Programmable Microfluidics Using Soft Lithography

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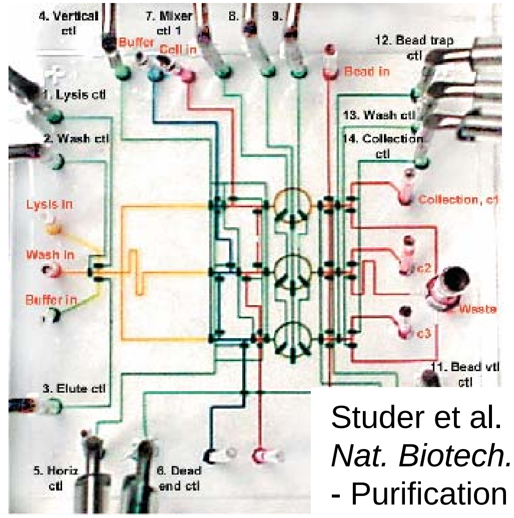
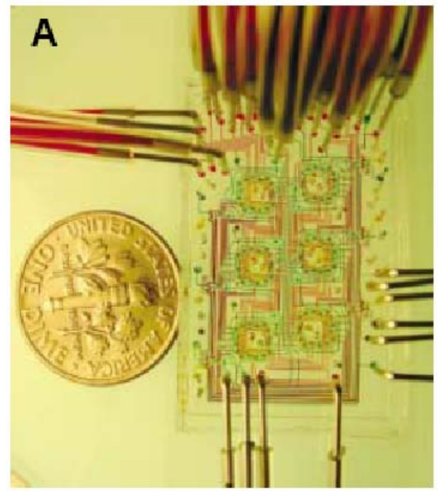
Soft Lithography: State of the Art…

- Areas of active bio research
  - protein crystallization, cell culturing, PCR, enzyme assays, particle synthesis, etc
- **Pro:**
  - Integrated valves and pumps
  - Rapid fabrication
  - Cost
- **Con:**
  - Application specific devices
  - Complicated control



Studer et al.
Nat. Biotech. (2004)
- Purification of Nucleic acids

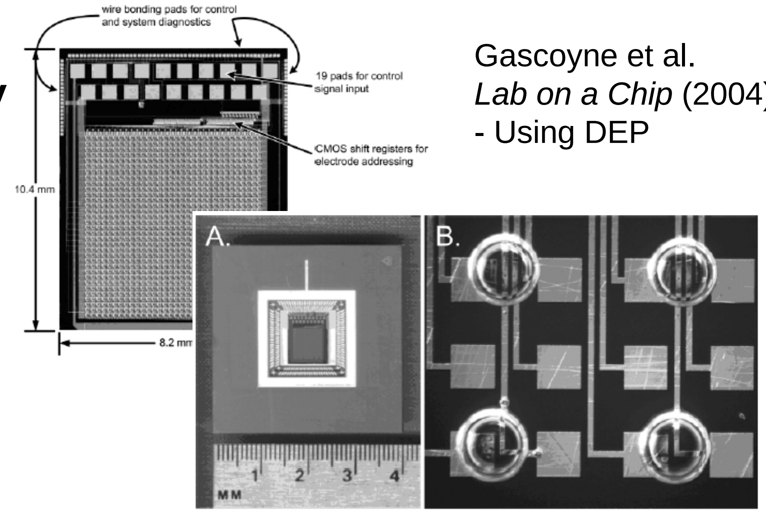


Ballagadde et al.
Science (2005)
- Microchemostat

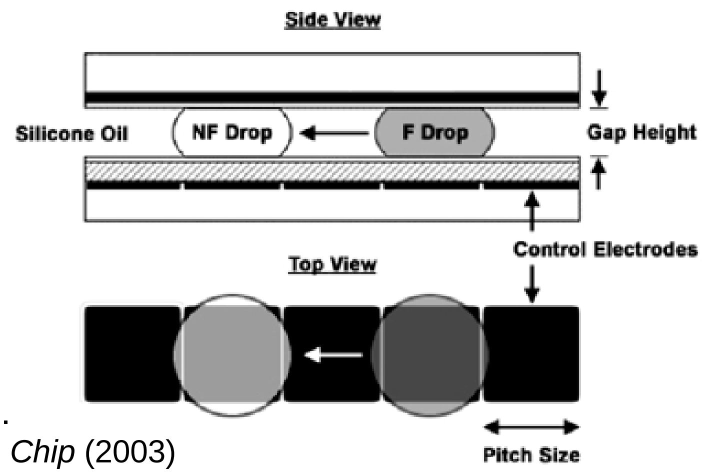
- M.A. Unger, H.P. Chou, T. Thorsen, A. Scherer and S.R. Quake, *Science*, **2000**, (288), 113-116.

…"Digital" Microfluidics?

