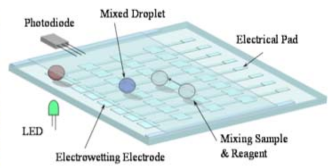
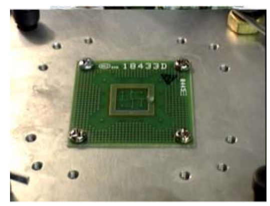
Digital Microfluidic Biochips: A Vision for Functional Diversity and More than Moore





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Acknowledgments

- Students: Tianhao Zhang, Fei Su, William Hwang, Phil Paik, Tao Xu, Vijay Srinivasan, Yang Zhao
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- Dr. S. (Krish) Krishnamoorthy, Baxter Healthcare Corporation
- Duke University's Microfluidics Research Lab (http://www.ee.duke.edu/research/microfluidics/)
- Advanced Liquid Logic (http://www.liquid-logic.com/): Start-up company spun out off Duke University's microfluidics research project

Advanced Liquid Logic, Inc.
nanoliter lab-on-a-chip powered by digital microfluidics

National Institutes of Health

DARPA

National Science Foundation
WHERE DISCOVERIES BEGIN

Embedded Tutorial Outline

- Motivation
- Technology Overview
  - Microarrays and channel-based microfluidics
  - “Digital” microfluidics: droplet-based biochips
- Design Automation Methods
  - Synthesis and module placement
  - Droplet Routing
  - Pin-Constrained Design
  - Case Studies
- Testing: Defects and Fault Models
- Conclusions

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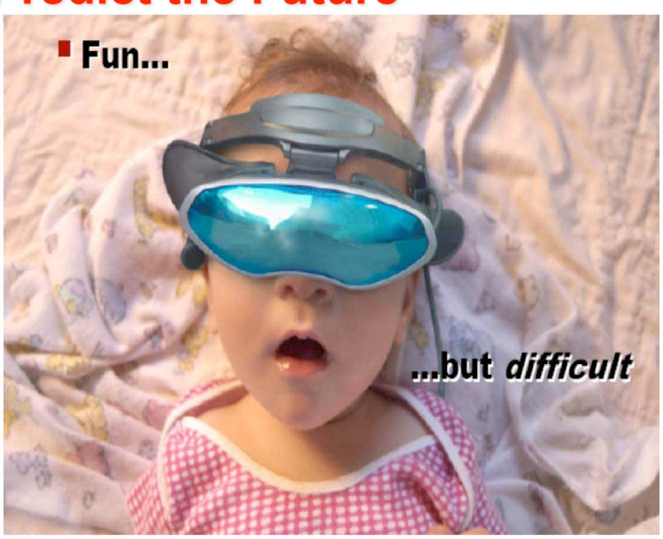
Predict the Future



Slide adapted from Rob Rutenbar’s ASP-DAC 2007 talk

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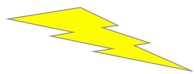
Motivation for Biochips

- Clinical diagnostics, e.g., healthcare for premature infants, point-of-care diagnosis of diseases
- "Bio-smoke alarm": environmental monitoring
- Massive parallel DNA analysis, automated drug discovery, protein crystallization

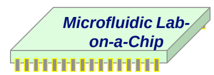
CLINICAL DIAGNOSTIC APPLICATION

Conventional Biochemical Analyzer

Shrink



Lab-on-a-chip for CLINICAL DIAGNOSTICS



20nl sample

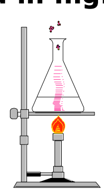
Higher throughput, minimal human intervention, smaller sample/reagent consumption, higher sensitivity, increased productivity

By the way, **what's a biochip?**

It's a miniature disposable for an HTS - High-Throughput Screening - (bio)analytical instrument

what does it do?

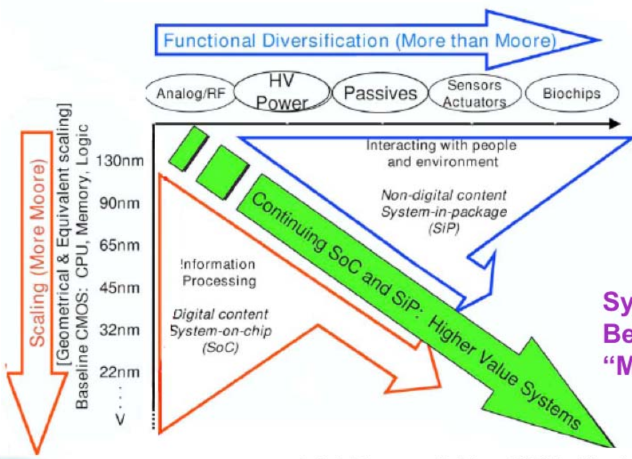
Essentially the same operations you did in high school chemistry class:



dispensing,
mixing,
detecting,
discarding,-

just a lot cheaper and a lot faster than you did

Why Do We Care?



System Driver for Beyond 2009: "Medical"

ITRS 2007

Intel Research Day 2007: Biochip prototype demonstrated for point-of-care diagnostics and lab testing

What are the main types of biochips?

Passive (array):
all liquid handling functions are performed by the instrument. The disposable is simply a patterned substrate.

Active (lab-on-chip, μ-TAS):
some active functions are performed by the chip itself. These may include flow control, pumping, separations where necessary, and even detection.

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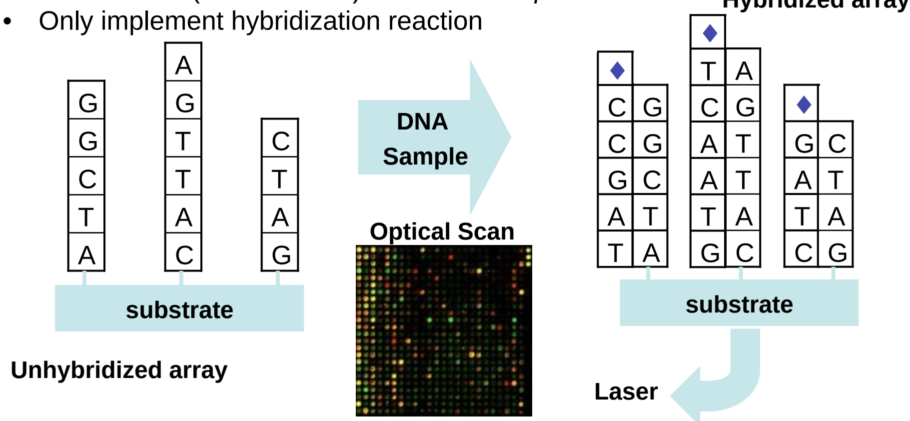
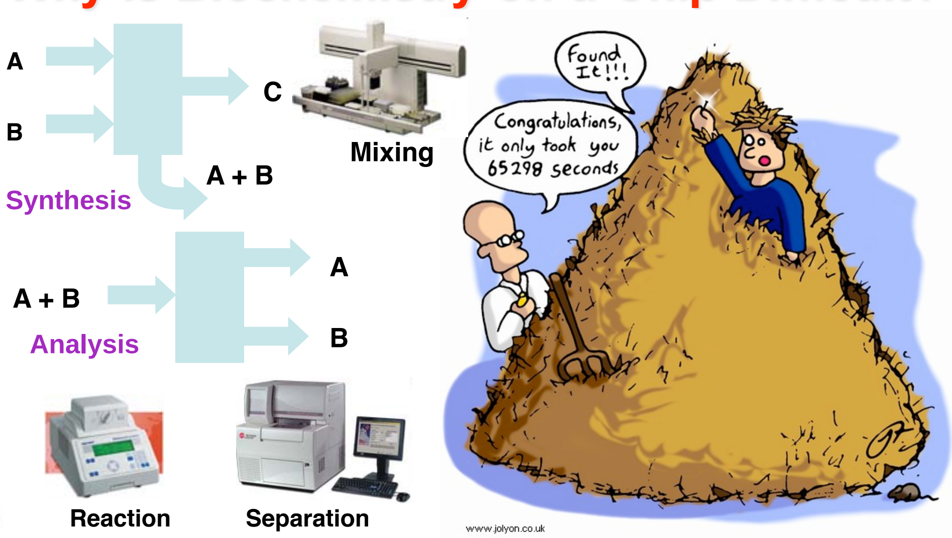
Microarrays

- DNA (or protein) microarray: piece of glass, plastic or silicon substrate
- Pieces of DNA (or antibodies) are affixed on a microscopic array
- Affixed DNA (or antibodies) are known as *probes*
- Only implement hybridization reaction



Why is Biochemistry-on-a-Chip Difficult?



