

# future of advanced cyber-physical microsystems

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sensor swarm

mobile

cloud



## computing

sensor swarm

microsystem



## microelectronics



#### microelectronics

#### 2014: 20.000.000.000



1947: 1



1971: 2.300

#### 2008: 47.000.000

cyber-physical systems



### smaller, faster, cheaper

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#### part 1

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- microfluidics
  - motivation
  - -technology
  - -design
  - applications



## microfluidics

## biochemical computing - ∰ why?

- Biotech
  - DNA analysis
- Medicine
  - Clinical diagnosis
  - Therapeutics
- Ecology
  - Monitoring the quality of air/water/food
- Pharmacy
  - Screening
  - Synthesis of new drugs







#### room

#### table

#### coin

#### smaller fluid volumes



4 mL of PCR master mix



\$191

100 reactions at 50 µL
each =
\$1.91 / reaction

1000 reactions at 5 µL
each =
\$0.19 / reaction

#### smaller sample sizes







#### Milliliters

#### Microliters

#### faster reactions



1/2 the size

1/8 the volume

8x the concentration!

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64x faster!!!



#### size matters!

#### Size matters!





#### 1 Liter - kitchen-sized fluidics!

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#### Size matters!

What's a microliter? 1/1.000.000'th of a Liter/ Volume of a poppy seed



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#### Size matters!



What's a nanoliter? Volume of a laser-printed period  $1/1000^{th}$  the volumen of a poppy seed

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#### Size matters

What's a picoliter? Volume of a human cell 1/1000<sup>th</sup> the volumen of a printed period

What's a femtoliter? Volume of a bacteria 1/1000<sup>th</sup> the volumen of a human cell

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#### miniaturization



cyber-physical systems



computer v.s. biochip

1971 - 2.300 transistors



Intel 4004 4-bit 10um, 2.300 transistors

2002 – 2.056 valves



Science 18 October 2002: Vol. 298 no. 5593 pp. 580-584



## microfluidic technology



### microfluidics



### switch configurations



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## Biochip Architecture



Microfluidic very<br/>large scaleValves combined to form more<br/>complex units, e.g, switches, mixers,<br/>multiplexers, micropumps.

Microfluidic mixer





#### Biochip Architecture

Microfluidic mixer





### microfluidics



### Microfluidic Mixer: Operational Phases





(iii) Op1

open
closed

(iv) Op2

Phase	$v_1$	$v_2$	<i>v</i> <sub>3</sub>	<i>v</i> <sub>4</sub>	$v_5$	$v_6$	$v_7$	$v_8$	<i>v</i> 9
1. Ip1	0	0	1	0	0	0	0	0	1
2. Ip2	0	1	0	0	0	0	1	0	0
3. Mix	1	0	0	Mix	Mix	Mix	0	1	0
4. Op1	0	0	1	0	0	0	0	0	1
5. Op2	0	1	0	0	0	0	1	0	0

## microfluidic storage device



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

#### Flow-Based Biochip Architecture





#### Schematic view

Functional view

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## microfluidic design

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cyber-physical systems

32



## microfluidic design



### Biocoder



#### Plasmid DNA Extraction – Miniprep (Excerpt)

Equipment:

Incubator

o Centrifuge

tubes

Sterile 1.5-ml

#### Solutions/reagents:

- Rich medium (LB, YT, or Terrific medium) containing appropriate antibiotic Alkaline Lysis Solution I
- (50 mM Glucose, 25 mM Tris-HC (pH 8.0), 10 mM EDTA (pH 8.0))
- freshly prepared Alkaline Lysis Solution II (0.2 N NaOH, 1% SDS (w/v))
- Alkaline Lysis Solution III (5 M sodium acetate, glacial acetic acid)
- a single colony of transformed bacteria

#### Steps:

1. Preparation of cells

Inoculate 2 ml Rich medium (LB, YT, or Terrific medium) containing appropriate antibiotic with a single colony of transformed bacteria and incubate with shaking for 12 hrs (overnight) at 37°C.

2. Measure out 1.5 ml of culture into sterile 1.5-ml microcentrifuge tube. Centrifuge at maximum speed for 30 secs at 4°C; gently aspirate out the supernatant and discard it. Leave the pellet as dry as possible.

#### 3. Lysis of Cells

Add 100 µl of Alkaline Lysis Solution I. Resuspend pellet by vortexing or by shaking vigorously.

