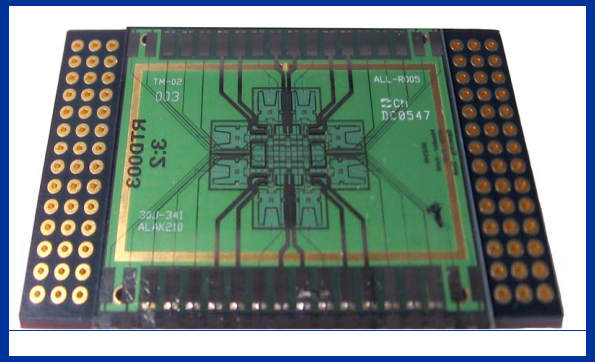
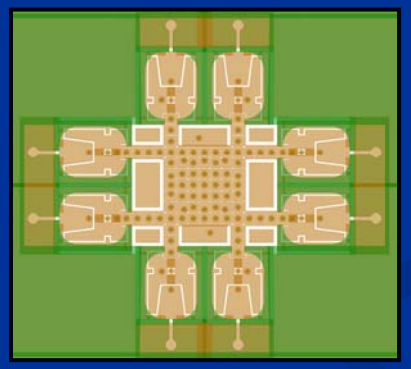
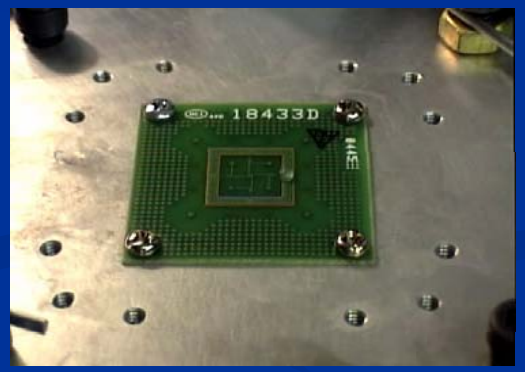
Automated Design of Digital Microfluidic Lab-on-Chip under Pin-Count Constraints







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- 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

Talk Outline

- **Motivation**
- **Technology overview**
- **Design of high-throughput pin-constrained lab-on-chip**
  - Array partitioning
  - Cross-referencing-based biochip
  - High-throughput droplet manipulation
- **Conclusions**

Applications and Advantages of Lab-on-Chip

Applications

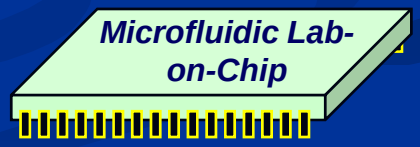
- Point-of-care clinical diagnostics, newborn screening
- Environmental monitoring
- Massively-parallel DNA sequencing
- Automated drug discovery

