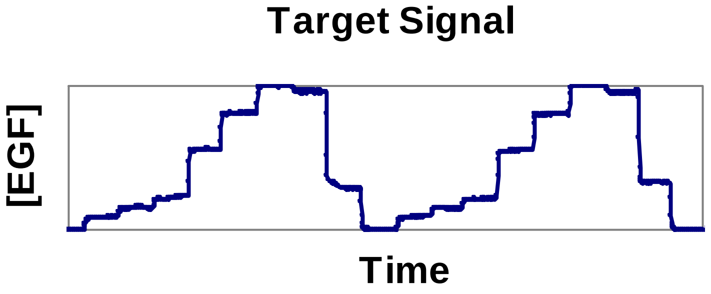
2. **How do mammalian signal transduction pathways respond to complex inputs?**
   - With Jeremy Gunawardena's and Todd Thorsen's groups
   - Isolate cells and stimulate with square wave, sine wave, etc.



Generating Complex Signals

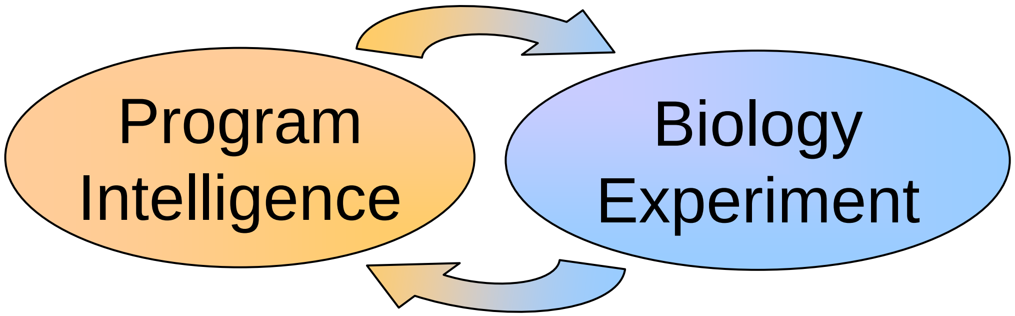
```
CellTrap cells = new CellTrap();
… // setup cell culture
while (true) {
    float target = targetSignal(getTime());
    Fluid f = mix(EGF, target,
                      WATER, 1-target);
    cells.drainAndFill(f);
    cells.useAfter(10*SEC);
}
```

Video courtesy David Craig



Additional Applications

- **Killer apps: react to feedback, redirect the experiment**
  - Recursive-descent search
  - Fixed-pH reaction
  - Directed evolution
  - Long, complex protocols



- **Application to biological computation**
  - Many emerging technologies:
    DNA computing, cellular signaling, biomolecular automata, …
  - But not yet able to assemble, sustain, and adapt themselves
  - Microfluidics provides a scaffold to explore underlying biology

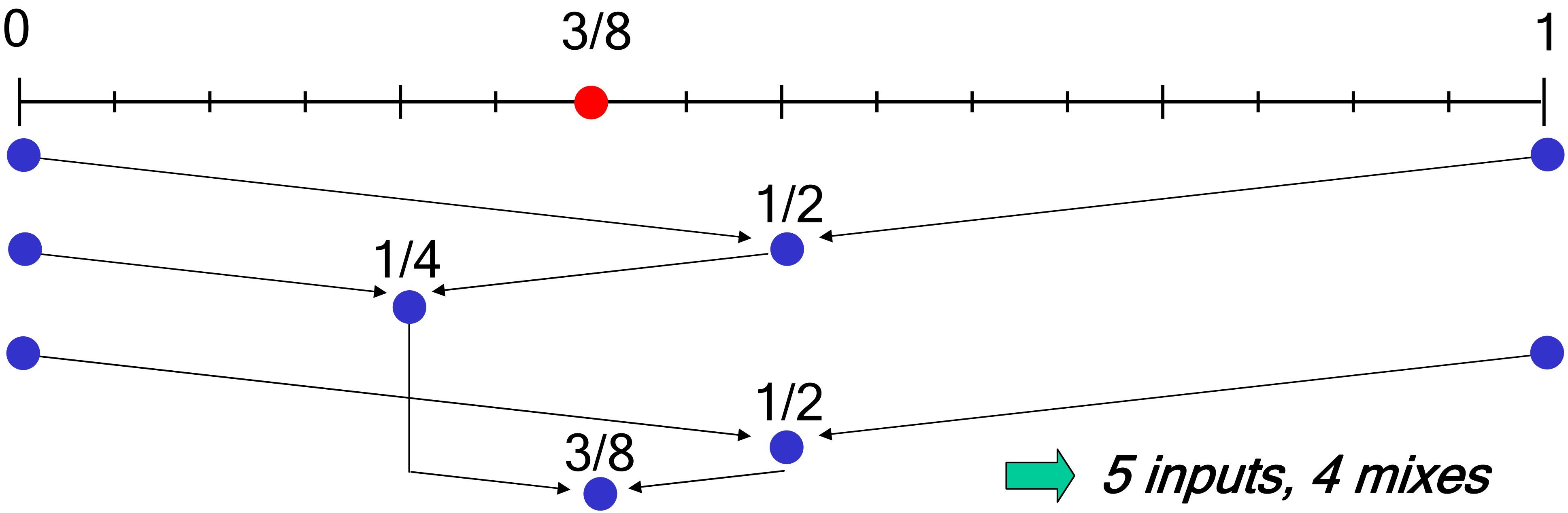
Compiler Optimizations

Algorithms for Efficient Mixing

- **Mixing is fundamental operation of microfluidics**
  – Prepare samples for analysis
  – Dilute concentrated substances
  – Control reagant volumes
  ➡ Analogous to ALU operations on microprocessors