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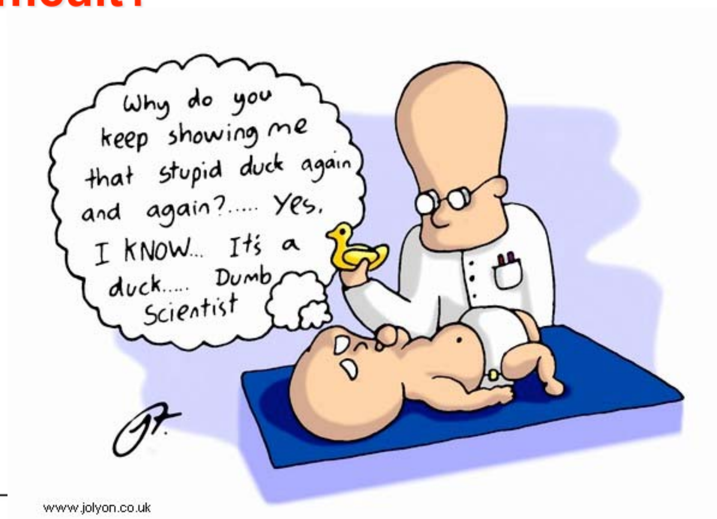


Motivation for Microfluidics

Test tubes

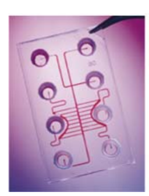
- ☐ Automation
- ☐ Integration
- ☐ Miniaturization

Robotics

- ☑ Automation
- ☑ Integration
- ☐ Miniaturization

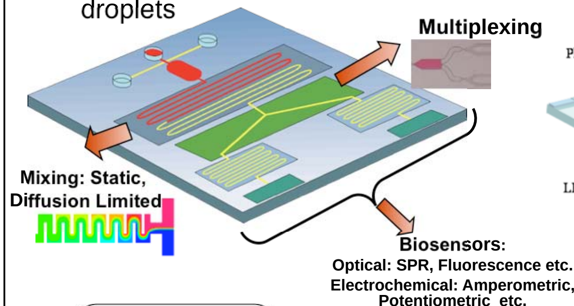
Microfluidics

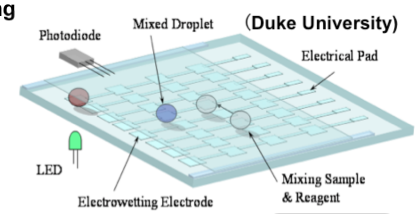
- ☑ Automation
- ☑ Integration
- ☑ Miniaturization



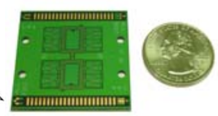
Microfluidics

- Continuous-flow lab-on-chip: Permanently etched microchannels, micropumps and microvalves
- Digital microfluidic lab-on-chip: Manipulation of liquids as discrete droplets





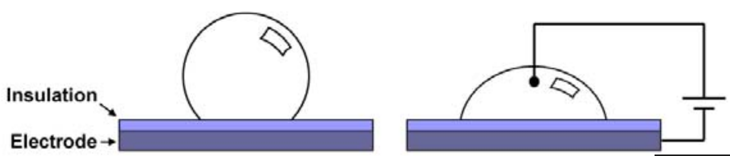
Printed circuit board lab-on-a-chip – inexpensive and readily manufacturable



Control electronics (shown) are suitable for handheld or benchtop applications

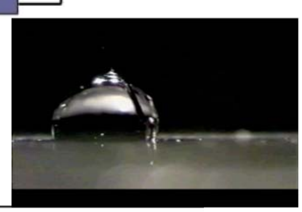
Electrowetting

- Novel microfluidic platform invented at Duke University
- Droplet actuation is achieved through an effect called *electrowetting*
  - Electrical modulation of the solid-liquid interfacial tension



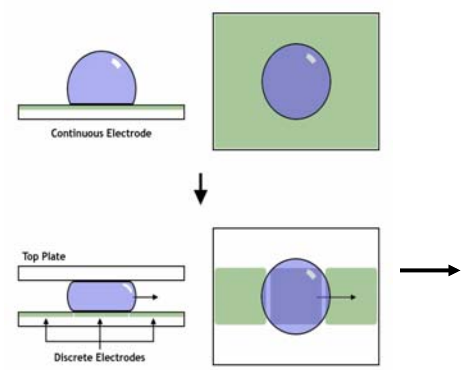
No Potential
A droplet on a hydrophobic surface originally has a large contact angle.

Applied Potential
The droplet's surface energy increases, which results in a reduced contact angle. The droplet now wets the surface.



What is Digital Microfluidics?

- Discretizing the bottom electrode into multiple electrodes, we can achieve lateral droplet movement

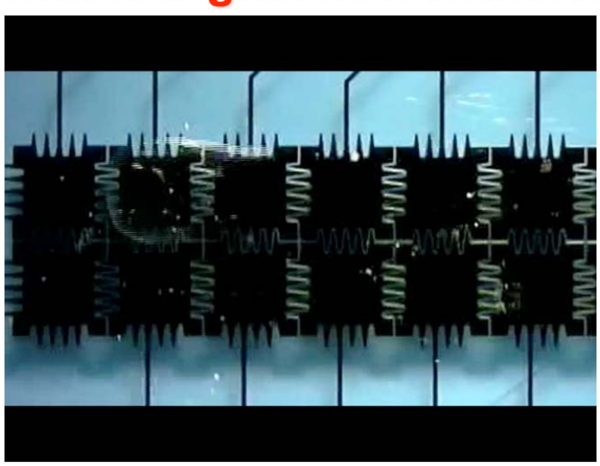


Droplet Transport (Side View)

Note: oil is typically used to fill between the top and bottom plates to prevent evaporation, cross-contamination

Pitch ~ 100 µm, Gap ~ 50 µm

What is Digital Microfluidics?

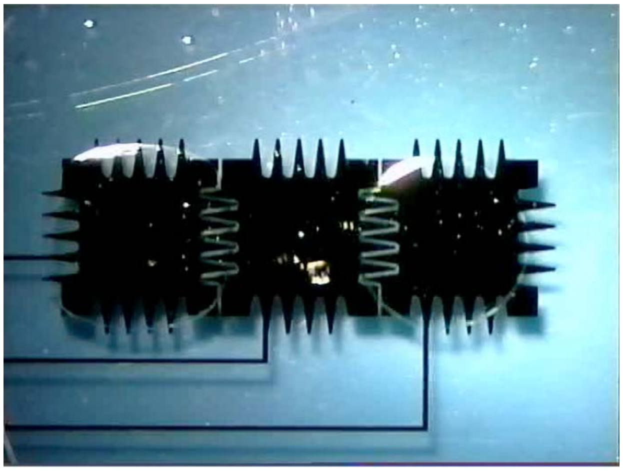


Transport
25 cm/s flow rates, order of magnitude higher than continuous-flow methods

For videos, go to www.ee.duke.edu/research/microfluidics
http://www.liquid-logic.com/technology.html

What is Digital Microfluidics?

Splitting/Merging



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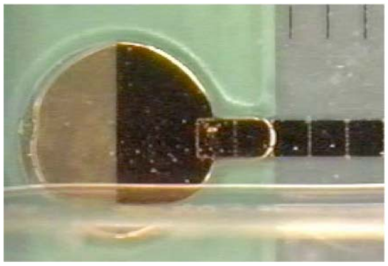
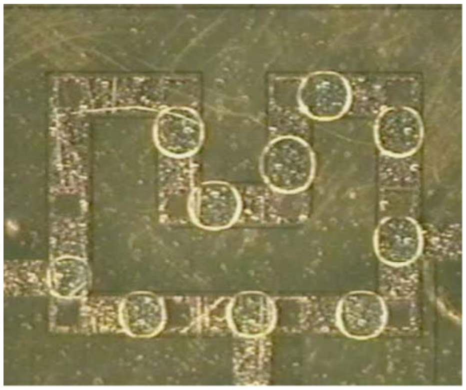
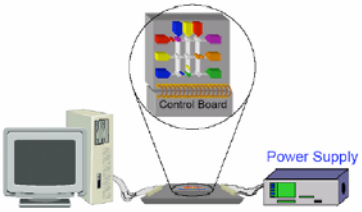
Demonstrations of Digital Microfluidics



Droplet Formation



Synchronization of many droplets



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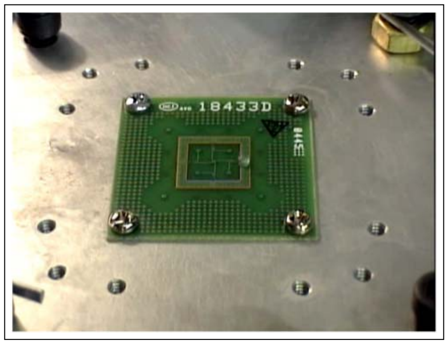
Advantages

- No bulky liquid pumps are required
  - Electrowetting uses microwatts of power
  - Can be easily battery powered