Conventional Biochemical Analyzer

Advantages

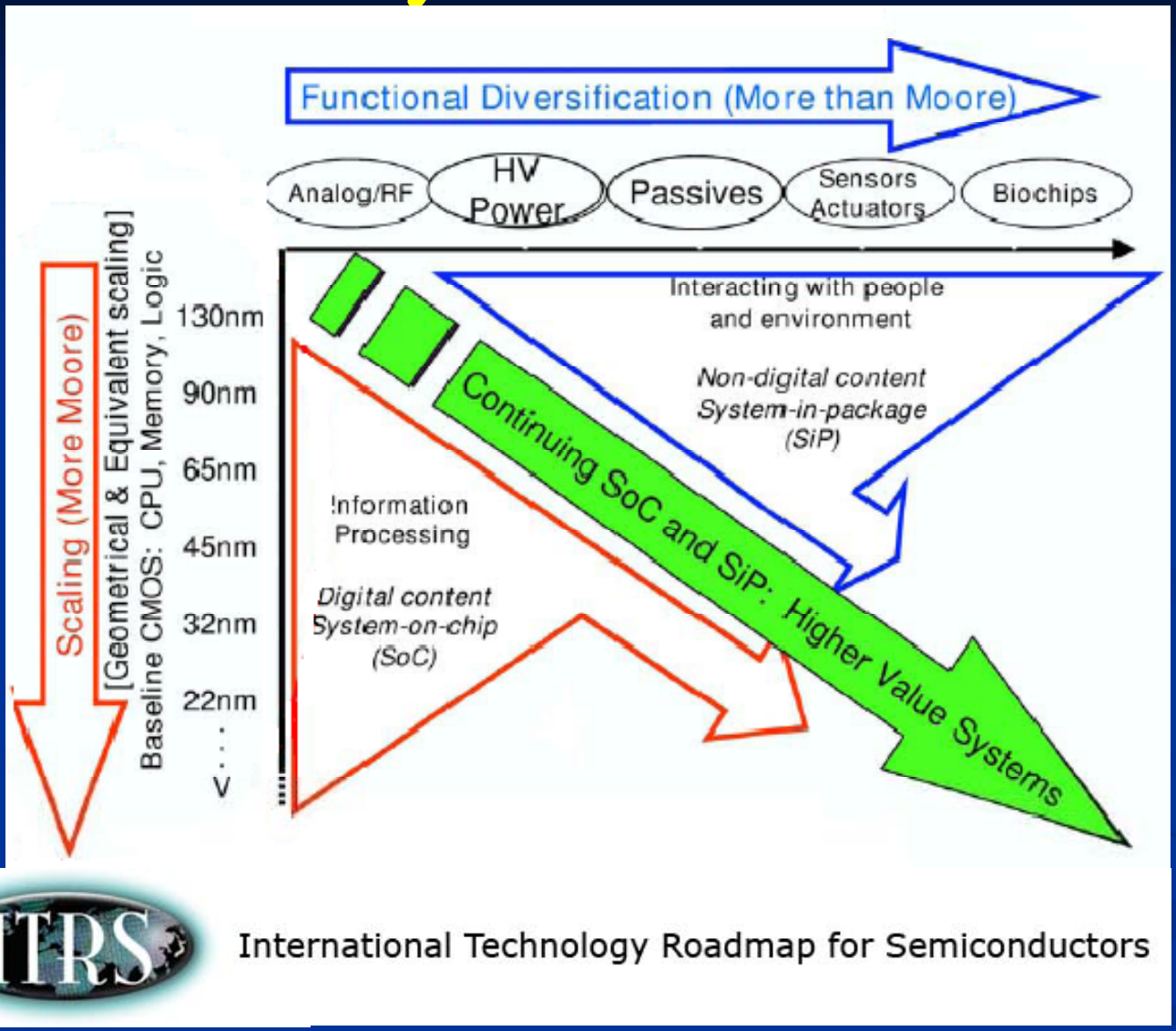
- Automated
- Small sample/reagent cost
- High sensitivity

Shrink



20nl sample

Why Do We Care?

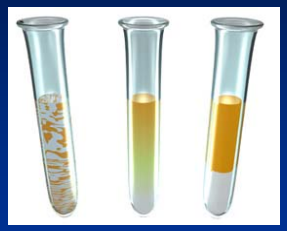


System Driver for 2009: "Medical"

Final Draft 2007

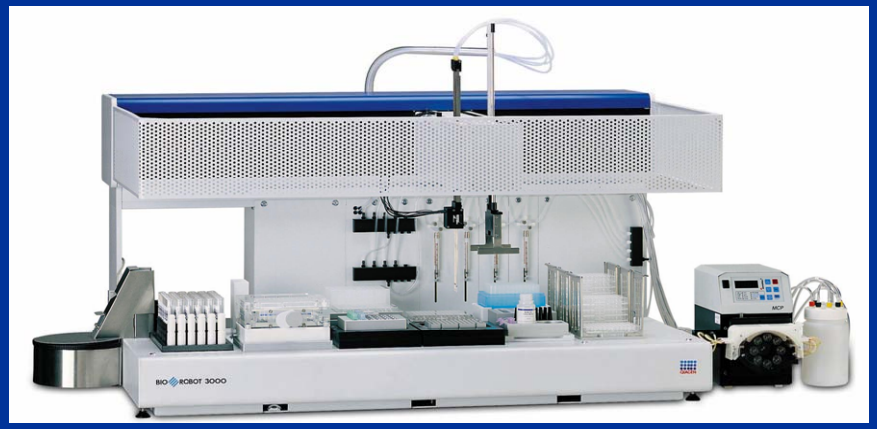
Intel Research Day 2007: Biochip prototype demonstrated for point-of-care diagnostics and lab testing