4. Add 200 µl of freshly prepared Alkaline Lysis Solution II. Close the tube tightly and invert the tube 5 times. Do not vortex! Store the tube on ice.



### Application and Platform Models







#### Table 2: Component Library (L): Flow Layer Model

		Execution
Component	Phases (P)	<b>Time</b> ( <i>C</i> )
Mixer	Ip1/ Ip2/ <b>Mix</b> / Op1/ Op2	0.5s
Filter	Ip/ Filter/ Op1/ Op2	20s
Detector	Ip/ <b>Detect</b> / op	5s
Separator	Ip1/ Ip2/ Separate/ Op1/ Op2	140s
Heater	Ip/ Heat/ Op	$20^{\circ}$ C/s

## Flow paths in the architecture


# Flow paths in the architecture



- Fluid transport latencies are comparable to operation execution times
- Handling communication is important!
- Enumerate flow paths in the architecture

$F_1 = (In_1, S_1, Mixer_1), 2 s$	$F_{18} = (Mixer_2, S_6, S_7, S_8, S_{10}, Out_1), 3.5 \text{ s}$	Routing Constraints:
$F_2 = (In_1, S_1, S_2, Mixer_2), 2.5 \text{ s}$	$F_{19} = (Mixer_3, S_7, S_6, S_5, Out_2, 3 s)$	-
$F_3 = (In_1, S_1, S_2, S_3, Mixer_3), 3 s$	$F_{20} = (Mixer_3, S_7, S_6, S_5, Heater_1), 3 s$	$F_1: F_2 \vee F_3 \vee F_4 \vee F_7 \vee F_{24}$
$F_4 = (In_2, S_4, S_3, S_2, S_1, Mixer_1), 3.5 \text{ s}$	$F_{21} = (Mixer_3, S_7, Filter_1), 2 s$	$F_2: F_1 \lor F_3 \lor F_4 \lor F_5 \lor F_7 \lor F_{24} \lor F_{25}$
$F_5 = (In_2, S_4, S_3, S_2, Mixer_2), 3 s$	$F_{22-x} = (Mixer_3, S_7, S_8, Storage-8), 2.5 s$	$F_3: F_1 \vee F_2 \vee F_4 \vee F_5 \vee F_6 \vee F_7 \vee F_{24}$
$F_6 = (In_2, S_4, S_3, Mixer_3), 2.5 \text{ s}$	$F_{23} = (Mixer_3, S_7, S_8, S_{10}, Out_1), 3 \text{ s}$	$\vee F_{25} \vee F_{26}$
$F_{7-x} = (In_1, S_1, S_2, S_3, S_4, Storage-8), 3.5 s$	$F_{24-x} = (Storage-8, S_4, S_3, S_2, S_1, Mixer_1), 3.5 \text{ s}$	$F_4: F_1 \vee F_2 \vee F_3 \vee F_5 \vee F_6 \vee F_7 \vee F_8$
$F_{8-x} = (In_2, S_4, Storage-8), 2 s$	$F_{25-x} = (Storage-8, S_4, S_3, S_2, Mixer_2, 3 s)$	$\vee F_{24} \vee F_{25} \vee F_{26}$
$F_9 = (Mixer_1, S_5, Out_2), 2 s$	$F_{26-x} = (Storage-8, S_4, S_3, Mixer_3), 2.5 \text{ s}$	$F_5: F_2 \vee F_3 \vee F_4 \vee F_6 \vee F_7 \vee F_8 \vee F_{24}$
$F_{10} = (Mixer_1, S_5, Heater_1), 2 s$	$F_{27-x} = (Storage-8, S_8, S_7, S_6, S_5, Heater_1), 3.5 s$	$\vee F_{25} \vee F_{26} \vee F_{27}$
$F_{11} = (Mixer_1, S_5, S_6, S_7, Filter_1), 3 s$	$F_{28-x} = (Storage-8, S_8, S_7, Filter_1), 2.5 s$	$F_6: F_3 \lor F_4 \lor F_5 \lor F_7 \lor F_8 \lor F_{24} \lor F_{25}$
$F_{12-x} = (Mixer_1, S_5, S_6, S_7, S_8, Storage-8), 3.5 s$	$F_{29-x} = (Storage-8, S_8, S_{10}, Out_1), 2.5 \text{ s}$	$\vee F_{26}$
$F_{13} = (Mixer_1, S_5, S_6, S_7, S_8, S_{10}, Out_1), 4 s$	$F_{30-x} = (Heater_1, S_9, S_{10}, S_8, Storage-8), 3 s$	$F_7: F_1 \vee F_2 \vee F_3 \vee F_4 \vee F_5 \vee F_6 \vee F_8$
$F_{14} = (Mixer_2, S_6, S_5, Out_2), 2.5 \text{ s}$	$F_{31} = (Heater_1, S_9, S_{10}, Out_1), 2.5 \text{ s}$	$\vee F_{24} \vee F_{25} \vee F_{26}$
$F_{15} = (Mixer_2, S_6, S_5, Heater_1), 2.5 \text{ s}$	$F_{32-x} = (Filter_1, S_9, S_{10}, S_8, Storage-8), 3 s$	
$F_{16} = (Mixer_2, S_6, S_7, Filter_1), 2.5 \text{ s}$	$F_{33} = (Filter_1, S_9, S_{10}, Out_1), 2.5 \text{ s}$	$F_{33}: F_{13} \lor F_{18} \lor F_{23} \lor F_{29} \lor F_{30} \lor F_{31}$
$F_{17-x} = (Mixer_2, S_6, S_7, S_8, Storage-8), 3 s$		$\vee F_{32}$