- Manipulation of discrete droplets on an electrode array using electric fields
  - "Droplet processors"
- **Pro:**
  - Flexible operation
  - Amenable to computer control
  - No sample diffusion
- **Con:**
  - Difficulties with various biological samples
  - Imprecise metering/splitting
    - Affects reagent concentration
  - Fabrication



Gascoyne et al.
Lab on a Chip (2004)
- Using DEP



Fair et al.
Lab on a Chip (2003)
- Using EWOD

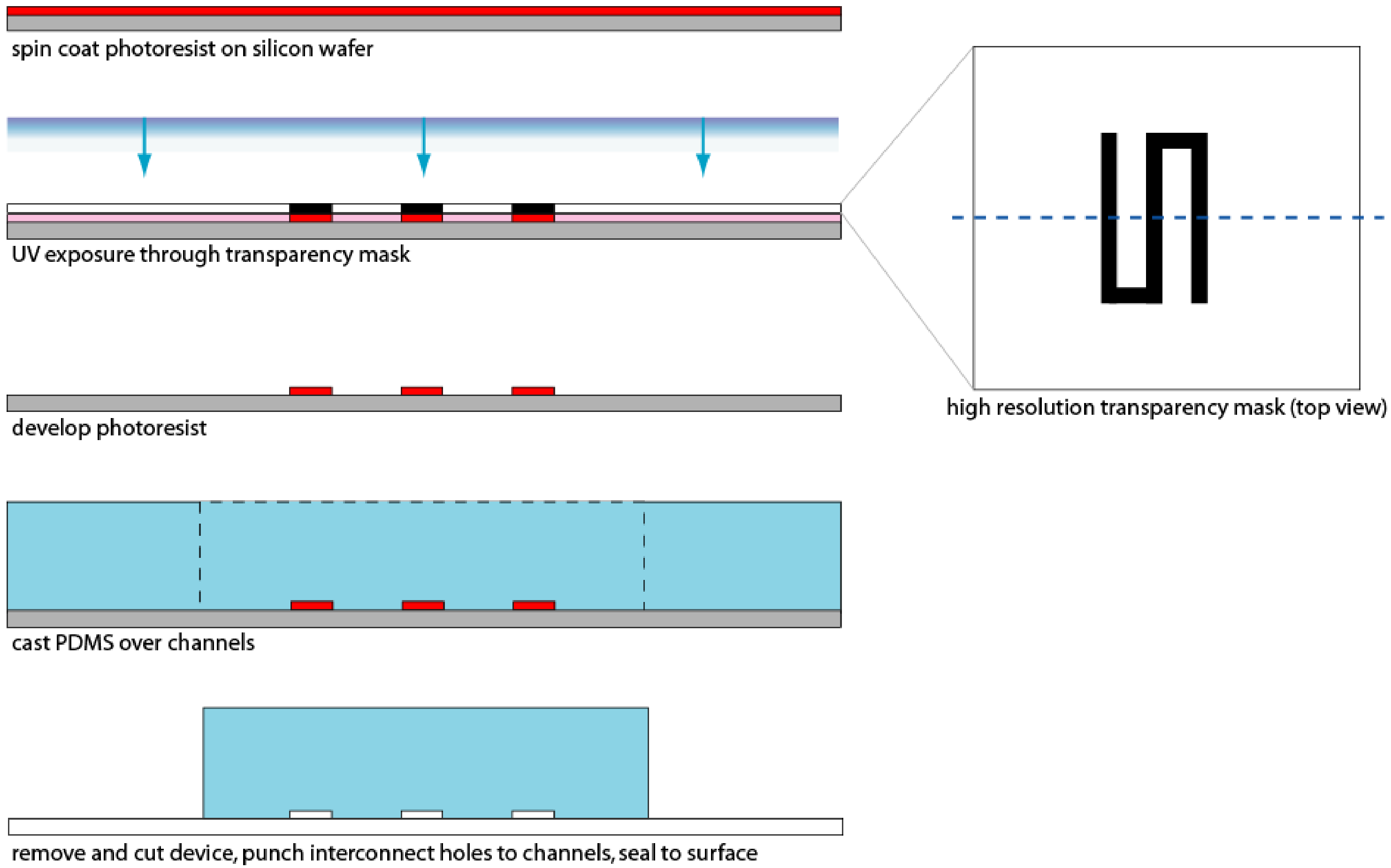
Motivation

- Idea: a biological lab on a single chip
  - Input channels for reagents
  - Chambers for mixing fluids
  - Sensors for reading properties
- Combined benefits of previous approaches:
  - Use “digital” samples that can be prepared, moved, stored, measured..
  - Increased precision/robustness of soft lithography
- General purpose, programmable devices
  - Can complex procedures be automated?
  - Enabling experiments to be designed like computer programs