Droplet Transport on PCB (Isometric View)

- Standard low-cost fabrication methods can be used
  - Continuous-flow systems use expensive lithographic techniques to create channels
  - Digital microfluidic chips are possible using solely PCB processes

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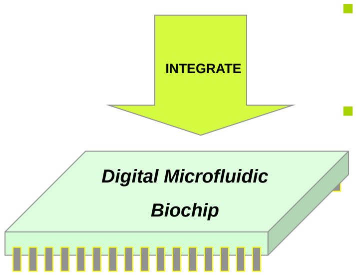
Capabilities

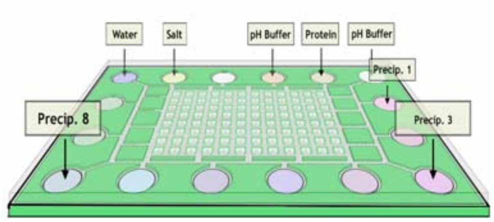
- Digital microfluidic lab-on-chip

TRANSPORT | DISPENSING | MIXERS | REACTORS | DETECTION



- Basic microfluidic functions (transport, splitting, merging, and mixing) have already been demonstrated on a 2-D array
- Highly reconfigurable system

Protein crystallization chip



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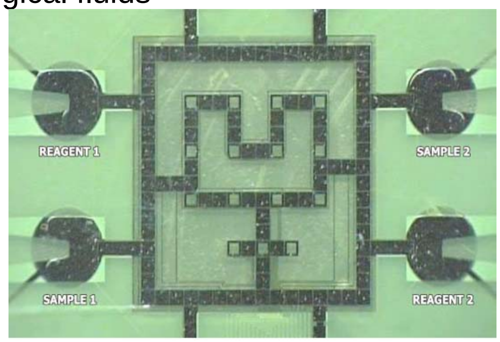
An Example

- Detection of lactate, glutamate and pyruvate has been demonstrated
- Biochip used for multiplexed in-vitro diagnostics on human physiological fluids



Pipelining of fluidic operations in fabricated microfluidic array

Computer-Aided Design: Vision

- Automate labor-intensive tasks, reduce burden on chip users
  - Map bioassays to a fabricated chip: schedule fluidic operations, determine droplet flow pathways, configure fluidic modules dynamically, etc.
  - Monitor the chip for defects that require remapping of bioassays
- Role of computer-aided design (CAD) tools
  - Reduce setup time associated with the use of these chips
  - Allow automatic reconfiguration of a faulty chip and remap the remaining steps of bioassay.
  - Develop capabilities that mirror compiler and operating system support provided to software programmers
  - Obviate the need for tedious remapping of assays to the chip by hand for each target application.
- **Similar to an FPGA?**

But, there are important differences

Logic ⟷ Interconnects

Manageable Design Approach

- Diverse biotechnology functions major source of requirements for microfluidic architecture

Biomedical Fluidic Functions: Func.1, Func.2,……,Func.n

- Agent Detection
- Precision Dispensing
- Enzyme Analysis
- Electrochromatography
- Capillary Electrophoresis
- Molecular/Protein Analysis
- Isotachophoretic Separation

Elemental Set of Operations: Op.1, Op.2,…………,Op.i

- Transport
- Mixing
- Flushing
- Filtering
- Analysis
- Detection
- Monitoring

Elemental Set of Components Comp. 1, Comp. 2,…,Comp. n

- Buffers
- Channels
- Valves
- Mixers

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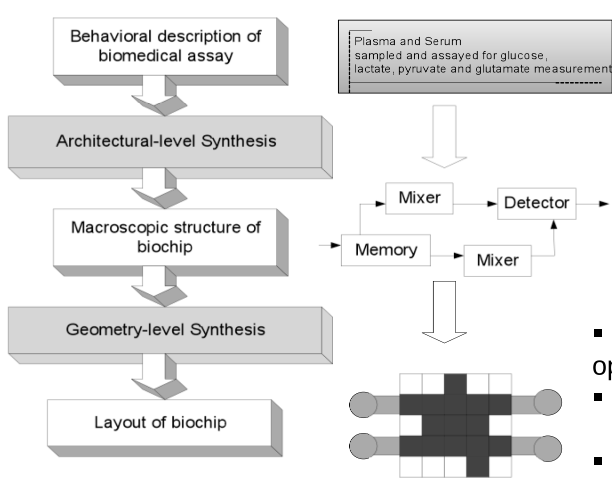
Design Automation: Biochip Synthesis

- Full-custom bottom-up design → Top-down system-level design



*S*1: Plasma, *S*2: Serum, *S*3: Urine, *S*4: Saliva

Assay1: Glucose assay, Assay2: Lactate assay, Assay3: Pyruvate assay, Assay4: Glutamate assay

*S*1, *S*2, *S*3 and *S*4 are assayed for Assay1, Assay2, Assay3 and Assay4.

- Scheduling of operations
- Binding to functional resources
- Physical design

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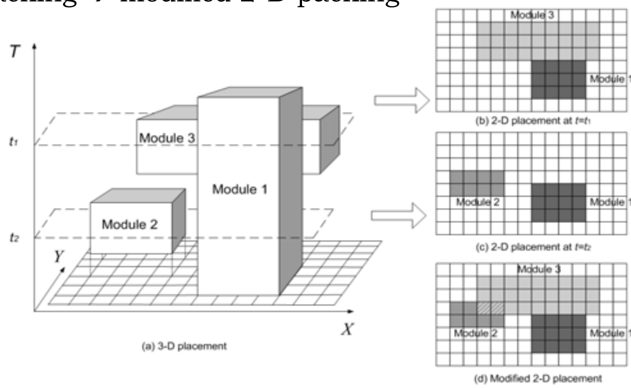
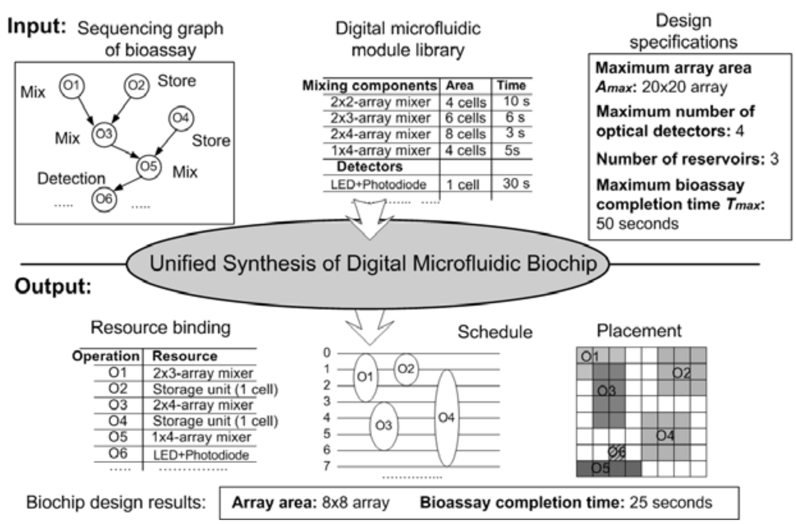
Physical Design: Module Placement

- Placement determines the locations of each module on the microfluidic array in order to optimize some design metrics
- High dynamic reconfigurability: module placement → 3-D packing → modified 2-D packing



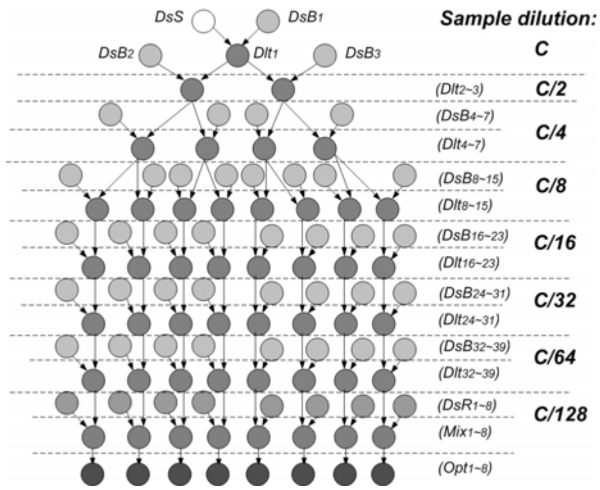
Reduction from 3_D placement to a modified 2-D placement

Unified Synthesis Methodology



Protein Assay

Sequencing graph model



- Maximum array area: *10x10*
- Maximum number of optical detectors: *4*
- Reservoir number: *1 for sample; 2 for buffer; 2 for reagent; 1 for waste*
- Maximum bioassay time: *400 s*