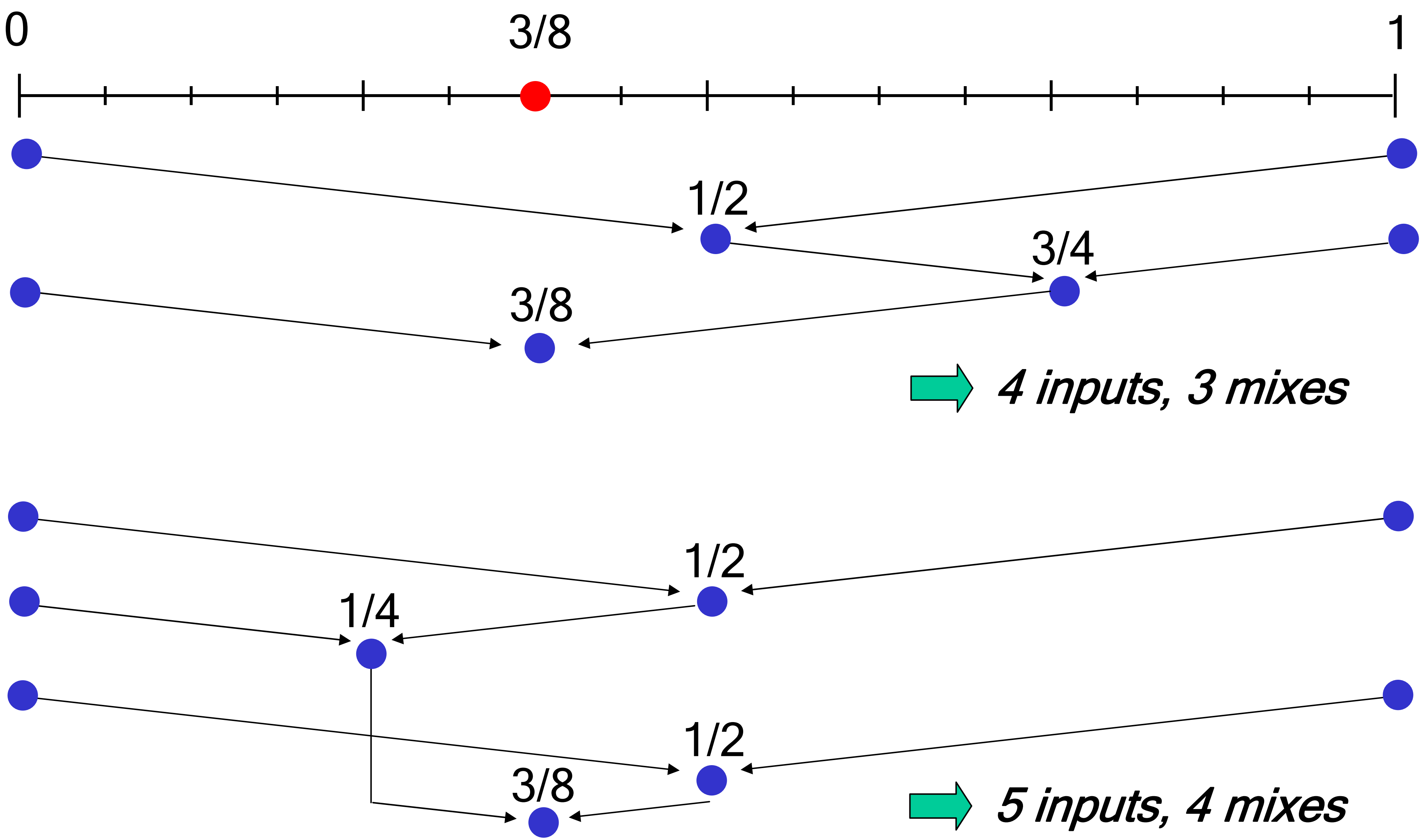
- **How to synthesize complex mixture using simple steps?**
  – Many systems support only 50/50 mixers
  – Should minimize number of mixes, reagent usage
  – Note: some mixtures only reachable within error tolerance ε
  ➡ Interesting scheduling and optimization problem

Why Not Binary Search?



5 inputs, 4 mixes

Why Not Binary Search?