### Flow paths <sub>In</sub>

 A flow path is reserved until completion of the operation, resulting in routing constraints



$F_1 = (In_1, S_1, Mixer_1), 2 \text{ s}$	$F_{18} = (Mixer_2, S_6, S_7, S_8, S_{10}, Out_1), 3.5 \text{ s}$	Routing Constraints:
$F_2 = (In_1, S_1, S_2, Mixer_2), 2.5 \text{ s}$	$F_{19} = (Mixer_3, S_7, S_6, S_5, Out_2, 3 s)$	
$F_3 = (In_1, S_1, S_2, S_3, Mixer_3), 3 \text{ s}$	$F_{20} = (Mixer_3, S_7, S_6, S_5, Heater_1), 3 s$	$F_1: F_2 \vee F_3 \vee F_4 \vee F_7 \vee F_{24}$
$F_4 = (In_2, S_4, S_3, S_2, S_1, Mixer_1), 3.5 \text{ s}$	$F_{21} = (Mixer_3, S_7, Filter_1), 2 s$	$F_2: F_1 \lor F_3 \lor F_4 \lor F_5 \lor F_7 \lor F_{24} \lor F_{25}$
$F_5 = (In_2, S_4, S_3, S_2, Mixer_2), 3 s$	$F_{22-x} = (Mixer_3, S_7, S_8, Storage-8), 2.5 s$	$F_3: F_1 \vee F_2 \vee F_4 \vee F_5 \vee F_6 \vee F_7 \vee F_{24}$
$F_6 = (In_2, S_4, S_3, Mixer_3), 2.5 \text{ s}$	$F_{23} = (Mixer_3, S_7, S_8, S_{10}, Out_1), 3 \text{ s}$	$\vee F_{25} \vee F_{26}$
$F_{7-x} = (In_1, S_1, S_2, S_3, S_4, Storage-8), 3.5 s$	$F_{24-x} = (Storage-8, S_4, S_3, S_2, S_1, Mixer_1), 3.5 \text{ s}$	$F_4: F_1 \vee F_2 \vee F_3 \vee F_5 \vee F_6 \vee F_7 \vee F_8$
$F_{8-x} = (In_2, S_4, Storage-8), 2 s$	$F_{25-x} = (Storage-8, S_4, S_3, S_2, Mixer_2, 3 s)$	$\vee F_{24} \vee F_{25} \vee F_{26}$
$F_9 = (Mixer_1, S_5, Out_2), 2 s$	$F_{26-x} = (Storage-8, S_4, S_3, Mixer_3), 2.5 \text{ s}$	$F_5: F_2 \vee F_3 \vee F_4 \vee F_6 \vee F_7 \vee F_8 \vee F_{24}$
$F_{10} = (Mixer_1, S_5, Heater_1), 2 s$	$F_{27-x} = (Storage-8, S_8, S_7, S_6, S_5, Heater_1), 3.5 s$	$\vee F_{25} \vee F_{26} \vee F_{27}$
$F_{11} = (Mixer_1, S_5, S_6, S_7, Filter_1), 3 s$	$F_{28-x} = (Storage-8, S_8, S_7, Filter_1), 2.5 s$	$F_6: F_3 \lor F_4 \lor F_5 \lor F_7 \lor F_8 \lor F_{24} \lor F_{25}$
$F_{12-x} = (Mixer_1, S_5, S_6, S_7, S_8, Storage-8), 3.5 s$	$F_{29-x} = (Storage-8, S_8, S_{10}, Out_1), 2.5 \text{ s}$	$\vee F_{26}$
$F_{13} = (Mixer_1, S_5, S_6, S_7, S_8, S_{10}, Out_1), 4 s$	$F_{30-x} = (Heater_1, S_9, S_{10}, S_8, Storage-8), 3 s$	$F_7: F_1 \vee F_2 \vee F_3 \vee F_4 \vee F_5 \vee F_6 \vee F_8$
$F_{14} = (Mixer_2, S_6, S_5, Out_2), 2.5 \text{ s}$	$F_{31} = (Heater_1, S_9, S_{10}, Out_1), 2.5 \text{ s}$	$\vee$ $F_{24} \vee$ $F_{25} \vee$ $F_{26}$
$F_{15} = (Mixer_2, S_6, S_5, Heater_1), 2.5 \text{ s}$	$F_{32-x} = (Filter_1, S_9, S_{10}, S_8, Storage-8), 3 s$	
$F_{16} = (Mixer_2, S_6, S_7, Filter_1), 2.5 \text{ s}$	$F_{33} = (Filter_1, S_9, S_{10}, Out_1), 2.5 \text{ s}$	$F_{33}: F_{13} \lor F_{18} \lor F_{23} \lor F_{29} \lor F_{30} \lor F_{31}$
$F_{17-x} = (Mixer_2, S_6, S_7, S_8, Storage-8), 3 \text{ s}$		$\vee F_{32}$