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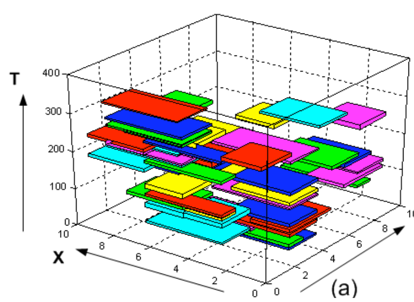
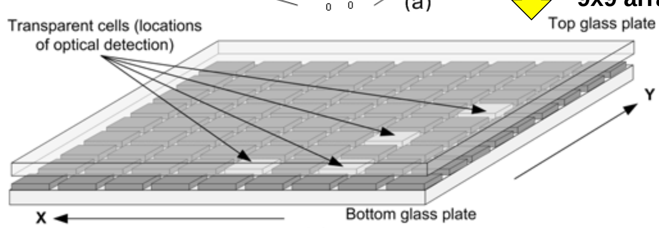
Synthesis Results



(a)

Bioassay completion time *T*: 363 seconds

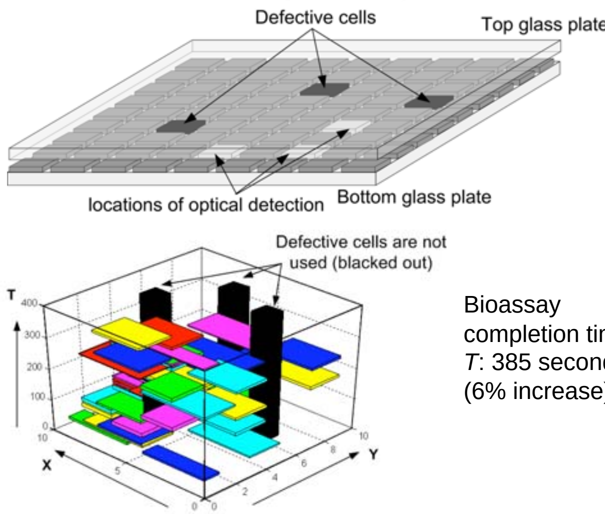
Biochip array: 9x9 array



(b)

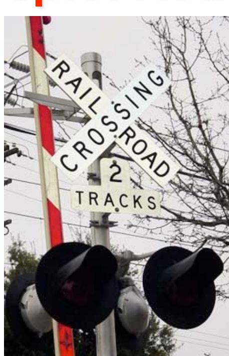
Experimental Evaluation (Cont.)

- Defect tolerance



Bioassay completion time *T*: 385 seconds (6% increase)

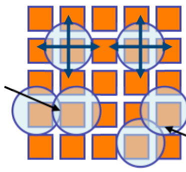
Droplet Routing



- …design problem fo… …dic
- …s from architectu… …s and …ent:
  - …let pathways using t… …the …ay; these routes are … …plets …es, or between mod… …orts …on-chip reservoirs)
- …outes with minim…
  - …he minimization of th… …VLSI routing
- Need to satisfy critical constraints
  - A set of fluidic constraints
  - Timing constraints: (the delay for each droplet route does not exceed some maximum value, e.g., 10% of a time-slot used in scheduling)

Fluidic Constraints

- Assume two given droplets as D_i and D_j, and let $X_i(t)$ and $Y_i(t)$ denote the location of D_i at time t



How to select the admissible locations at time t +1?

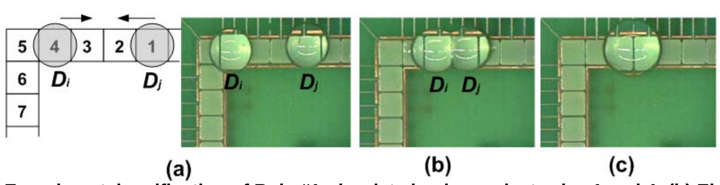
Rule #1: $|X_i(t+1) - X_j(t+1)| \geq 2$ or $|Y_i(t+1) - Y_j(t+1)| \geq 2$, i.e., their new locations are not adjacent to each other.

Rule #2: $|X_i(t+1) - X_j(t)| \geq 2$ or $|Y_i(t+1) - Y_j(t)| \geq 2$, i.e., the activated cell for D_i cannot be adjacent to D_j.

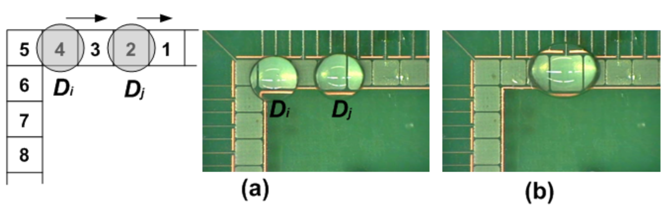
Rule #3: $|X_i(t) - X_j(t+1)| \geq 2$ or $|Y_i(t) - Y_j(t+1)| \geq 2$.

Static fluidic constraint (Rule #1) **Dynamic fluidic constraints** (Rules #2 and #3)

Experimental Verification

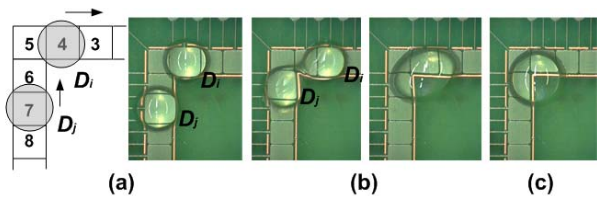


(a) Experimental verification of Rule #1: droplets begin on electrodes 1 and 4; (b) Electrodes 2 and 3 are activated, and 1 and 4 deactivated; (c) Merged droplet.



(a) Experimental verification of Rule #2: droplets begin on electrodes 2 and 4; (b) Electrodes 1 and 3 are activated, and 2 and 4 deactivated.

Experimental Verification (Cont.)



(a) Experimental verification of Rule #3: droplets begin on electrodes 4 and 7; (b) Electrodes 3 and 6 are activated, and 4 and 7 deactivated; (c) Merged droplet.

- To demonstrate that adherence to Rule #1 is not sufficient to prevent merging. Both Rule #2 and Rule #3 must also be satisfied during droplet routing.
- These rules are not only used for rule checking, but they can also provide guidelines to modify droplet motion (e.g., force some droplets to remain stationary in a time-slot) to avoid constraint violation if necessary

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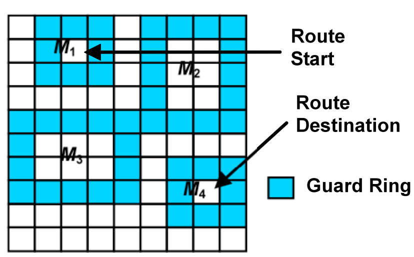
Drawback of Unified Synthesis Method

- Routing-oblivious synthesis
  - No guarantee of feasible routing pathways
- Requires powerful post-synthesis routing tool
  - Time-consuming method



No pathway exists between M_1 and M_4

Routing considerations needed for synthesis!

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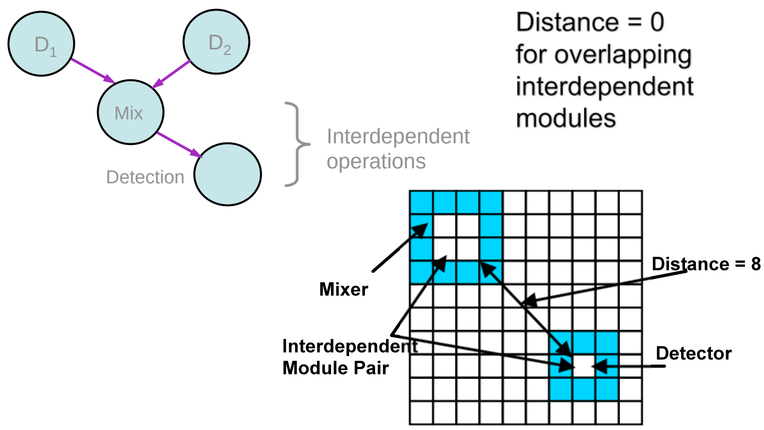
Routing-Aware Synthesis

- **Routability estimation**
  - Interdependent modules
  - Distance between interdependent modules



Routing-Aware Unified Synthesis

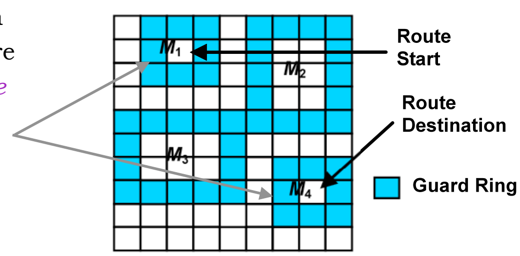
- **Routing distance**

Average distances between all the interdependent module pairs

$$D(G) \approx \sum D(M_i, M_k) \; / \; N_{int}$$

- $\{M_i, M_k\}$ — interdependent module pair
- N_{int} — # of interdependent module pairs in a given design G