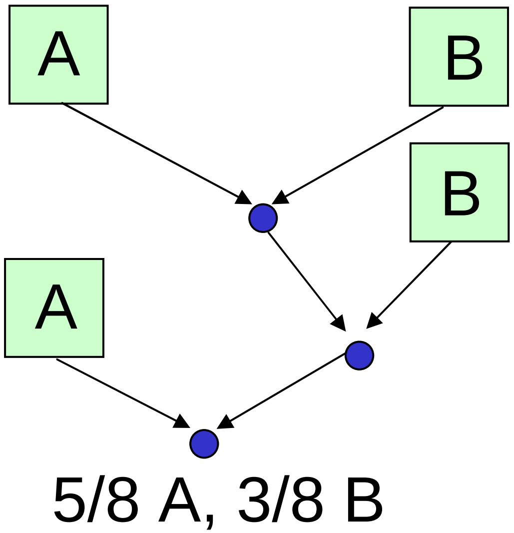


Min-Mix Algorithm

- **Simple algorithm yields minimal number of mixes**
  - For any number of reagents, to any reachable concentration
  - Also minimizes reagent usage on certain chips

Min-Mix Algorithm: Key Insights

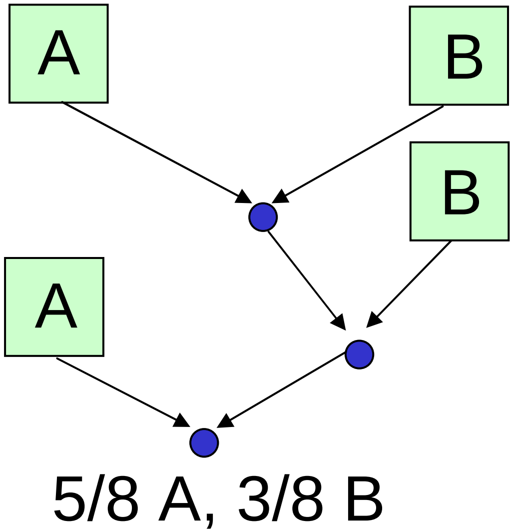
1. The mixing process can be represented by a tree.



Min-Mix Algorithm: Key Insights

1. The mixing process can be represented by a tree.

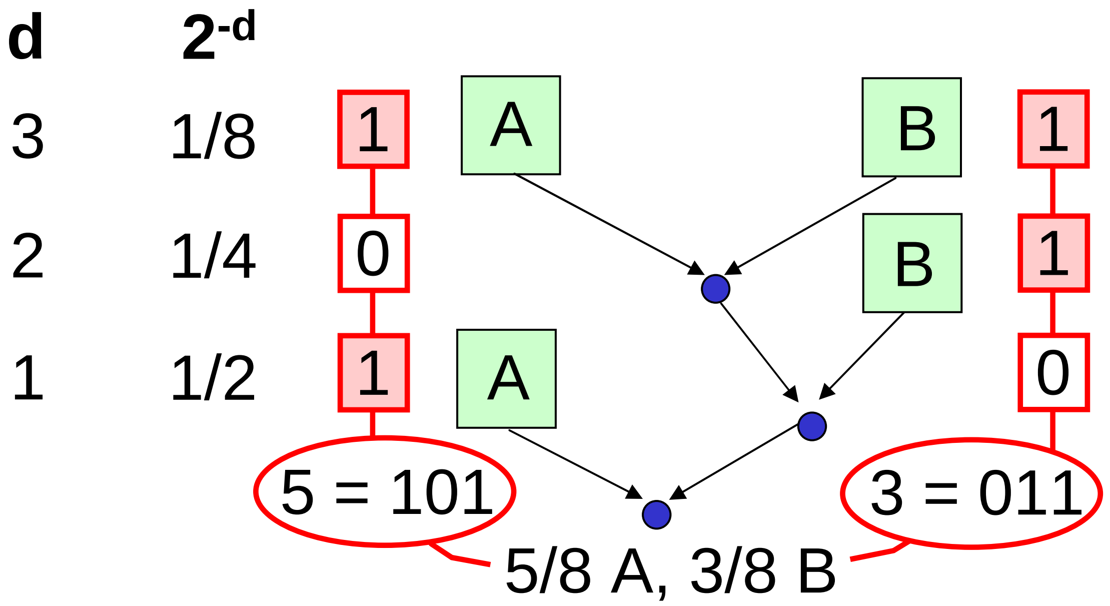
d	**2^{-d}**
3	1/8
2	1/4
1	1/2



2. The contribution of an input sample to the overall mixture is 2^{-d}, where d is the depth of the sample in the tree

Min-Mix Algorithm: Key Insights

1. The mixing process can be represented by a tree.



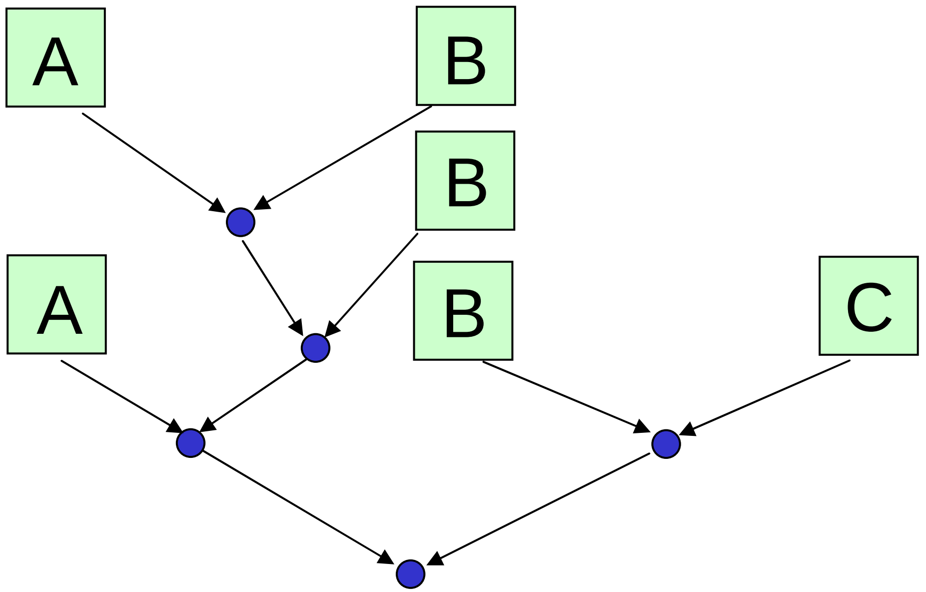
2. The contribution of an input sample to the overall mixture is 2^{-d}, where d is the depth of the sample in the tree