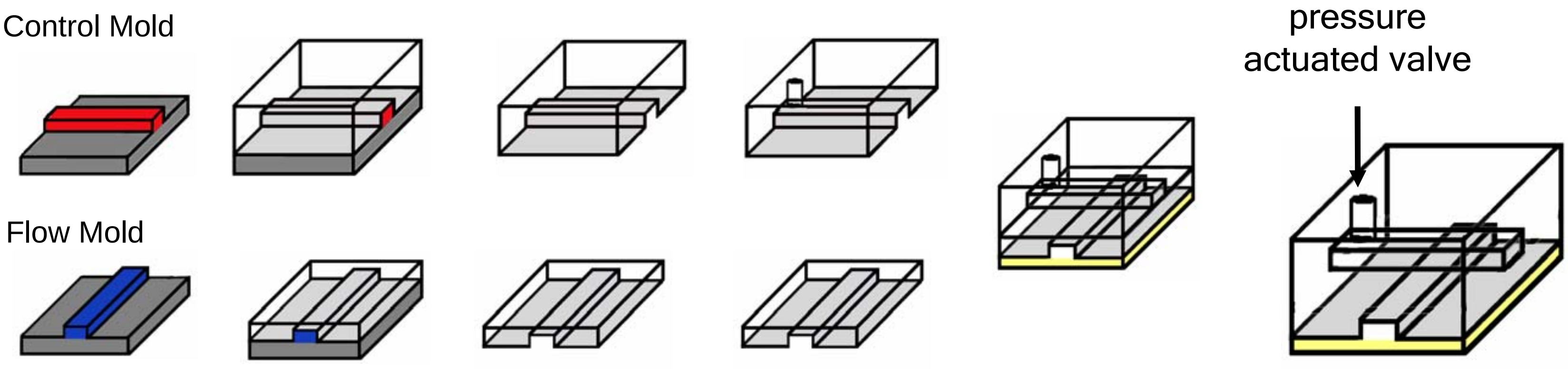
Outline

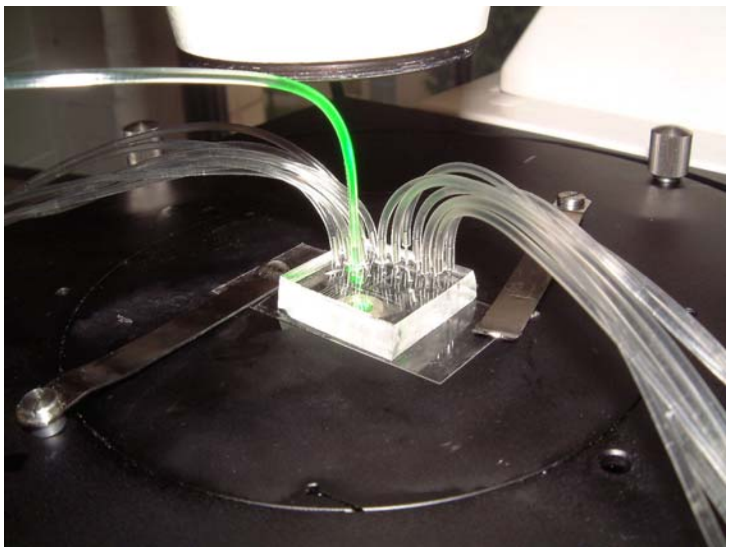
1. Motivation and Background
2. Our Contributions
    1. Sample Transport
    2. Sample Alignment
    3. Device Implementation
3. Future Work and Conclusions

Our approach: Soft Lithography



Multilayer Soft Lithography (MSL)





- Pressurized reservoirs of sample are connected via tubing
- Computer controlled micro-solenoids actuate valves
- Relative widths and pressure differences between F&C govern valve performance

Urbanski and Thies, 2005

Challenges to consider

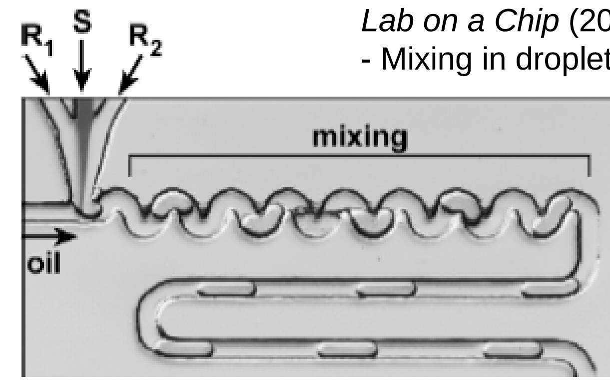
General purpose implementation using MSL involves specific challenges:

- Evaporation
- Metering
- Sample integrity
- Transport
- Alignment

Discrete Samples

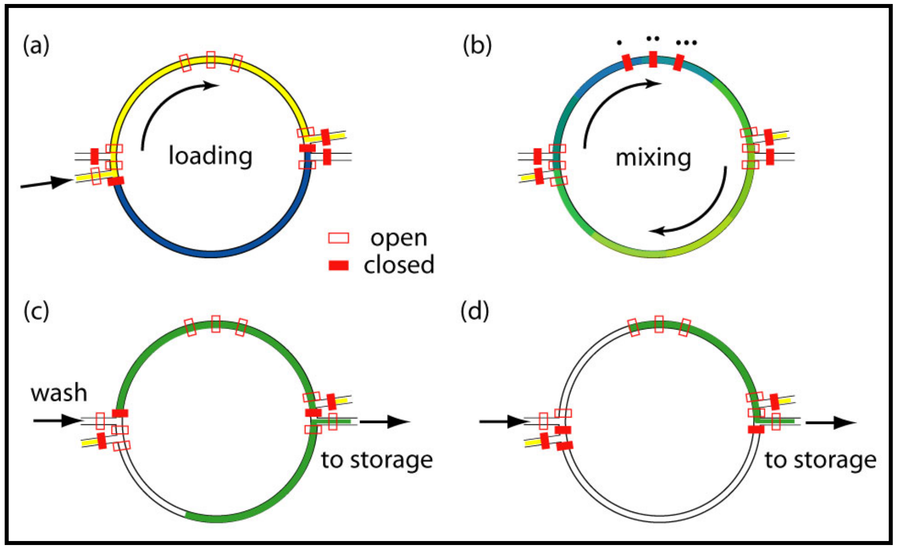
- Advantages of discrete samples
  - No sample dispersion
  - “Toolbox” methods for generating, splitting, merging, storing samples
  - Droplets can behave as microreactors

Ismagilov et al.
Lab on a Chip (2004)
- Mixing in droplets



<u>Our Approach:</u>

- Require *arbitrary* sample manipulation
- Individually meter aqueous samples into an immiscible continuous phase
- Individually composed samples



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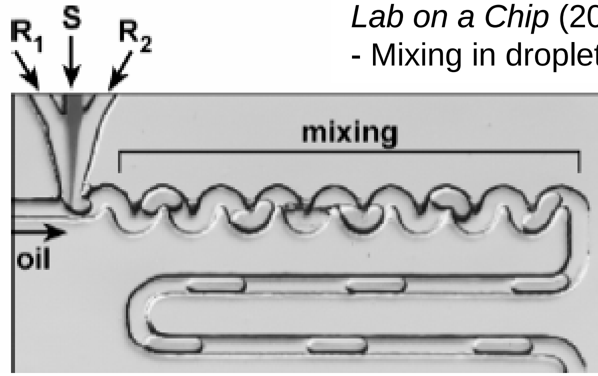

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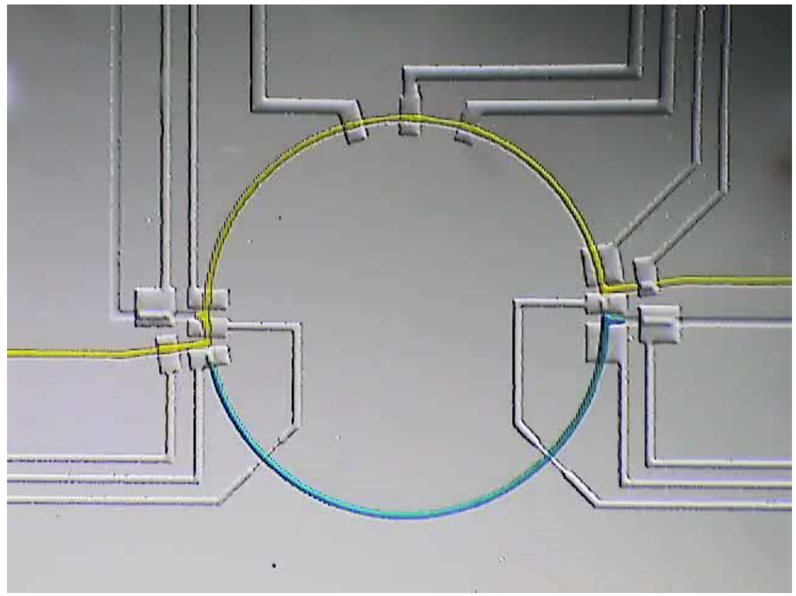
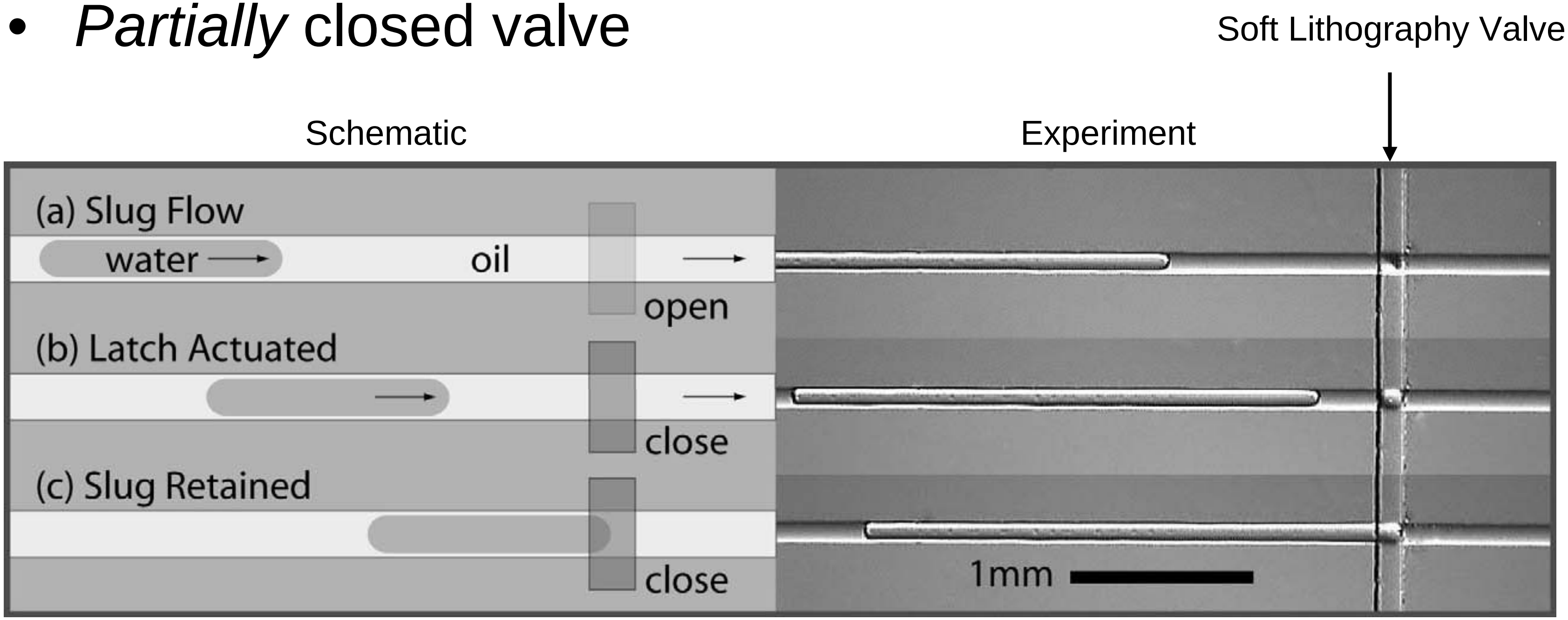