Motivation for Microfluidics



Test tubes

- ☐ Automation
- ☐ Integration
- ☐ Miniaturization

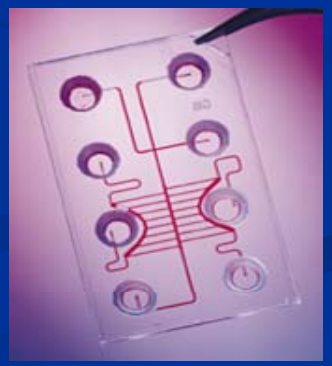


Robotics

- ☑ Automation
- ☑ Integration
- ☐ Miniaturization

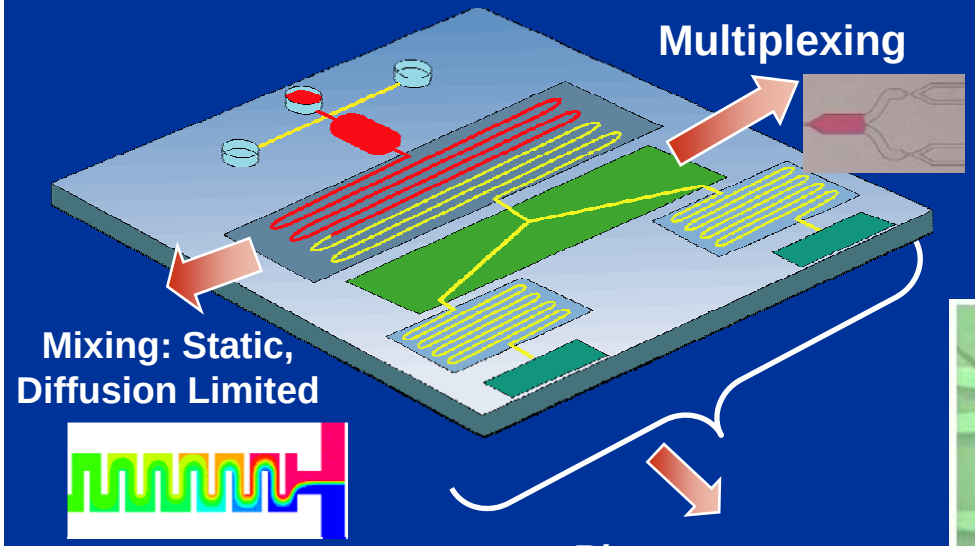
Microfluidics

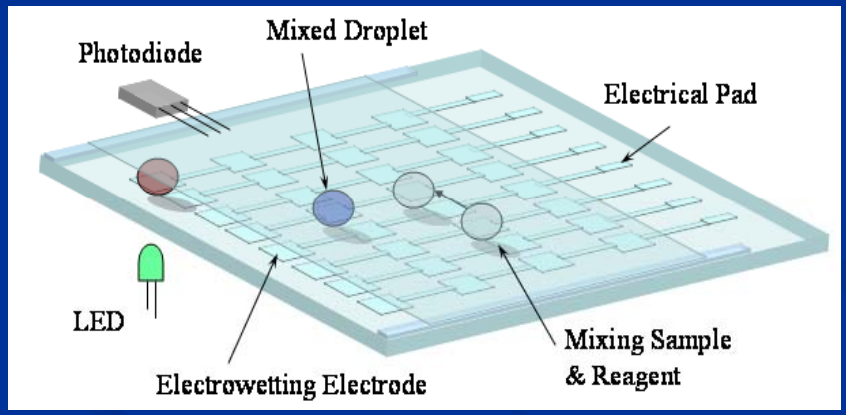
- ☑ Automation
- ☑ Integration
- ☑ Miniaturization