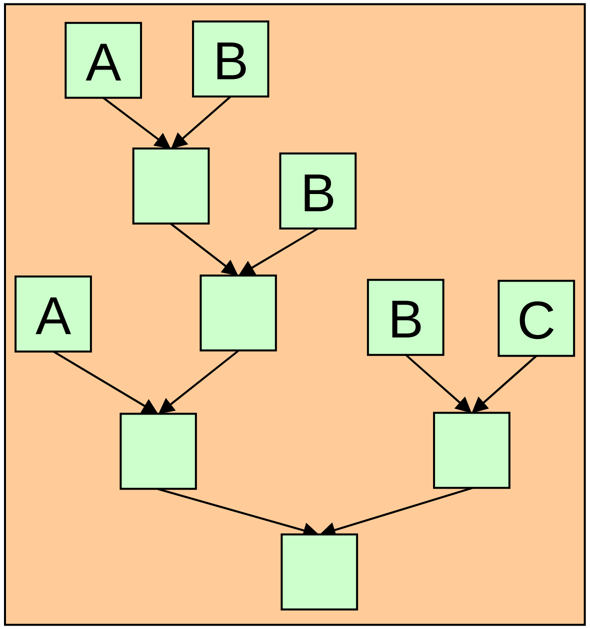
3. In the optimal mixing tree, a reagent appears at depths corresponding to the binary representation of its overall concentration.

Min-Mix Algorithm

- **Example: mix 5/16 A, 7/16 B, 4/16 C**

d	$\mathbf{2^{-d}}$
4	1/16
3	1/8
2	1/4
1	1/2





A=5 **B**=7 **C**=4

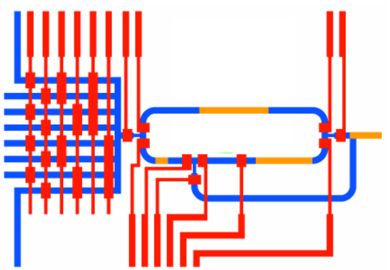
=0101 =0111 =0100

- **To mix k fluids with precision 1/n:**
  - Min-mix algorithm: O(k log n) mixes
  - Binary search: O(k n) mixes

[Natural Computing 2007]