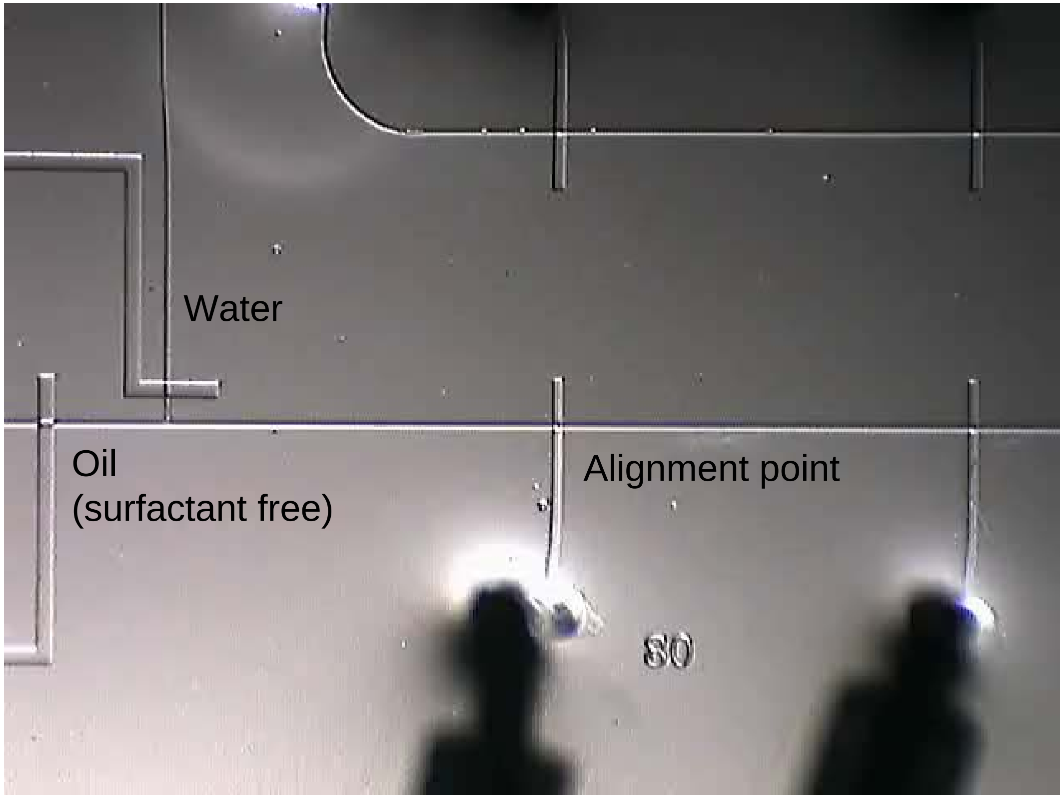
Slug Alignment – “Latching”

- Analogous to the 1-bit logic element…
- *Partially* closed valve



- Enables **open loop** control of emulsified samples – timing may be used to align slugs though the channels
- Scalable and robust