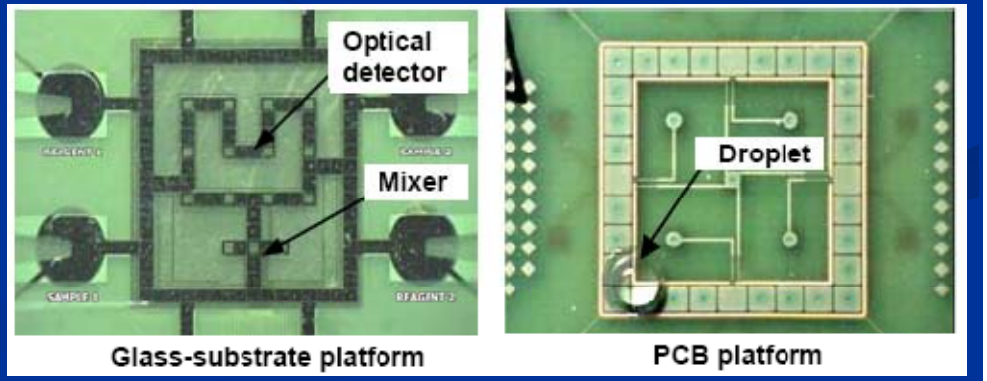


Microfluidics

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

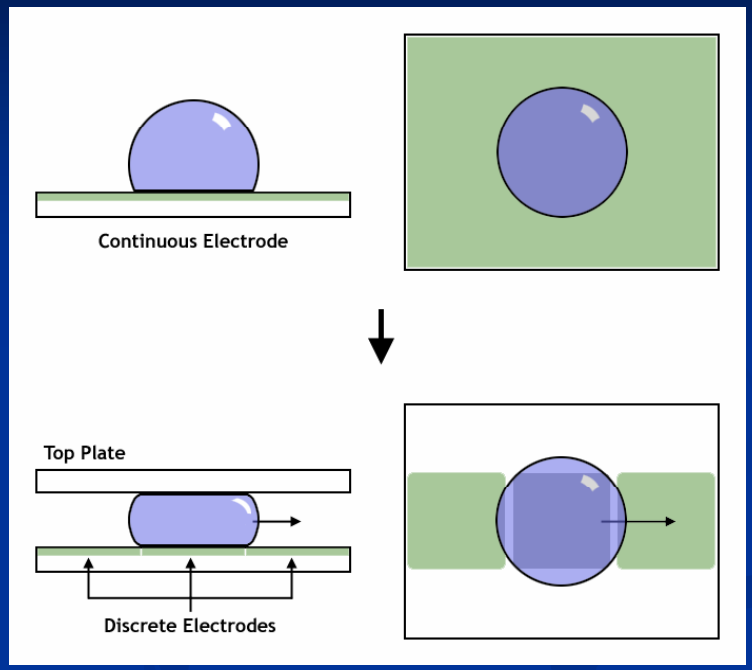


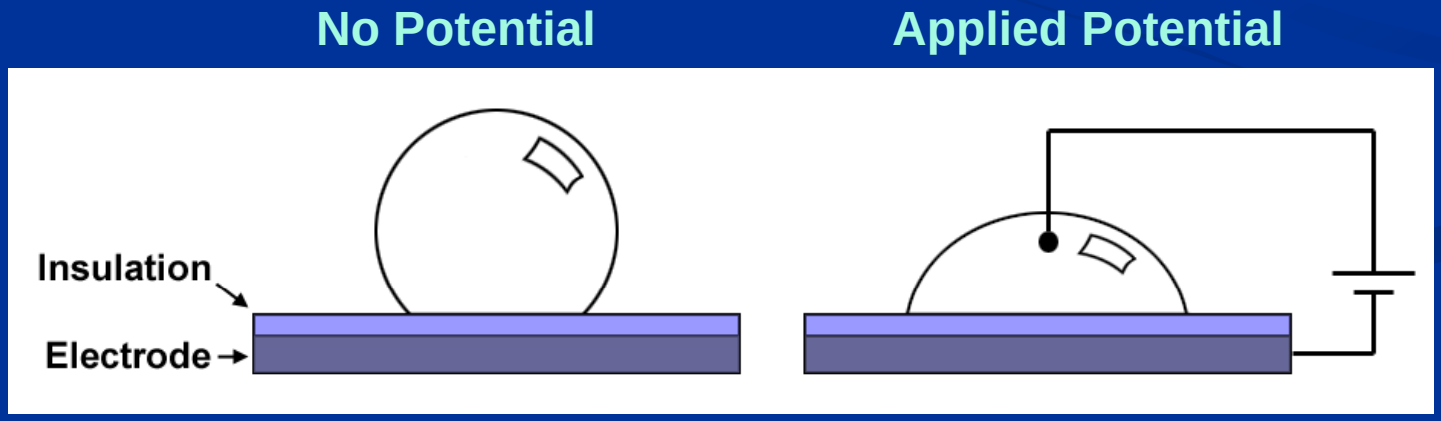




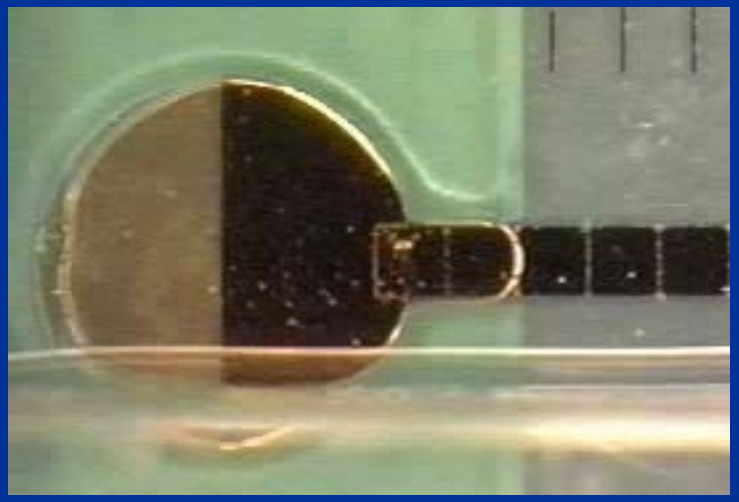
What is Digital Microfluidics?