Synthesized results with high routing distance are likely to have *unroutable interdependent module pairs*



Routing-Aware Unified Synthesis

- **Routability**

  $R(G) = -D(G)$

- **Integrate into unified synthesis method**

  for every chromosome design (layout) do routability estimation
  Add to cost function

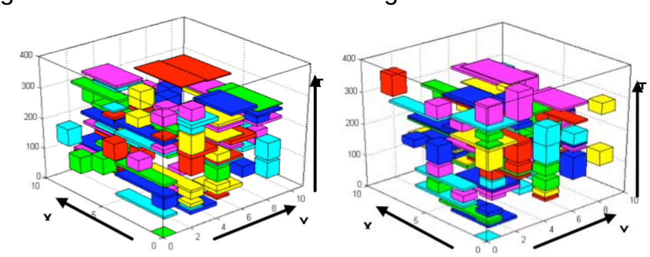
  $Fitness = \alpha Area + \beta Time + \gamma Routability$

  α,β,γ are weights that can be fine-tuned according to different design specifications

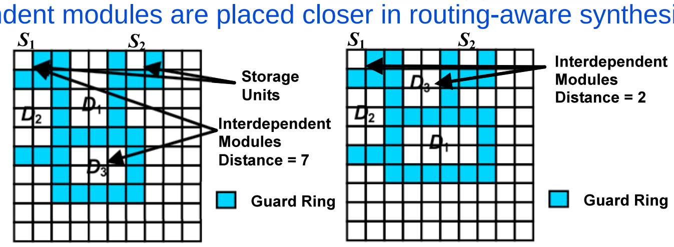
- **Candidate designs with low routability are discarded during evolution**

Experimental Evaluation (Protein Assay)

- Routing-oblivious method versus routing-aware method

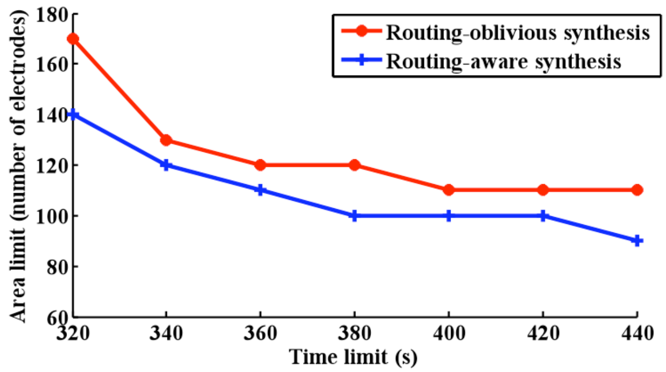


Interdependent modules are placed closer in routing-aware synthesis



Experimental Evaluation

- Feasible design region
  - Feasibility boundary point:
    no other points (T_m, A_n) such that G_{ij} is routable and $T_m < T_i$, $A_n < A_j$.
  - Feasibility frontier
    Feasible design region – area above the feasibility frontier

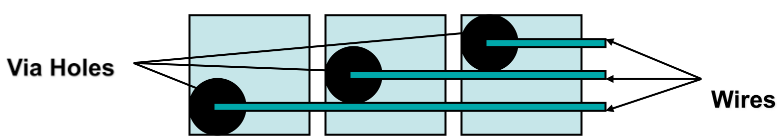


Design of Pin-Constrained Biochips

Direct Addressing

- Each electrode connected to an independent pin
- For large arrays (e.g., > 100 x 100 electrodes)
  - Too many control pins ⇒ high fabrication cost
  - Wiring plan not available

PCB design: 250 um via hole, 500 um x 500 um electrode



Nevertheless, we need high-throughput *and* low cost:

DNA sequencing (10^6 base pairs), Protein crystallization (10^3 candidate conditions)

Disposable, marketability, $1 per chip

Pin-Constrained Biochip Design

- **Cross-referencing**

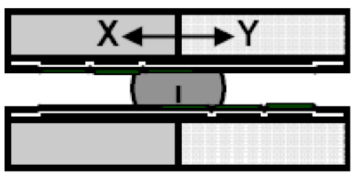
  Orthogonally placed pins on top and bottom plates

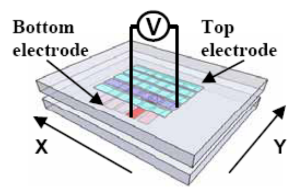
  Advantage

  k = n x m → *n + m for a n by m microfluidic array*

  Disadvantage

  Suffer from *electrode interference*



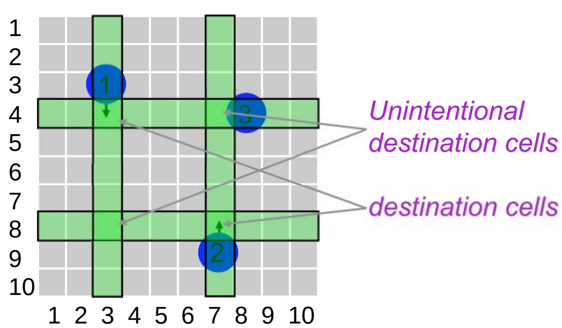


Electrode Interference

- **Unintentional Electrode Actuation**

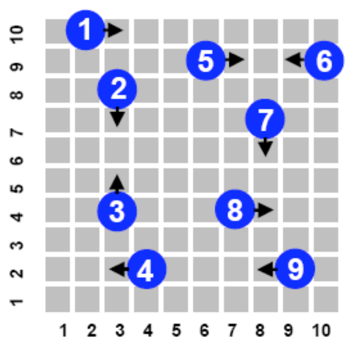
  Selected column and row pins may intersect at multiple electrodes

- **Unintentional Droplet Manipulation**



Efficient Droplet manipulation Method

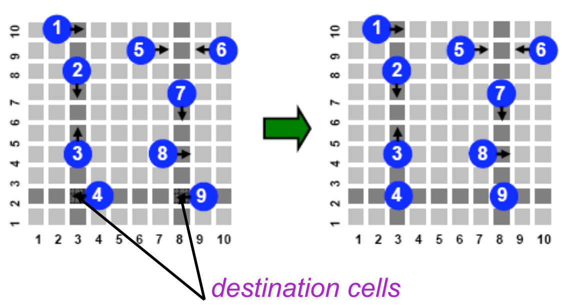
- **Goal**
  - Improve droplet manipulation concurrency on cross-referencing-based biochips.



9 steps needed if moving one droplet at a time (too slow)

Efficient Droplet Manipulation Method

- **Observation**
  - Droplet manipulations whose *destination cells* belongs to the same column/row can be carried out without electrode interferences as long as fluidic constraints are not violated.



Efficient Droplet Manipulation Method

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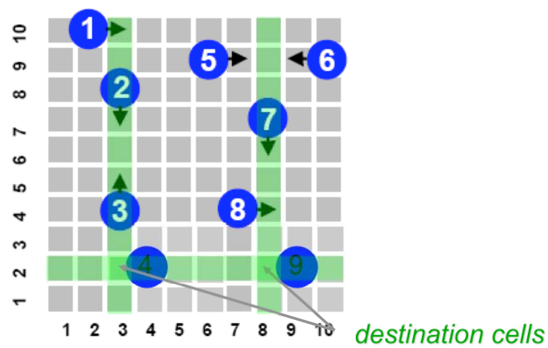


Efficient Droplet Manipulation Method

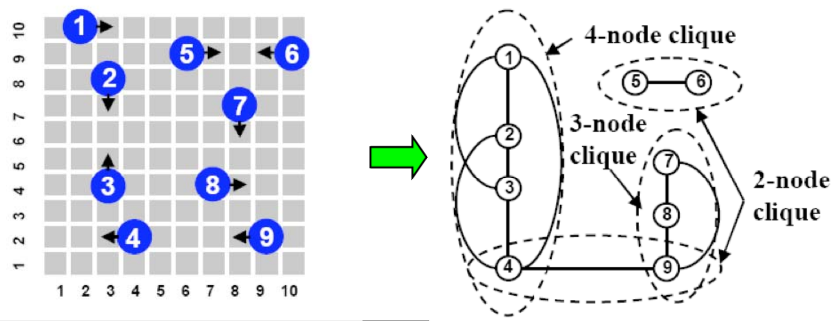
- **Methodology**
  - Group droplet manipulations according to their *destination cells*
  - All manipulations in a group can be executed simultaneously

The goal is to find the optimal grouping plan which results in the minimum number of groups.