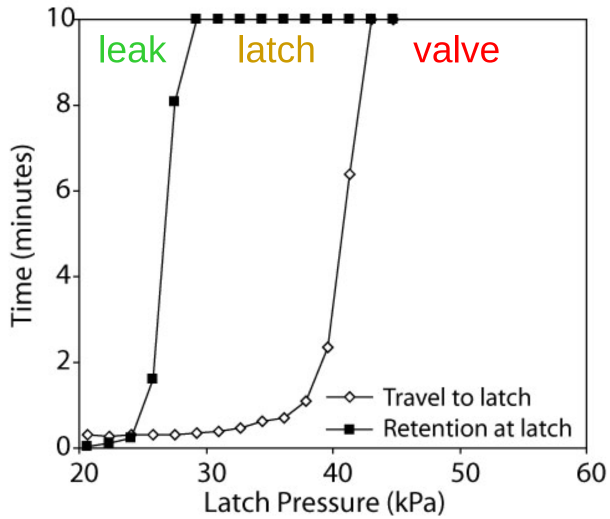
Latch Demonstration



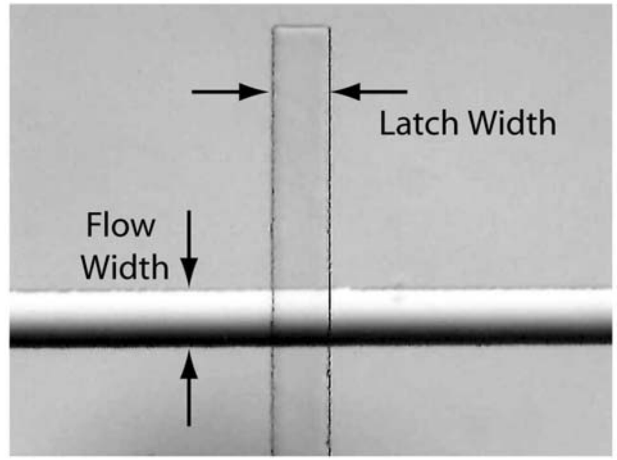
- Aqueous slugs are dispensed into a continuous oil phase, latched, and released
- Oil port remains open

Latch Characterization

Operating Window



50F/
50C



- Goal: determine optimal operating points to retain slugs without hindering the flow of samples
- Operating window defined by tuning latch pressures

Latch Characterization

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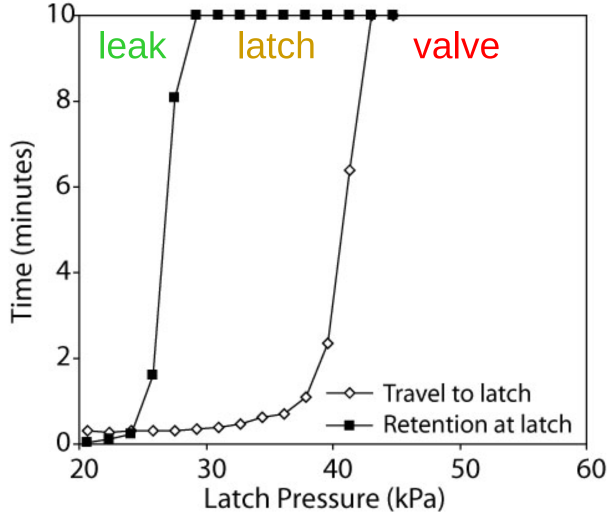

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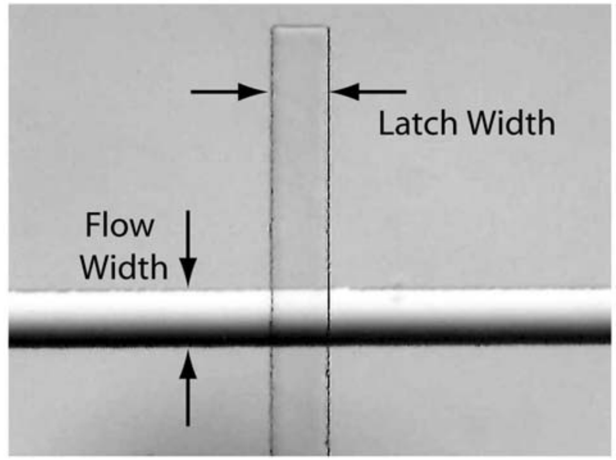
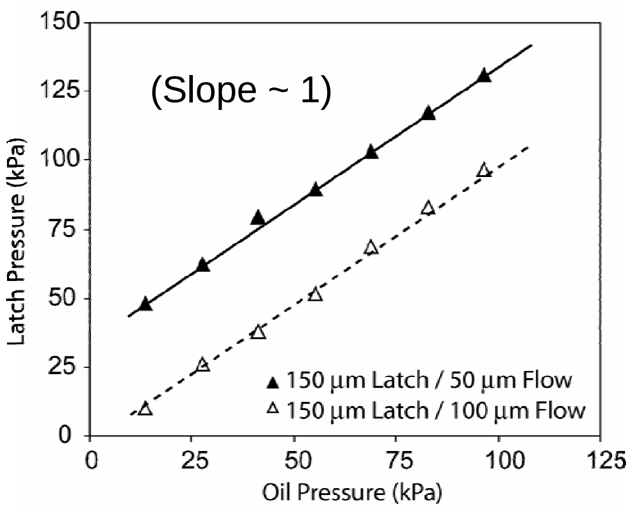