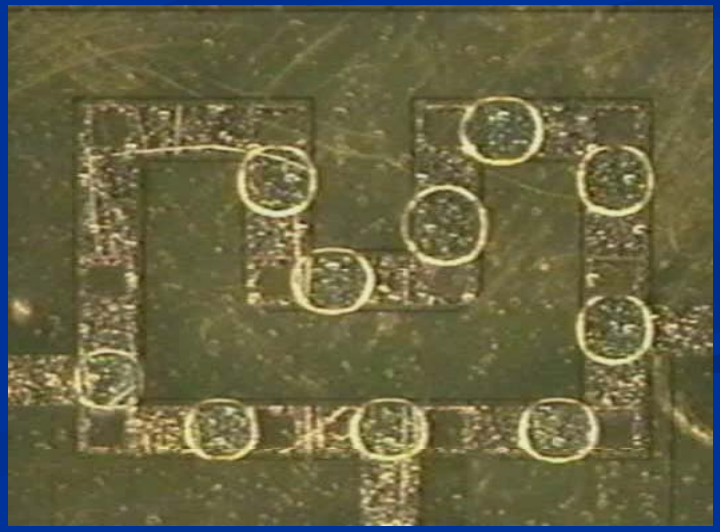
- Droplet actuation is achieved through an effect called *electrowetting*
  - Electrical modulation of the solid-liquid interfacial tension





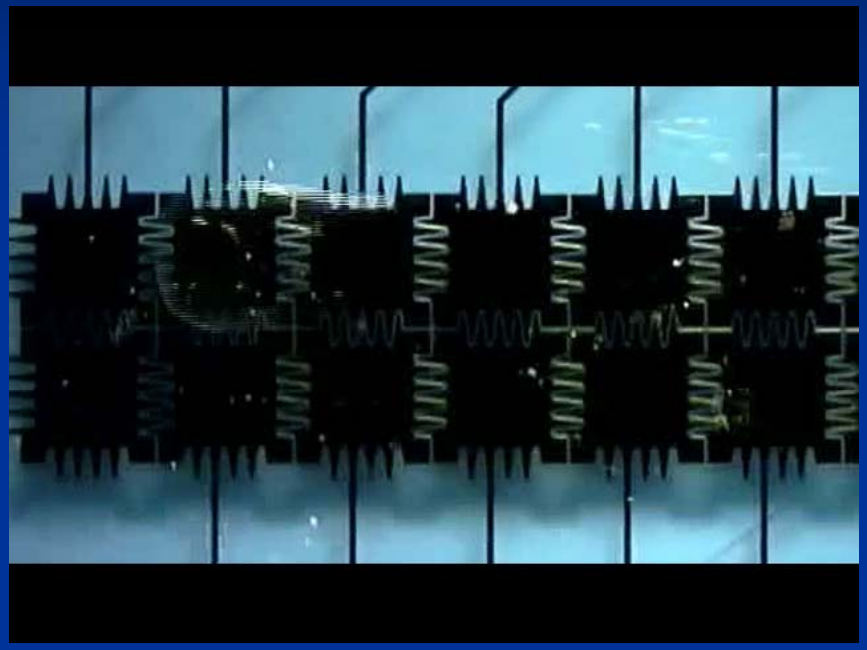
Demonstrations





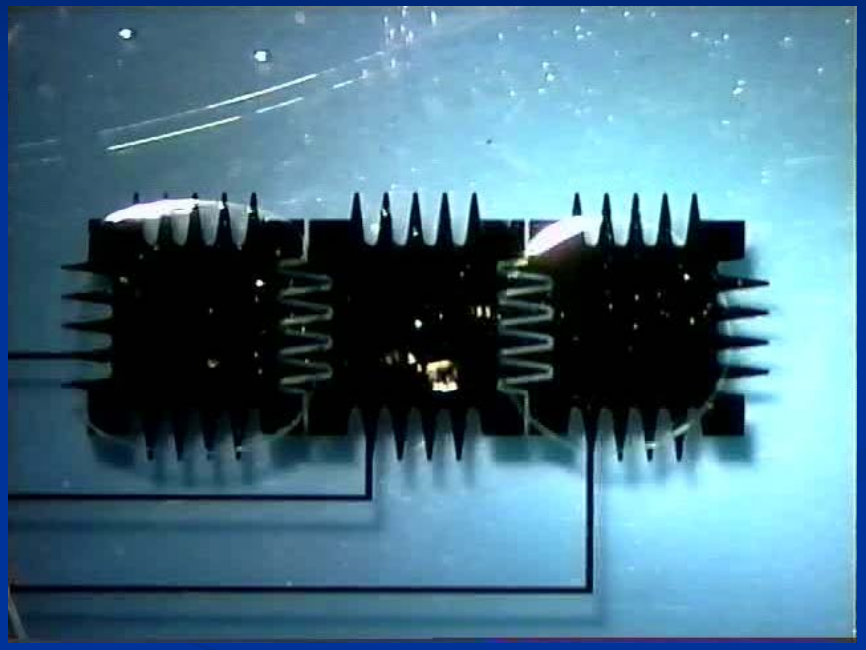
Video source: www.ee.duke.edu/research/microfluidics