Work In Progress

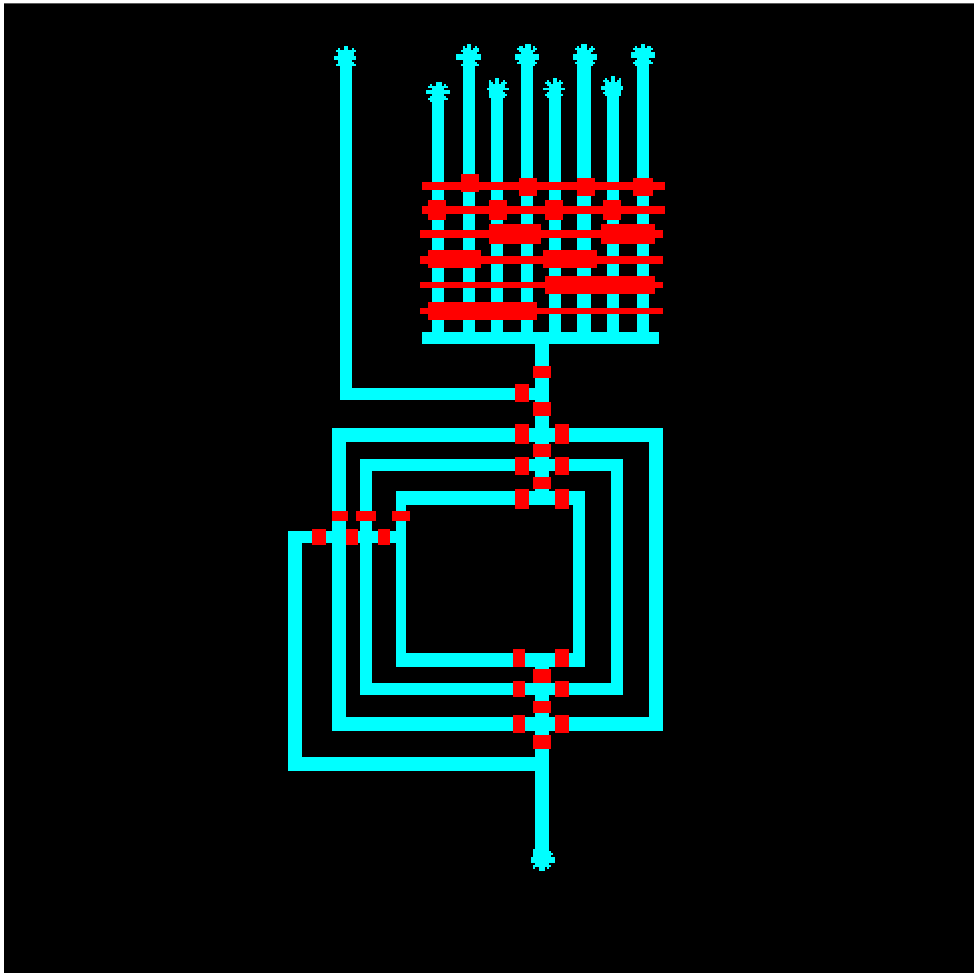
CAD Tools for Microfluidic Chips



- **Microfluidic design tools are in their infancy**
  - Most groups use Adobe Illustrator or AutoCAD
  - Limited automation; every line drawn by hand
- **Due to fast fabrication, redesign is very frequent**
  - Student can do multiple design cycles per week

First Step: Automatic Routing

- **First target: automate the routing of control channels**
  - Connecting valves to pneumatic ports is very tedious
  - Simple constraints govern the channel placement
- **AutoCAD plugin automates this task**
  - Developed With Nada Amin



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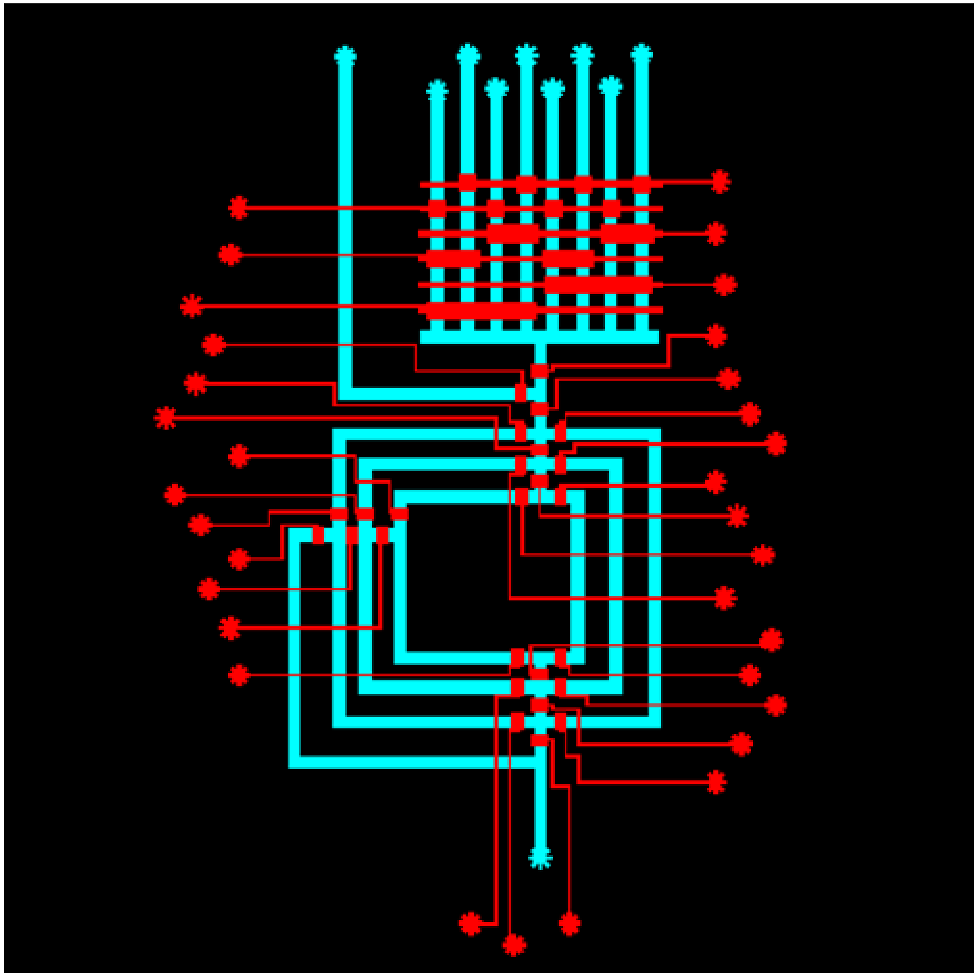