Operating points



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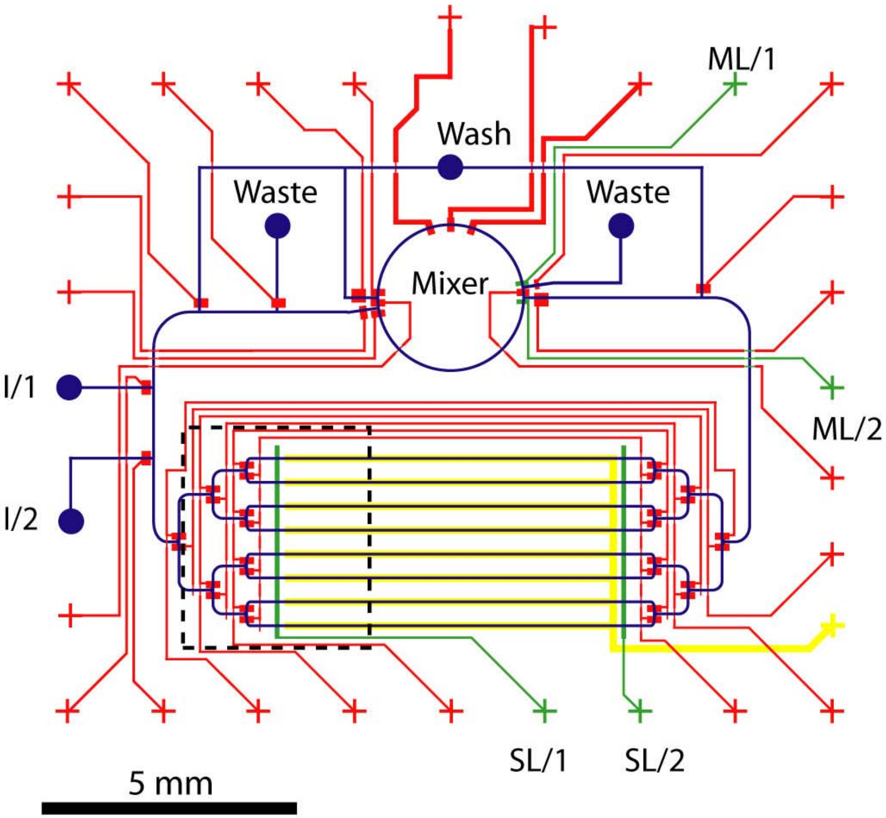
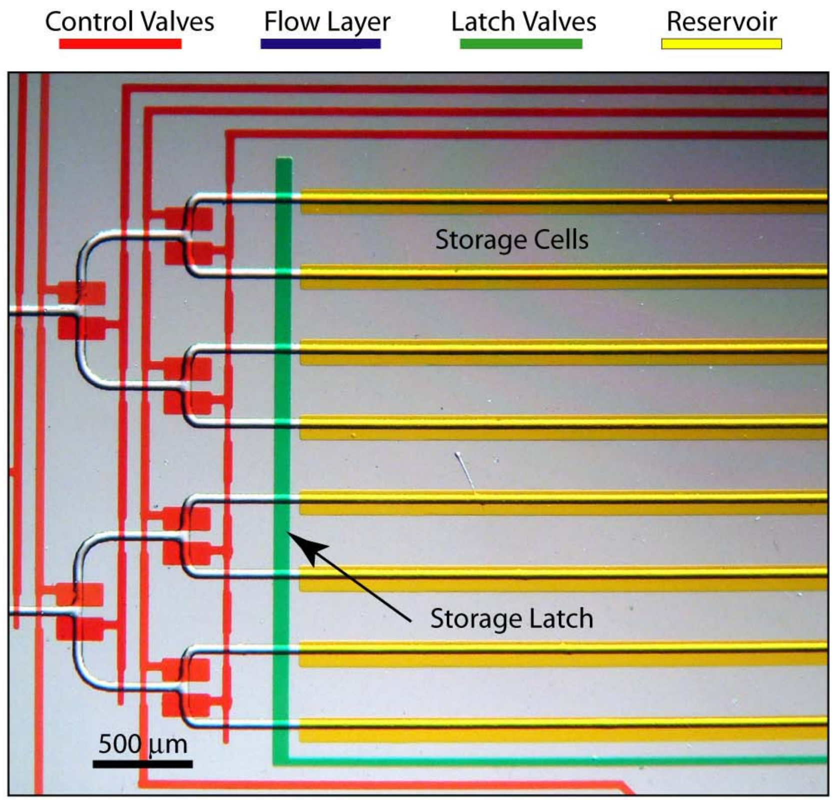
General Purpose Architecture