# microfluidic control



## microfluidic control





### challenge



#### the pretty picture

#### the reality!



# off-chip control



# control synthesis

- Scheduling determines when valves are to be switch on/off
- Control synthesis layouts the control flow layer
- Sharing of control lines?



# control synthesis



Valve	Time Steps (s)					
No.	0	2	4	5	8	
1	0	0	Х	Х	0	
2	0	0	1	1	0	
3	0	1	0	0	1	
4	1	0	0	0	0	
5	0	1	0	0	1	
6	0	0	1	1	0	
7	1	0	0	0	0	
8	0	0	Mix	Mix	0	
9	0	0	Mix	Mix	0	
10	0	0	Mix	Mix	0	
27	0	0	Х	Х	Х	
28	0	0	1	1	1	
29	0	1	0	0	0	

Could be green!

But if all X=0, we can remove the control of this valve



# control synthesis



# did we solve the problem?





# on-chip control?

### on-chip bubble logic

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# Monolithic membrane valves













#### Monolithic membrane valves





W.H. Grover et al., Sensors and Actuators B 89, 315 (2003).

Tailon Volvo Test Chilp 070214 uku

Carry Out

X2f

#### Micropneumatic Digital Logic Structures for Integrated Microdevice Computation and Control

Erik C. Jensen, William H. Grover, and Richard A. Mathies









# integration



# Integration







# microfluidic technologies

# 3D printed microfluidics

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KrisnacyBerarpgavial USSterWsiterbi School of Engineeraing

# Paper-based microfluidic #





# digital microfluidics





# Digital microfluidic design

# Biochemical application #



#### library $\mathcal{L}$

module	Operation	Area (cells)	Time (sec)
M1	Mixing	2x4	3
M2	Mixing	2x2	4
D1	Dilution	2x4	4
D2	Dilution	2x2	5

array C



Mapping biochemical applications

- Allocation  ${\mathcal A}$ 
  - Determine modules  $\mathcal{M}_k$  from library  $\mathcal{L}$
- Binding  ${\mathcal B}$ 
  - Assign each operation  $O_i$  to a module  $\mathcal{M}_k$
- Schedule S
  - Determine start time  $t_i^{start}$  of each operation  $O_i$
- Placement  $\mathcal{P}$ 
  - Place modules on the  $m \times n$  array
- Synthesis  $\Psi$ 
  - Given <G, C,  $\mathcal{L}$ >, find  $\Psi = \langle \mathcal{A}, \mathcal{B}, \mathcal{S}, \mathcal{P} \rangle$  which minimize the schedule length  $\delta_{\mathcal{G}}$