Efficient Droplet Manipulation Method

- **Problem formulation**

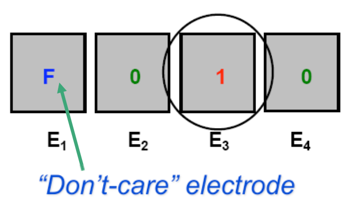
  Destination cells → Nodes
  Destination cells in one column/row → a Clique
  Grouping → Clique partitioning
  Optimal grouping → Minimal clique-partitioning *(NP-Complete)*

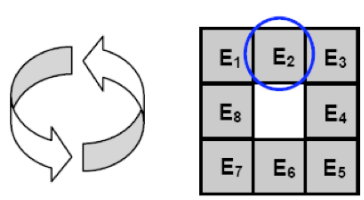


Broadcast Electrode-Addressing

- **Observation**

  "Don't-Cares" in Electrode-Actuation Sequences
  Electrode control inputs: 3 values
  "1" –- activated
  "0" –- deactivated
  "x" –- can be either "1" or "0"
  Therefore, activation sequences can be combined by interpreting "x"





Example: A droplet routed counterclockwise on a loop of electrodes

Electrode	1	2	3	4	5	6	7	8
Activation Sequence	0	1	0	0	X	X	X	X
	1	0	0	X	X	X	X	0
	0	0	X	X	X	X	0	1
	0	X	X	X	X	0	1	0
	X	X	X	X	0	1	0	0
	X	X	X	0	1	0	0	X
	X	X	0	1	0	0	X	X
	X	0	1	0	0	X	X	X

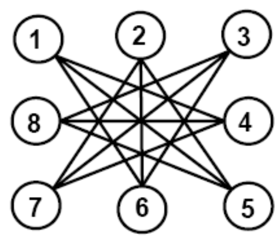
Corresponding electrode activation sequences

Solution Based on Clique Partitioning

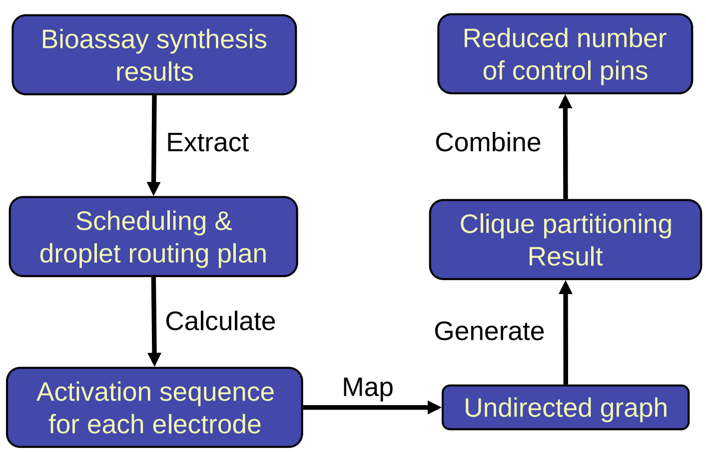
- **Idea**
  - Combining compatible sequences to reduce # of control pins
- **Clique partitioning based method**

  Electrodes → Nodes
  Electrodes with compatible activation sequences → a clique
  Optimal combination → Minimal clique-partitioning

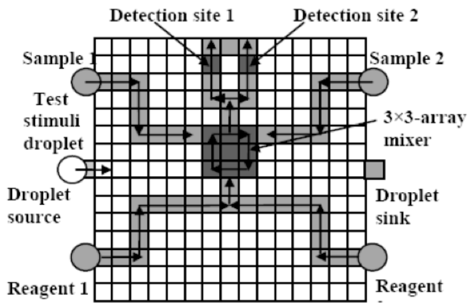
Electrode	1	2	3	4	5	6	7	8
Activation Sequence	0	1	0	0	X	X	X	X
	1	0	0	X	X	X	X	0
	0	0	X	X	X	X	0	1
	0	X	X	X	X	0	1	0
	X	X	X	X	0	1	0	0
	X	X	X	0	1	0	0	X
	X	X	0	1	0	0	X	X
	X	0	1	0	0	X	X	X



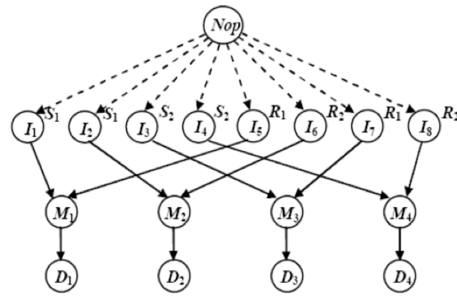
Solution Based on Clique Partitioning



Application to a Multiplexed Bioassay



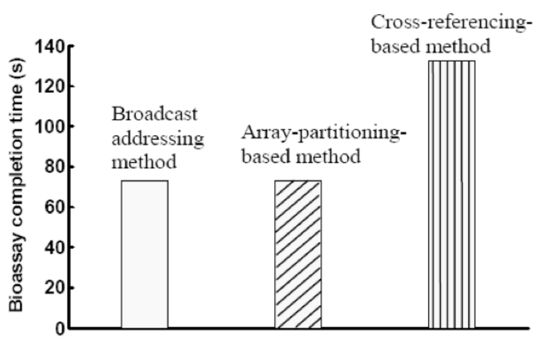
A biochip target execution of a multiplexed assay



Sequencing graph model of the multiplexed assay

- A glucose assay and a lactate assay based on colorimetric enzymatic reactions
- 4 pairs of droplets – {S1, R1}, {S1, R2}, {S2, R1}, {S2, R2}, are mixed in the mixer in the middle of the chip, the mixed droplets are routed to the detector for analysis

Results



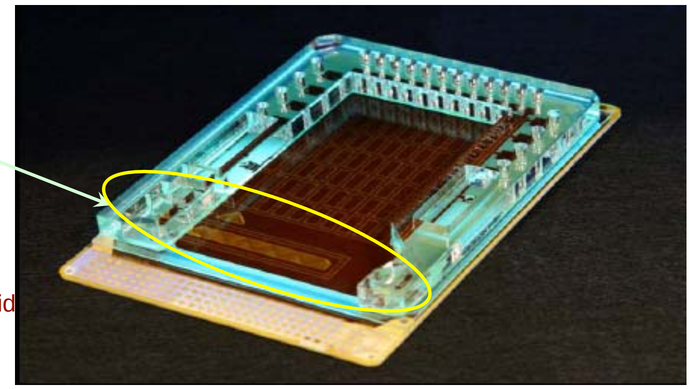
Comparison of bioassay completion time using different addressing methods

Addressing methods	Broadcast addressing	Array-partitioning-based method	Cross-referencing-based method
# of control pins	*25*	*35*	*30*

Case Study 1 (Presented at BioCAS 2009)

- Fabricated platform
  - *1140* electrodes; *64* input pins; *12* reactors
- 3-plex assay: diagnosis of acute myocardial infarction
  - Sample: serum
  - Assays: troponin-I, myoglobin, and creatine kinase-MB

Detection Region



(Product of Advanced Liquid Logic, Inc.)

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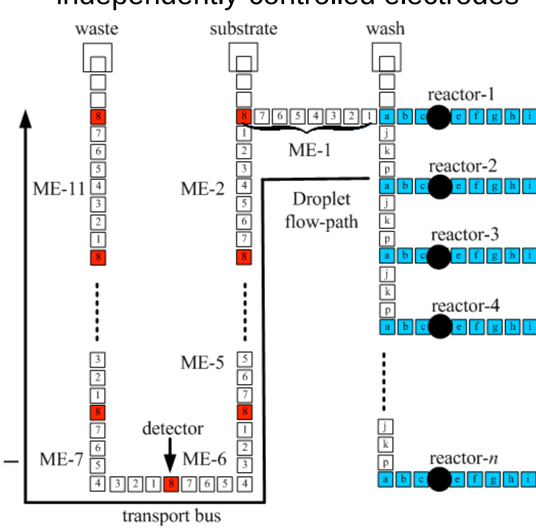
Chip Layout for *n*-plex Assay

- *n*-plex assay: a sample is analyzed for n different reagents
- Pin-constrained design: one *meta-electrode* consists of eight independently-controlled electrodes



Specifications

- 3 reservoirs
  - Waste, substrate, wash
- *N* reactors
  - For mixing and splitting
- 1 transport bus
  - 11 meta-electrodes
- 1 optical detector

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Droplet Routing Optimization

- Droplet routing task
  - Transport each of *n* product droplets to the detection site, then to the waste reservoir
  - Each product droplet mixes with one substrate droplet before the detection
  - Route three wash droplets serially after each product droplet
  - Move next product droplet into the transport bus until the previous one leaves the detection site

Optimization problem: Given the prototype chip layout and pin assignment, optimize the schedule for the detection process, to minimize the completion time for the detection of *n* product droplets.