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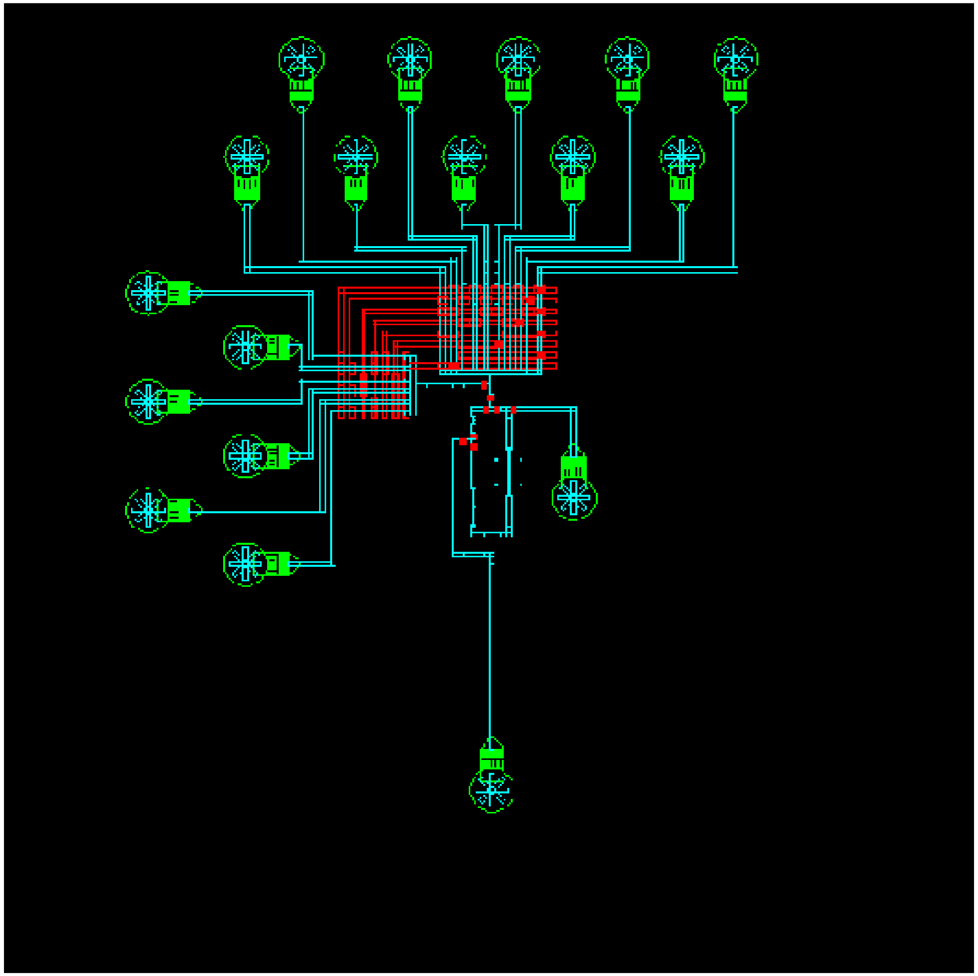

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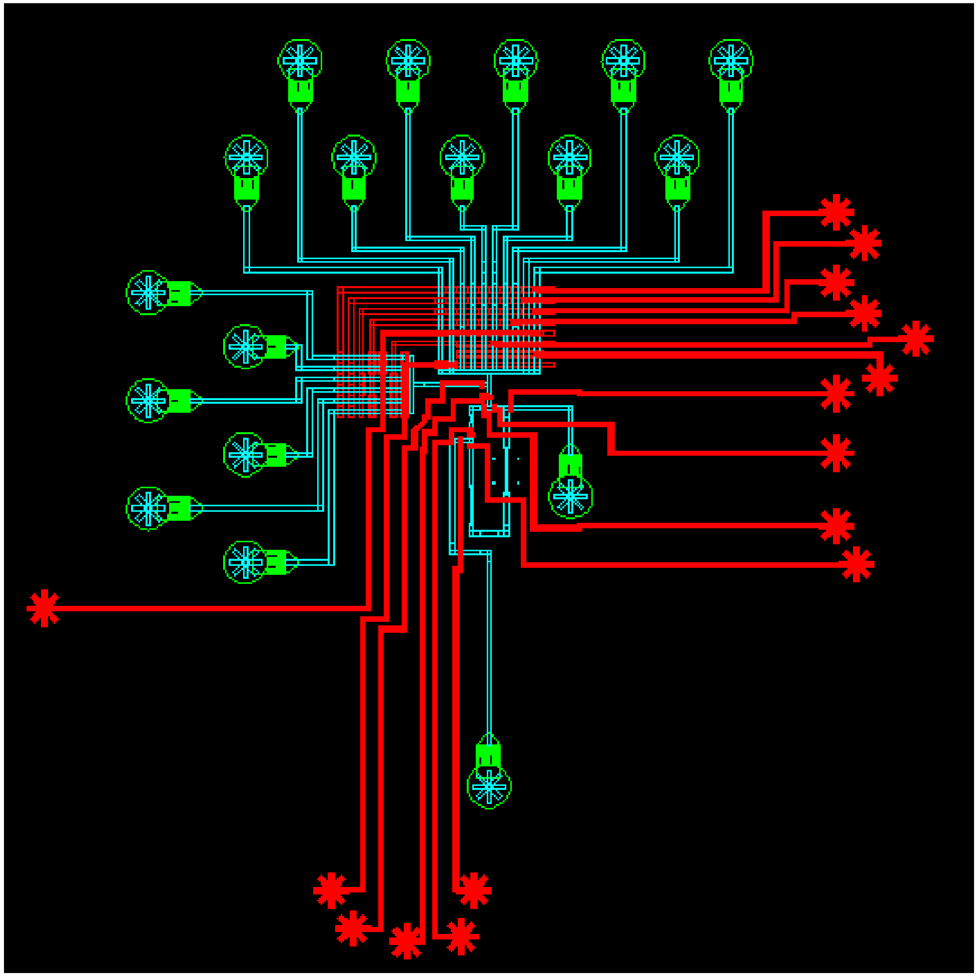