Some Basic Operations



Transport

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



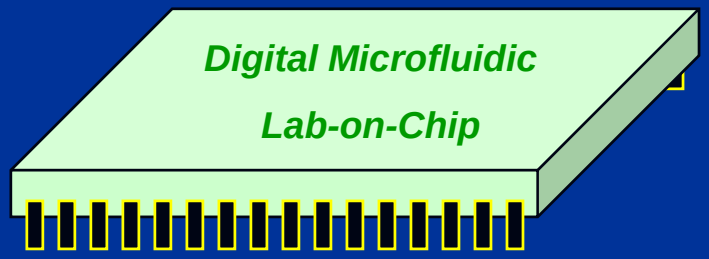
Splitting/Merging

Current Capabilities

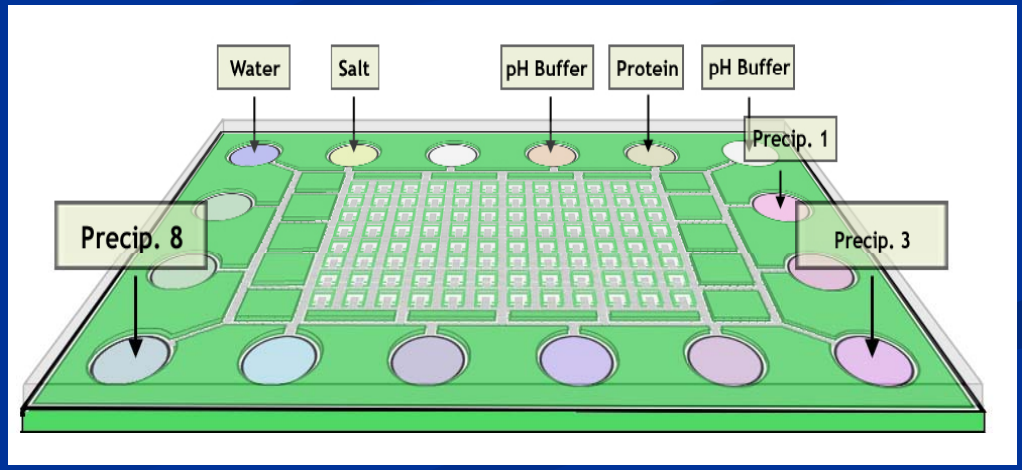
- Digital microfluidic lab-on-chip

TRANSPORT	DISPENSING	MIXERS	REACTORS	DETECTION

INTEGRATE



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



Protein crystallization chip
(under development)

Emerging Trends and Needs for Lab-on-Chip

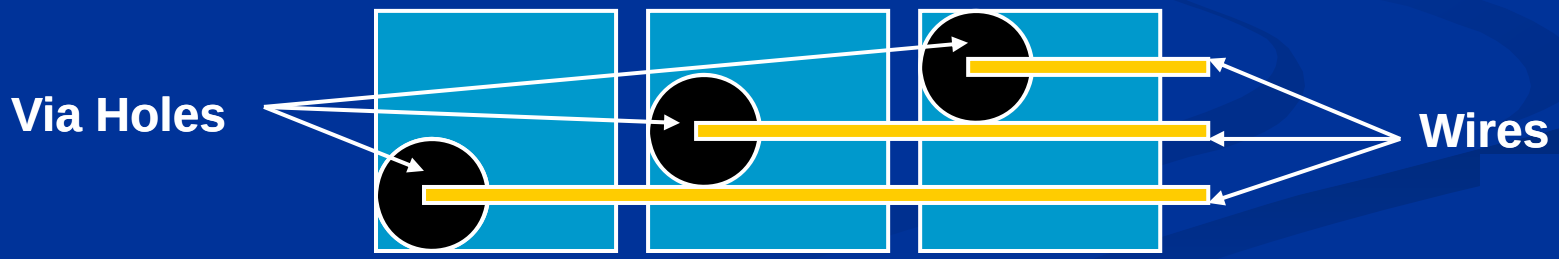
- **High throughput**
  - DNA sequencing, 10^6 base pairs
  - Protein crystallization, 10^3 candidate conditions
- **Low cost**
  - Disposable, low-cost, less than $1/chip
  - PCB design
    - Rapid prototyping and inexpensive mass-fabrication
    - Copper layer for electrodes (coplanar grounding rails)
    - Solder mask for insulator
    - Teflon AF coating for hydrophobicity
  - Disposable PCB device plugged into controller circuit board, programmed and powered with USB port