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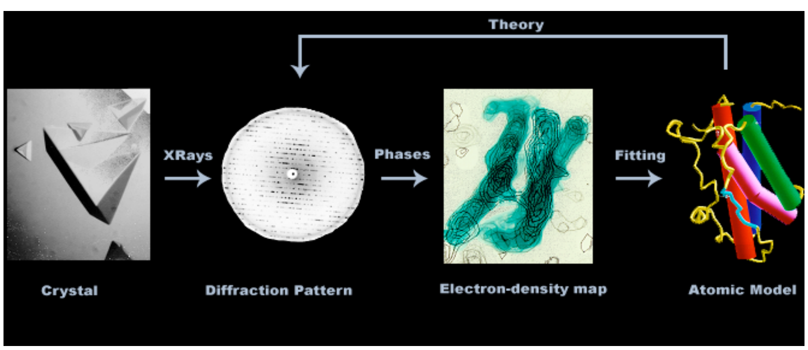
Case Study 2: Protein Crystallization

(ICCAD 2008, TCAD 2010)



www.utechproduct.com

- To understand the 3D structure for effective protein engineering, bioseparations, rational drug design, controlled drug delivery

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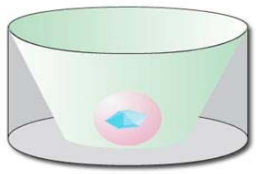
Protein Crystallization



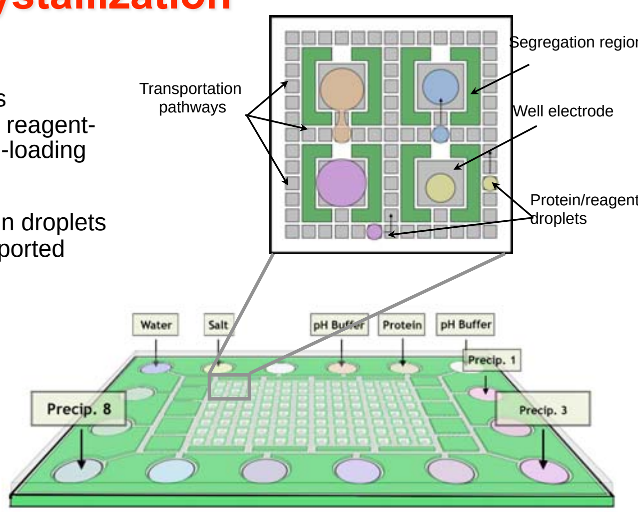
A protein sample is pipetted in preparation for an experiment.

www.hwi.buffalo.edu

- A multi-parametric process
- A large number of experiments (10^3 to 10^4) required to “hit” upon the correct parameters
- Substantial protein consumption and long time durations
- Can we use microfluidics to perform protein crystallization on a chip?

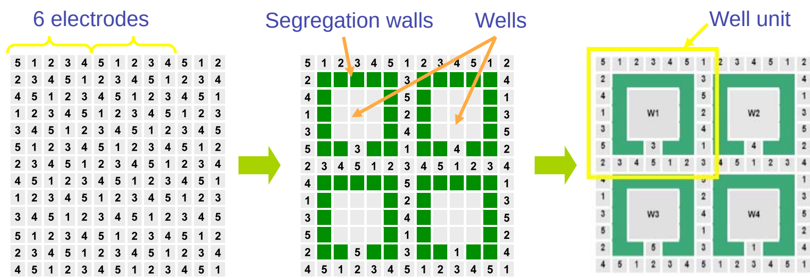
Multi-Well-Plate Biochip Design for Protein Crystallization

- 96 on-chip wells
- Electrode pathways connecting wells to reagent-loading and protein-loading ports.
- Reagent and protein droplets automatically transported



Pin-Constrained Chip Design

- Start with a electrode array with no cells reserved
- Apply the Connect-5 algorithm
- Disconnect the electrodes making up the segregation regions and wells from their control pins
- Group the electrodes occupied by each well and connect each group to a single control pin
- *1284 pins → 181 pins!*
- *No loss of concurrency or flexibility of droplet movement!*



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Solution Preparation (BioCAS 2008)

- Goal :
  - uses stock solutions to derive various mixed solutions with the required concentration levels.
- Basic
  - Required by almost all experiments
- Repetitive
  - 10^3~10^4 copies
- Critical
  - Key of successful experiment

www.bam.de

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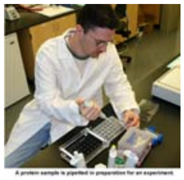
Solution Preparation

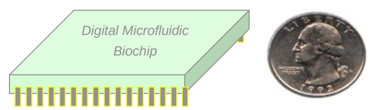


Manually

- High liquid consumption
- Time-consuming
- Error-prone

Robotics

- Expensive
- Fragile



Microfluidics

- Automated
- High-throughput
- Inexpensive < $2

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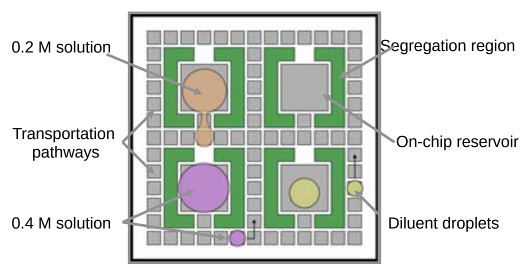
Concentration Manipulation using Mixing and Dispensing

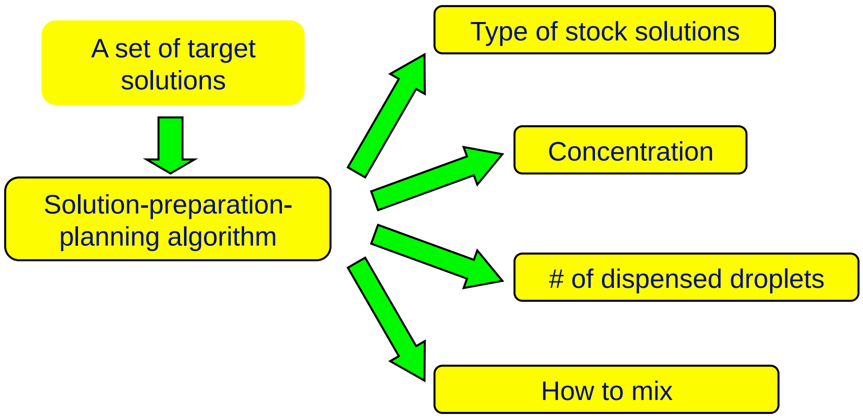
- Dispensing-mixing-and-dispensing sequence



- Modulation resolution

$$\text{Modulation resolution} = \frac{\text{concentration of stock solution} \times \text{volume of a unit droplet}}{\text{capacity of mixing reservoir}}$$

Solution-Preparation-Planning Algorithm



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Solution-Preparation-Planning Example

- Determine the reagent concentrations in the stock solution

$$\text{Modulation resolution} = \frac{\text{concentration of stock solution} \times \text{volume of a unit droplet}}{\text{capacity of mixing reservoir}}$$

$$\text{Concentration of stock solution} = \frac{\text{Modulation resolution} \times \text{capacity of mixing reservoir}}{\text{volume of a unit droplet}}$$

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Solution-Preparation-Planning Example

- Determine the modulation resolution
  - *(not too fine)*

Condition ID	Reagent_ID	Reagent concentration		*n*
MembFac_02	polyethylene glycol 4000	12	% w/v	6
MembFac_03	polyethylene glycol 4000	10	% w/v	5
MembFac_05	polyethylene glycol 4000	12	% w/v	6
MembFac_13	polyethylene glycol 4000	12	% w/v	5
MembFac_17	polyethylene glycol 4000	12	% w/v	5
MembFac_23	polyethylene glycol 4000	12	% w/v	6

modulation resolution
= *GCD*(12, 10, 12, 12, 12, 12), i.e., 2% w/v (*Works for any other units)*

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Solution-Preparation-Planning Example

- Determine the # of droplets to be dispensed from each stock solution reservoir

$$\#\text{ of droplets routed from stock solution} = \frac{\text{Concentration of the reagent in the target solution}}{\text{Modulation resolution}}$$

	Reagent_ID	Stock solution	Concentration	# of droplets
MembFac_30	zinc acetate dihydrate	S4	1 M	1
	sodium acetate trihydrate	S2	1 M	1
	polyethylene glycol 4000	S3	20% w/v	6
	diluent	—	—	2
	Note: total number of droplets = 1+1+6+2 = 10 unit droplets = capacity of mixing reservoir			

Fill up the mixing reservoir with diluents

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Experimental Results and Comparison

- Manual operation
  - Pipette with resolution of 20 µl
  - consumes 22 ml of reagent stock solutions
  - takes 1.5 hours.
- Digital microfluidics and the solution-preparation planning algorithm
  - *only 18 minutes!*
  - *12 µl of reagent solutions!*

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Testing of Digital Microfluidics Biochips