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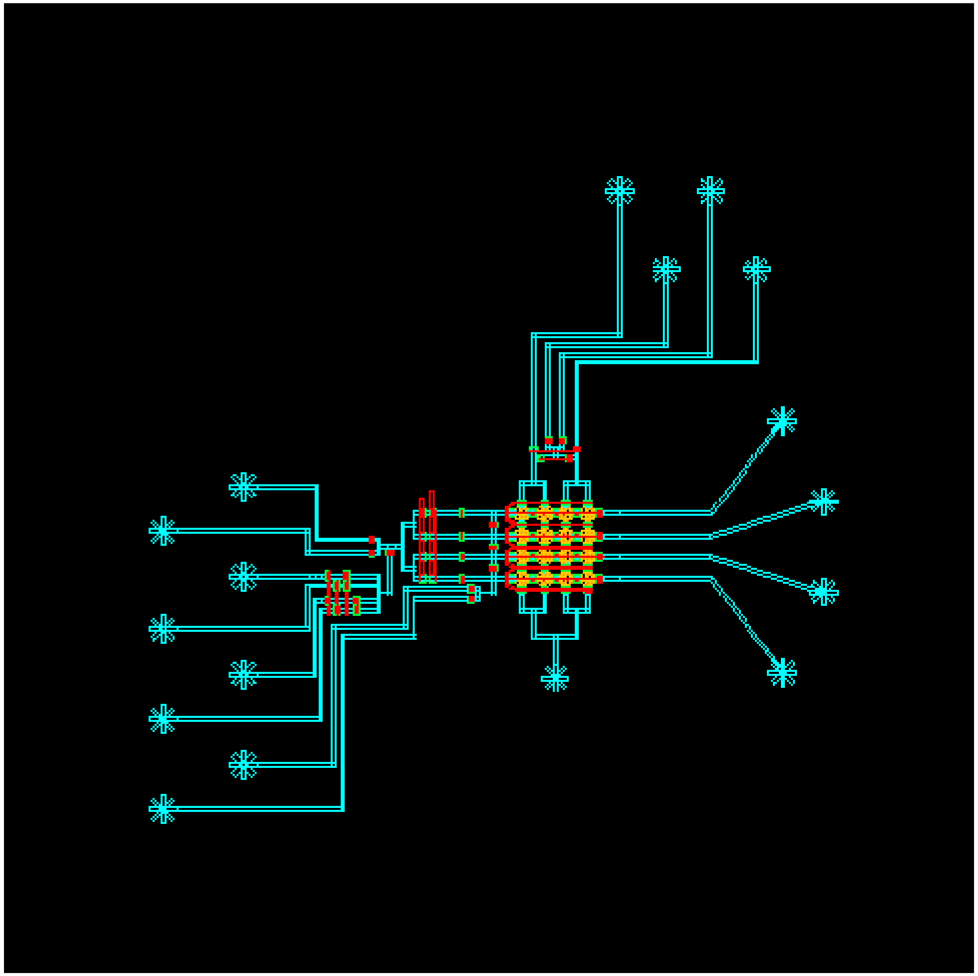

