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Harvard Medical School

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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

[Farfel/Stefanovic] [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)
Moore’s Law of Microfluidics: Valve Density Doubles Every 4 Months

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);
  }
  ```

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

450 Valve Operations
Our Approach: “Write Once, Run Anywhere”

- Example: Gradient generation

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- Hidden from programmer:
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```
setValve(0, HIGH);  setValve(1, HIGH);
setValve(2, LOW);   setValve(3, HIGH);
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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);
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```

450 Valve Operations
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setValve(2, LOW); setValve(3, HIGH);
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setValve(18, HIGH); setValve(19, LOW);
```
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

 Fluidic Hardware Primitives
- valves, multiplexers, mixers, latches

Silicon Analog
- C
- x86
- Pentium III, Pentium IV
- transistors, registers, …
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**Benefits:**
- Division of labor
- Portability
- Scalability
- Expressivity

**Fluidic Hardware Primitives**
- valves, multiplexers, mixers, latches
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chip 1
chip 2
chip 3
Primitive 1: A Valve (Quake et al.)

Control Layer

0. Start with mask of channels

Flow Layer
Primitive 1: A Valve (Quake et al.)

1. Deposit pattern on silicon wafer
Primitive 1: A Valve (Quake et al.)

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

- Thick layer (poured)
- Thin layer (spin-coated)
Primitive 1: A Valve (Quake et al.)

3. Bake at 80° C (primary cure), then release PDMS from mold
Primitive 1: A Valve (Quake et al.)

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

Flow Layer
Primitive 1: A Valve (Quake et al.)

Control Layer

Flow Layer

5. Align flow layer over control layer
Primitive 1: A Valve (Quake et al.)

6. Bake at 80° C (secondary cure)
Primitive 1: A Valve (Quake et al.)

Control Layer

Flow Layer

7. When pressure is high, control channel pinches flow channel to form a valve
Primitive 2: A Multiplexerer (Thorsen et al.)

Bit 2  Bit 1  Bit 0
0  1  0  1  0  1

Input

Output 7
Output 6
Output 5
Output 4
Output 3
Output 2
Output 1
Output 0

flow layer
control layer
Primitive 2: A Multiplexer (Thorsen et al.)

Example: select 3 = 011
Primitive 2: A Multiplexer (Thorsen et al.)

Example: select 3 = 011
Primitive 2: A Multiplexerer (Thorsen et al.)

Example: select 3 = 011
Primitive 3: A Mixer (Quake et al.)

1. Load sample on top
Primitive 3: A Mixer (Quake et al.)

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
  - C-shaped rings / microsieves
  - Holographic optical traps
  - Dialectrophoresis

- In our chips: U-Shaped Microsieves in PDMS Chambers

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
Toward “General Purpose” Microfluidic Chips

- **Inputs**
- **Sensors and Actuators**
- **Fluidic Storage (RAM)**
- **Outputs**

![Diagram of microfluidic chip components: inputs, sensors and actuators, fluidic storage, and outputs.](image-url)
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
- Soft error Handling?
- Randomized Gates [Palem]
- Replenish charge (GAIN)
- Loss of charge

Instruction Set Architecture (ISA)
- Expose loss in ISA
  - Compiler deals with it

High-Level Language
- Expose loss in language
  - User deals with it

Hardware
- Replenish fluids?
  - Maybe (e.g., with water)
  - But may affect chemistry

Microfluidics
- 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 src₁, int src₂, int dst)
  - Ex: mix(1, 2, 3)

    | Storage Cells | Mixer |
    |---------------|-------|
    | 1             |       |
    | 2             |       |
    | 3             |       |
    | 4             |       |
  - To allow for lossy transport, only 1 unit of mixture retained
Gradient Generation in Fluidic ISA
Gradient Generation in Fluidic ISA