Stimuli: Test droplets; **Response**: Presence/absence of droplets

Cause of defect	**Defect type**	**No. cells**	**Fault model**	**Observable error**
Excessive actuation voltage applied to electrode	Dielectric breakdown	1	Droplet-electrode short (short between the droplet and the electrode)	Droplet undergoes electrolysis; prevents further transportation
Electrode actuation for excessive duration	Irreversible charge concentration on electrode	1	Electrode-stuck-on (electrode remains constantly activated)	Unintentional droplet operations or stuck droplets
Excessive mechanical force applied to chip	Misalignment of parallel plates (electrodes and ground plane)	1	Pressure gradient (net static pressure in some direction)	Droplet transportation without activation voltage
Coating failure	Non-uniform dielectric layer	1	Dielectric islands (islands of Teflon coating)	Fragmentation of droplets and their motion is prevented

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More Defects in Digital Microfluidic Biochips

Cause of defect	Defect type	No. cells	Fault model	Observable error
Abnormal metal layer deposition and etch variation during fabrication	Grounding failure	1	Floating droplets (droplet not anchored)	Failure of droplet transportation
	Broken wire to Control source	1	Electrode open (actuation not possible)	Failure to activate the electrode for droplet transportation
	Metal connection between adjacent electrodes	2	Electrode short (short between electrodes)	A droplet resides in the middle of the two shorted electrodes, and its transport cannot be achieved
Particle contamination or liquid residue	Particle connects two adjacent electrodes	2	Electrode short	
Protein absorption during bioassay	Sample residue on electrode surface	1	Resistive open at electrode	Droplet transportation is impeded.
			Contamination	Assay results are outside the range of possible outcomes

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Electrical Detection Mechanism

- Minimally invasive
- Easy to implement (alleviate the need for external devices)
- Fault effect should be unambiguous

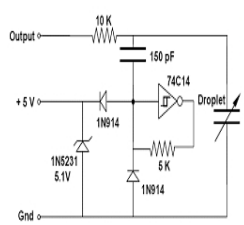
⇨ ***Electrically control and track test stimuli droplets***

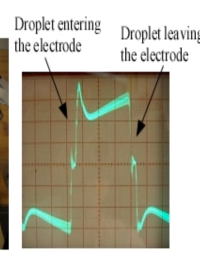
Periodic square waveform

Capacitive changes reflected in electrical signals (Fluidic domain to electrical domain)

- If there is a droplet, output=1; otherwise, output=0
- Fault-free : there is a droplet between sink electrodes

  Faulty: there is no droplet.





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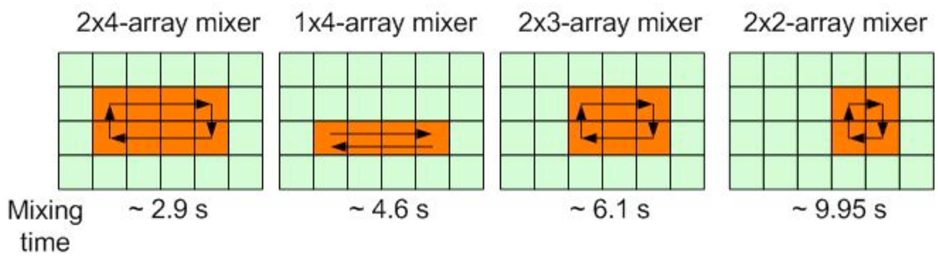
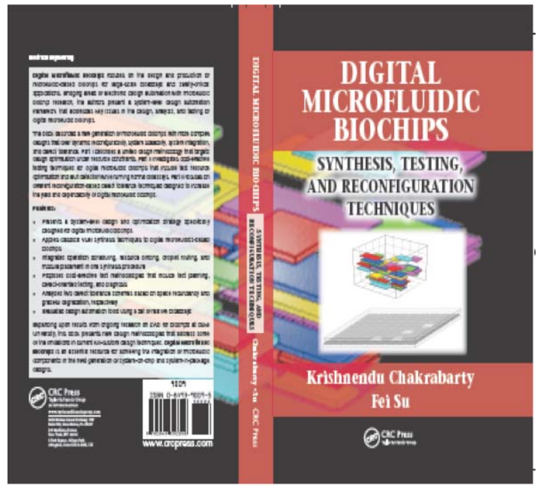
Reconfigurability

- Common microfluidic operations
  - Different modules with different performance levels (e.g., several mixers for mixing)
  - Reconfiguration by changing the control voltages of the corresponding electrodes



Conclusions

- Digital microfluidics offers a viable platform for lab-on-chip for clinical diagnostics and biomolecular recognition
- Design automation challenges
  - Automated synthesis: scheduling, resource binding, module placement; droplet routing; testing and reconfiguration
- Bridge between different research communities: bioMEMS, microfluidics, electronics CAD and chip design, biochemistry
- Growing interest in the electronics CAD and circuits/systems communities
  - Special session on biochips at CODES+ISSS'2005 (appeared in CFP now)
  - Special issue on biochips in *IEEE Transactions on CAD* (Feb 2006), *IEEE Design & Test of Computers* (Jan/Feb'07), invited papers in TCAD 2010, TCAS-I 2010
  - Workshop on biochips at DATE'06
  - Tutorials on digital microfluidic lab-on-chip at DATE'07, ISCAS'08-'10, VDAT 2007; embedded tutorials at VLSI Design'05, ISPD'08
  - Other notable activities in digital microfluidics: Microsoft Research (India), Indian Statistical Inst. (Kolkata), University of California at Los Angeles, University of Toronto, Drexel University, IMEC (Belgium), Univ. Freiburg (Germany), Philips (Netherlands), Fraunhofer Institute (Berlin, Germany), National Taiwan Univ., Tech. Univ. Denmark, Univ. Texas,, and many more….



2006 X, 406 p. Hardcover
ISBN-10: 1-4020-5122-0, ISBN-13: 978-1-4020-5122-7

ISBN: 0849390095
Publication Date: 10/5/2006, 248 p.

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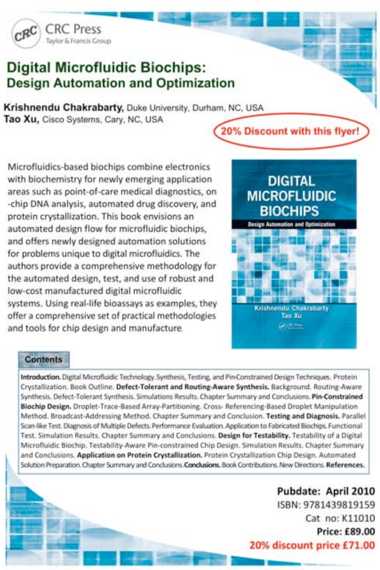

See also: Tutorial paper in *IEEE Transactions on Circuits and Systems* I, January 2010

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Glass Chip Platform Development

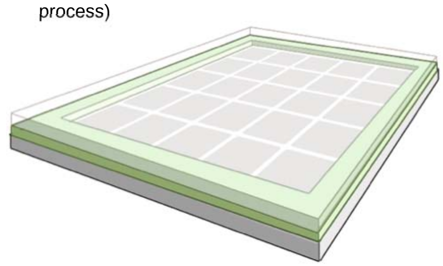
Top Plate (Optional) (i.e. glass or plastic)
Gasket Layer (100 to 600 μm) (proprietary)
Hydrophobic Layer (50 nm) (i.e. Teflon dip coated)
Insulator Layer (1 to 25 μm) (i.e. parylene)
Patterned Metal on Substrate (i.e. chrome on glass via lift-off process)

Chip Assembly

Top plate is either glued or fixed in place by pressure

Contacts are made either through the top or bottom

Droplets are either dispensed by hand or formed from on-chip reservoirs



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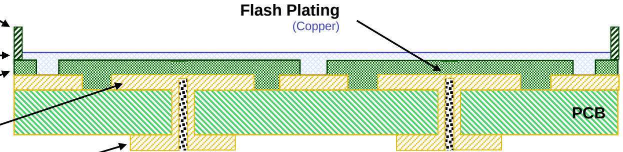
PCB Chip Platform Development

Fabrication Process

Gasket Layer (Dry Soldermask)
Hydrophobic Layer (Teflon AF)
Dielectric (LPI Soldermask)
Top Metal Layer (Copper)
Bottom Metal Layer (Copper)
Flash Plating (Copper)



Via Hole Filling (Non Conductive Epoxy)

- PCB Material – Mitsui BN300 – 64 mil
- Top Metal Layer (Electrodes) – Cu – 15μm
- Bottom Metal Layer (Contacts) – Cu – 15μm
- Dielectric – LPI Soldermask – 25 μm
- Via Hole Filling – Non-conductive Epoxy
- Hydrophobic Layer – Teflon AF – 0.05 to 1.0 μm
- Gasket (spacer) – Dry Film Soldermask (Vacrel 8140) – 4 mils (~95μm after processing)

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