Electrode-Addressing Problem

Direct Addressing:

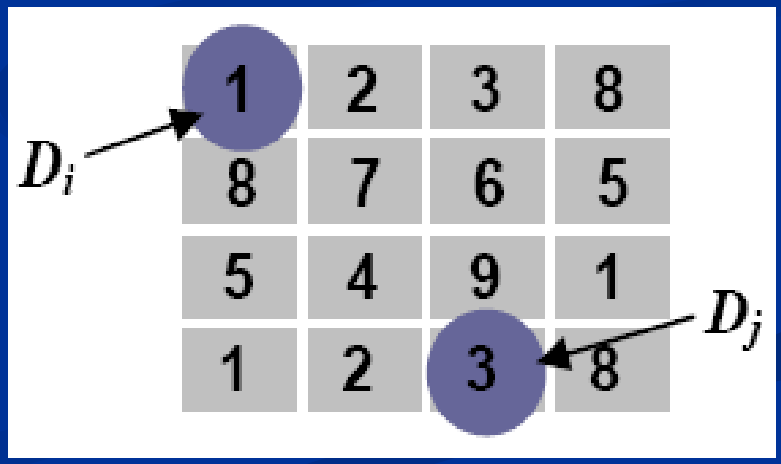
- Each electrode connected to an independent pin
- For larger arrays (e.g., > 100 x 100 electrodes)
  - Too many control pins → high fabrication cost
  - Complicated wiring, too many PCB layers, high cost

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



Solution Based on Array Partitioning

- Pin-constrained array design
  - **Advantage**: Reduce number of independent pins for n x m array from $n \times m$ to $k \leq n \times m$
    - $k = 5$ is fewest # of control pins to control single droplet
  - **Disadvantage**: Potential for unintentional interference between multiple droplets: no way to concurrently move D_i to position (1,2) and D_j to position (4,4)
- Solution
  - Single droplet: Addressing each electrode and its neighbors with distinct pins
  - Multiple droplets: Partition the chip
- Need for stall cycles?

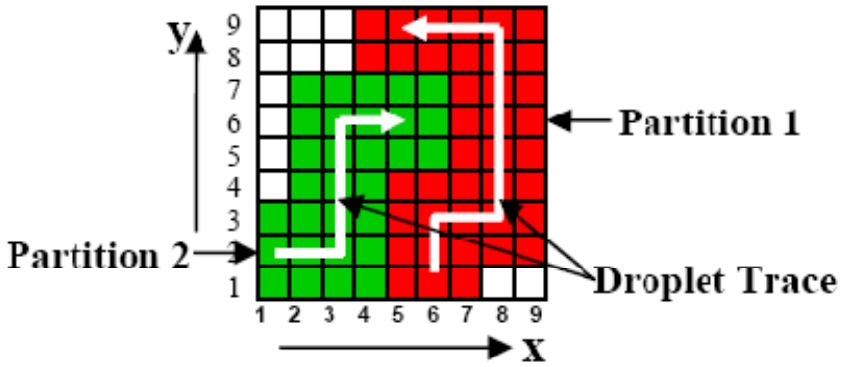


Partitioning for Pin-Constrained Designs

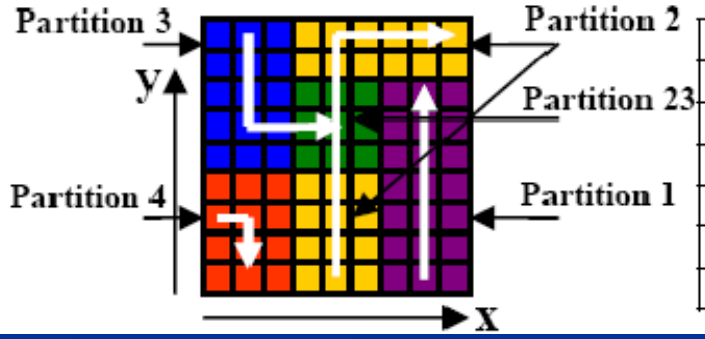
- *Droplet Trace*
  - all the cells traversed by a droplet in its lifetime
- Scheduling and placement information needed
- Partitioning rules
  - non-overlapping partitions
  - spatially overlapping partitions
  - temporally overlapping partitions

	Detector1(x,y)	Detector2(x,y)	Detector3(x,y)
Droplet 1	(8, 3)	(8, 9)	(5, 9)
Droplet 2	(3, 2)	(3, 6)	(5, 6)