- Input / Output
- Rotary Mixer
- Channel Network with Purge
- Addressable Storage
- Latches – Mixer to Storage / Storage to Mixer

Details:

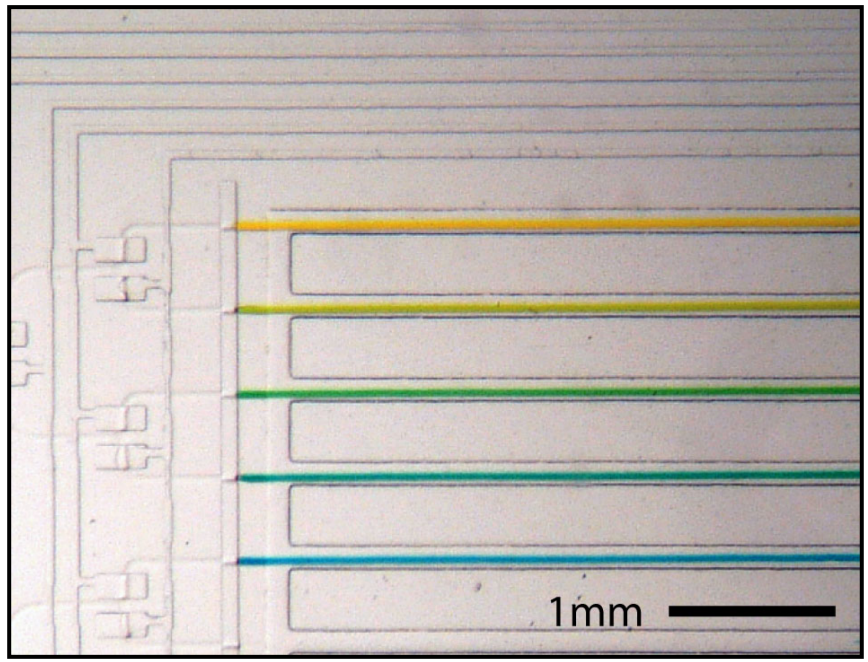
- J.P. Urbanski, W. Thies, C. Rhodes, S. Amarasinghe and T. Thorsen, *Lab on a Chip,* **2006**, 6(1), 96-104.

Programming and Automation

- Example program:

```
Fluid yellow = input(1);
Fluid blue = input(2);
Fluid[] gradient = new Fluid[5];
   for (int i=0; i<=4; i++) {
        gradient[i] = mix(blue, yellow, i/4.0, 1-i/4.0);
  }
```

- Software language allows simple programs to be written – *without requiring knowledge of the device architecture*
- Device driver for a particular chip – maps primitive operations (mix, store etc) to combination of valve operations



A linear gradient of two fluids
(yellow and blue food colorings)

Current Focus and Implementation

- Device level
  - Quantify accuracy and error tolerance of mixing operations
  - Integrate feedback from sensors in conjunction with proof of concept biological applications

- First Model System
  - Enzyme kinetic assays using β-Galactosidase
- Metabolic Assessments of Cell Cultures
  - In collaboration with M. Johnson, D. Gardner, Colorado Center for Reproductive Medicine

Conclusions

- Demonstrated first system for digital microfluidics using soft lithography medium
- Microfluidic latch is a novel alignment mechanism, crucial for precise and scalable operation
- Using a programming language, scientists will be able to automate complex experiments without requiring microfluidic expertise

Acknowledgments

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- Jeremy Levitan (ME/Math)

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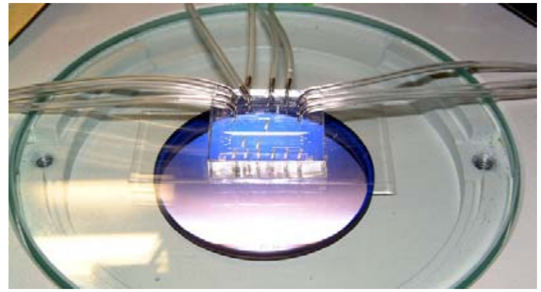
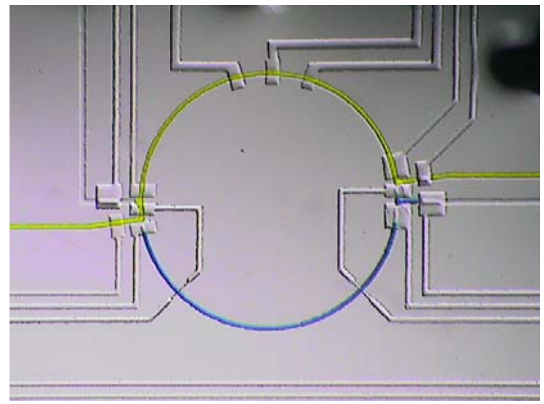
- NSF





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