<table>
<thead>
<tr>
<th>Direct Control</th>
<th>Fluidic ISA</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 450 valve actuations</td>
<td></td>
</tr>
<tr>
<td>- only works on 1 chip</td>
<td></td>
</tr>
<tr>
<td>- 15 instructions</td>
<td></td>
</tr>
<tr>
<td>- portable across chips</td>
<td></td>
</tr>
</tbody>
</table>

```plaintext
wait(2000);
setValve(14, HIGH); setValve(2, LOW);
wait(1000);
setValve(4, HIGH); setValve(12, LOW);
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wait(2000);
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setValve(4, LOW); setValve(5, HIGH);
setValve(6, HIGH); setValve(7, LOW);
setValve(8, LOW); setValue(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);
```

```plaintext
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);
```
Implementation: Oil-Driven Chip

<table>
<thead>
<tr>
<th></th>
<th>Inputs</th>
<th>Storage Cells</th>
<th>Background Phase</th>
<th>Wash Phase</th>
<th>Mixing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chip 1</td>
<td>2</td>
<td>8</td>
<td>Oil</td>
<td>—</td>
<td>Rotary</td>
</tr>
</tbody>
</table>
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
}
```

<table>
<thead>
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Implementation 2: Air-Driven Chip

<table>
<thead>
<tr>
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<th>Storage Cells</th>
<th>Background Phase</th>
<th>Wash Phase</th>
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</tr>
</thead>
<tbody>
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<td>2</td>
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<td>Oil</td>
<td>—</td>
<td>Rotary</td>
</tr>
<tr>
<td>Chip 2</td>
<td>4</td>
<td>32</td>
<td>Air</td>
<td>Water</td>
<td>In channels</td>
</tr>
</tbody>
</table>
Implementation 2: Air-Driven Chip

```plaintext
mix (S₁, S₂, D) {
    1. Load S₁
    2. Load S₂
    3. Mix / Store into D
    4. Wash S₁
    5. Wash S₂
}
```

<table>
<thead>
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Fluidic Abstraction Layers

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chip 1

chip 2

chip 3
Abstraction 1: Managing Fluid Storage

Fluidic ISA

- 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

- 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

```java
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:

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

```java
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

- Allows mixing fluids in any proportion, not just 50/50
  - **Fluid mix** (Fluid F₁, float p₁, Fluid f₂, float F₂)
    → Returns Fluid that is p₁ parts F₁ and p₂ parts F₂
  - 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

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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
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)

```java
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 $[\text{min}, \text{max}]$ 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 \( \rightarrow \) 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

• Implemented as a Java library
  – Allows flexible integration with general-purpose Java code

• Targets microfluidic chips or auto-generated simulator

```java
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);
```
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);
}
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 reagent 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 $\varepsilon$
  - Interesting scheduling and optimization problem
Why Not Binary Search?

5 inputs, 4 mixes
Why Not Binary Search?

4 inputs, 3 mixes

5 inputs, 4 mixes
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.

![Diagram of Min-Mix Algorithm]

\[ \frac{5}{8} A, \frac{3}{8} B \]
Min-Mix Algorithm: Key Insights

1. The mixing process can be represented by a tree. 
   
   \[ \begin{array}{c|c}
     d & 2^{-d} \\
     \hline
     3 & 1/8 \\
     2 & 1/4 \\
     1 & 1/2 \\
   \end{array} \]

   ![Diagram of a tree with nodes A and B and their contributions]

   5/8 A, 3/8 B

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.

<table>
<thead>
<tr>
<th>d</th>
<th>$2^{-d}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1/8</td>
</tr>
<tr>
<td>2</td>
<td>1/4</td>
</tr>
<tr>
<td>1</td>
<td>1/2</td>
</tr>
</tbody>
</table>

![Diagram showing the mixing process](image)

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

<table>
<thead>
<tr>
<th>d</th>
<th>2^{-d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1/16</td>
</tr>
<tr>
<td>3</td>
<td>1/8</td>
</tr>
<tr>
<td>2</td>
<td>1/4</td>
</tr>
<tr>
<td>1</td>
<td>1/2</td>
</tr>
</tbody>
</table>

\[ A = 5 = 0101 \quad B = 7 = 0111 \quad C = 4 = 0100 \]

• 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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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