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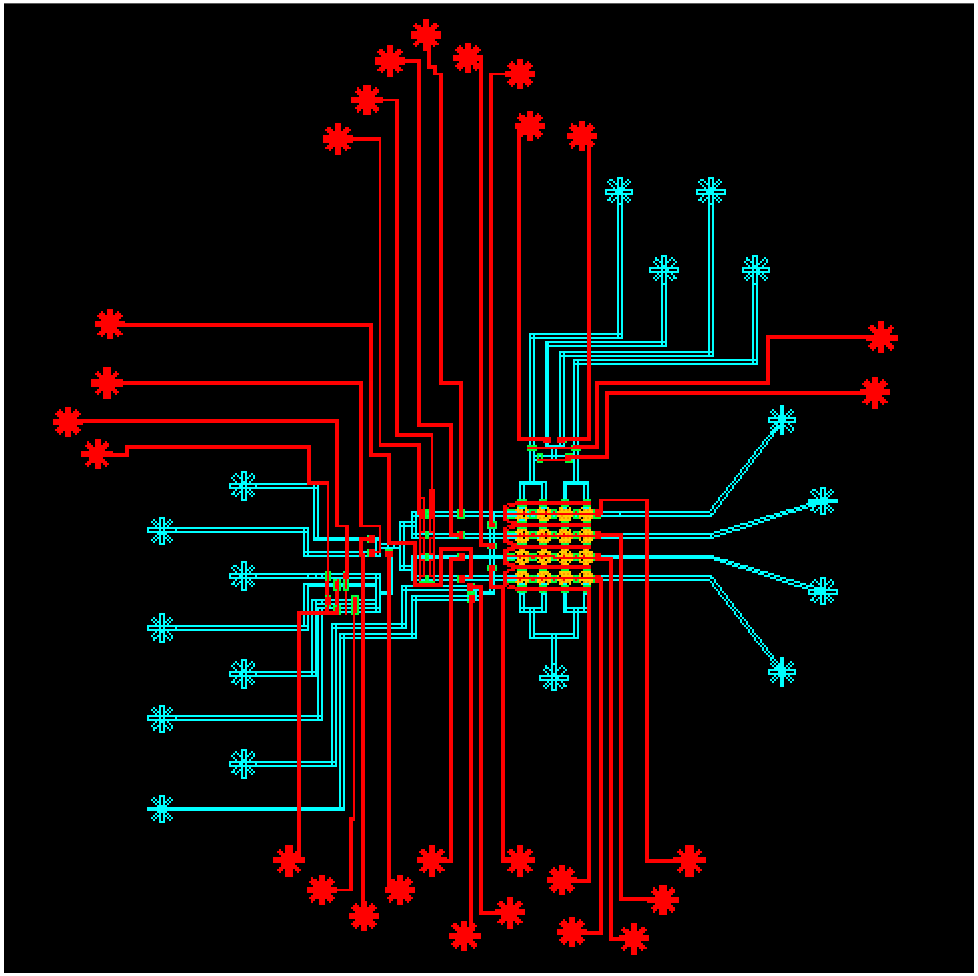
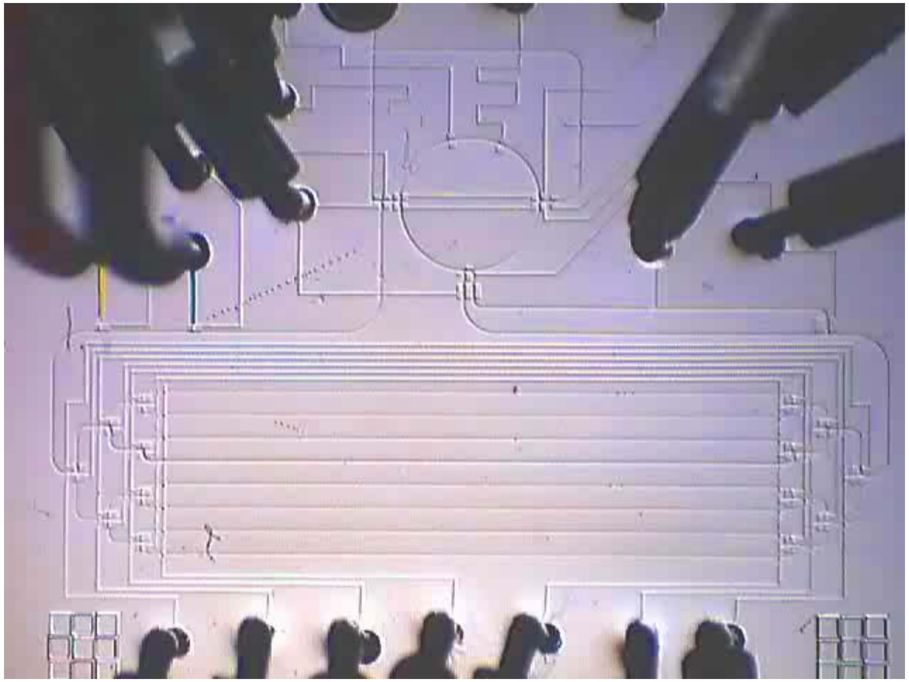


Related Work

- **Aquacore – builds on our work, ISA + architecture** [Amin et al.]
- **Automatic generation / scheduling of biology protocols**
  - Robot scientist: generates/tests genetic hypotheses [King et al.]
  - EDNAC computer for automatically solving 3-SAT [Johnson]
  - Compile SAT to microfluidic chips [Landweber et al.] [van Noort]
  - Mapping sequence graphs to grid-based chips [Su/Chakrabarty]
- **Custom microfluidic chips for biological computation**
  - DNA computing [Grover & Mathies] [van Noort et al.] [McCaskill] [Livstone, Weiss, & Landweber] [Gehani & Reif] [Farfel & Stefanovic]
  - Self-assembly [Somei, Kaneda, Fujii, & Murata] [Whitesides et al.]
- **General-purpose microfluidic chips**
  - Using electrowetting, with flexible mixing [Fair et al.]
  - Using dialectrophoresis, with retargettable GUI [Gascoyne et al.]
  - Using Braille displays as programmable actuators [Gu et al.]

Conclusions

- **Abstraction layers for programmable microfluidics**
  - General-purpose chips
  - Fluidic ISA
  - BioStream language
  - Mixing algorithms



- **Vision for microfluidics: everyone uses standard chip**
- **Vision for software: a defacto language for experimental science**
  - Download a colleague's code, run it on your chip
  - Compose modules and libraries to enable complex experiments that are impossible to perform today

http://cag.csail.mit.edu/biostream

Extra Slides

How Can Computer Scientists Contribute?

- **Applying the ideas from our field to a new domain**
  - Sometimes requires deep adaptations (e.g., digital gain)
- **Our contributions:**
  - First soft-lithography digital architecture with sample alignment
  - First demonstration of portability: same code, multiple chips
  - New high-level programming abstractions for microfluidics
  - First O(lg n) mixing algorithm for unit volumes (vs O(n))
- **Open problems:**
  - Adapt unique (linear) types for microfluidics
  - Sound scheduling under timing constraints
  - Dynamic optimization of *slow* co-processors (lazy vectorization?)
  - Mixing algorithms for different ISA’s (e.g., lossless mixing)
  - Generate a CAD layout from a problem description