### Scheduling





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## Scheduling











Overlapping modules

Concurrent biochemical applications

#### Scheduling with placement










### Scheduling with placement









### Scheduling with dynamic placement





t+4

7

12

13

t

6

5

D2





### module-based design tasks





#### Allocation

Operation	Area(cells)	Time(s)
Mix/Dlt	2x4	2.8
Mix/Dlt	1x4	4.6
Mix/Dlt	2x3	5.6
Mix/Dlt	2x2	9.96























![](_page_79_Figure_2.jpeg)

![](_page_80_Figure_1.jpeg)

![](_page_80_Figure_2.jpeg)

![](_page_81_Figure_1.jpeg)

![](_page_81_Figure_2.jpeg)

![](_page_82_Figure_1.jpeg)

![](_page_82_Figure_2.jpeg)

![](_page_83_Figure_1.jpeg)

![](_page_83_Figure_2.jpeg)

![](_page_84_Figure_1.jpeg)

![](_page_84_Figure_2.jpeg)

![](_page_85_Figure_1.jpeg)

![](_page_85_Figure_2.jpeg)

![](_page_86_Figure_1.jpeg)

![](_page_86_Figure_2.jpeg)

### 

![](_page_87_Figure_1.jpeg)

- For module-based synthesis we know the completion time from the module library.
  - But now there are no modules, the droplets can move anywhere.
    - How can we find out the operation completion times?

# characterizing operations<sup>∰</sup>

![](_page_88_Figure_1.jpeg)

- If the droplet does not move: very slow mixing by diffusion
- If the droplet moves, how long does it take to complete?
- Mixing percentages:
   p<sup>0</sup>, p<sup>90</sup>, p<sup>180</sup> ?

# characterizing operations<sup>∰</sup>

Operation	Area(cells)	Time(s)	•
Mix/Dlt	2x4	2.8	
Mix/Dlt	1x4	4.6	•
Mix/Dlt	2x3	5.6	
Mix/Dlt	2x2	9.96	

- We know how long an operation takes on modules
- Starting from this, can determine the percentages?

### decomposing modules

Safe, conservative estimates

 $\begin{array}{rll} p^{90} &=& 0.1\%, & p^{180} = -0.5\%, \\ p^{0} &=& 0.29\% & and & 0.58\% \end{array}$ 

Operation	Area(cells)	Time(s)
Mix/DIt	2x4	2.8
Mix/Dlt	1x4	4.6
Mix/Dlt	2x3	5.6
Mix/Dlt	2x2	9.96

![](_page_90_Figure_4.jpeg)

![](_page_90_Figure_5.jpeg)

![](_page_90_Figure_6.jpeg)

![](_page_90_Figure_7.jpeg)

Moving a droplet one cell takes 0.01 s.

![](_page_91_Figure_1.jpeg)

![](_page_92_Figure_1.jpeg)

### routing- vs. module-based≝

Routing-Based Synthesis

![](_page_93_Figure_2.jpeg)

Module-Based Synthesis

![](_page_93_Figure_4.jpeg)

![](_page_94_Picture_0.jpeg)

### OpenDrop

![](_page_94_Picture_2.jpeg)

### OpenDrop Digital Microfluidics on Printed Circuit Board

# digital microfluidics on paper! ₩

![](_page_95_Figure_1.jpeg)

![](_page_96_Picture_0.jpeg)

### summary part 1

• microelectronic

- microfluidic
  - continous flow microfluidics
    biochips
  - -on-chip control
  - -digital microfluidics biochips

![](_page_97_Picture_0.jpeg)

### part 2

### micromolecular systems

![](_page_98_Picture_0.jpeg)

# biochip books

- fault-tolerant digital microfluidic biochips
  - Paul Pop, Mirela Alistart,
     Elena Stuart, Jan Madsen
  - Springer 2015

Part Meridia Alacar David State State Fault-Tolerant Digital Microfluidic Biochips Frederice and rectors

- Microfluidic very large scale integration (VLSI): modeling, simulation, testing, compilation and physical synthesis
  - Paul Pop,Wajid Hassan Minhass,
     Jan Madsen, Seetal Potluri
  - Springer 2016

![](_page_99_Picture_0.jpeg)

### thank you for your attention!

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 $f(x+\Delta x) = \sum_{i=0}^{\infty} \frac{(\Delta x)^i}{i!} f^{(i)}(x)$