(a)



(b)

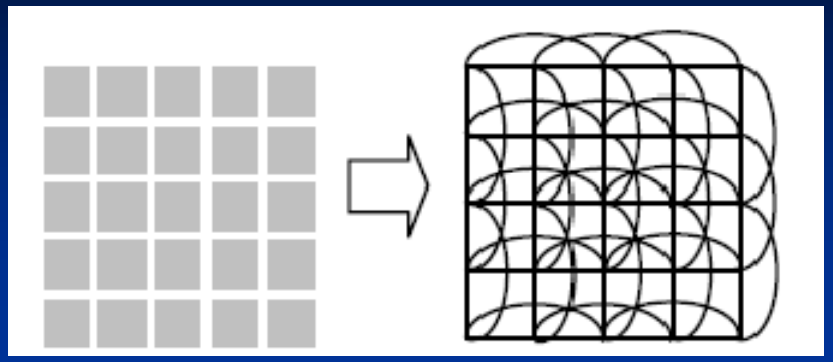


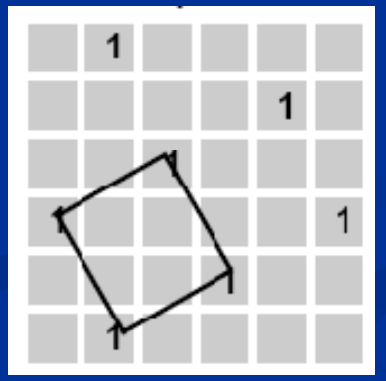
Partition	Time Span
1	1-7
2	5-16
3	7-14
4	17-20
23.2	10-11
23.3	13-14

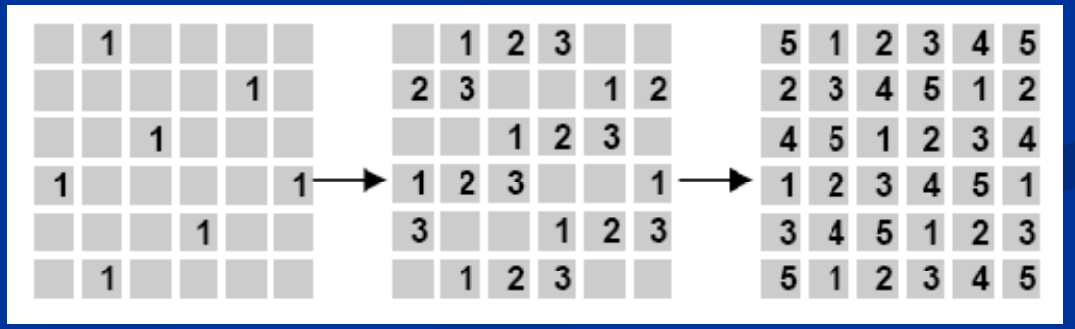
Pin Assignment in Each Partition

- Goal
  - Addressing each electrode and its neighbors with distinct pins
- Problem formulation
  - Vertex coloring problem from graph theory

  5 pins (colors) are sufficient for each partition!
- *Connect-5* algorithm
  - Bagua structure
  - Tiling the Bagua structure



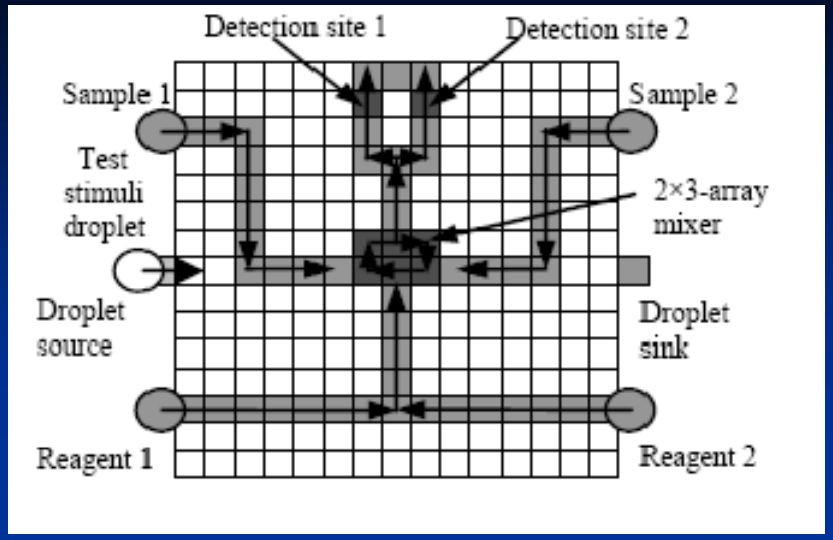




An Example

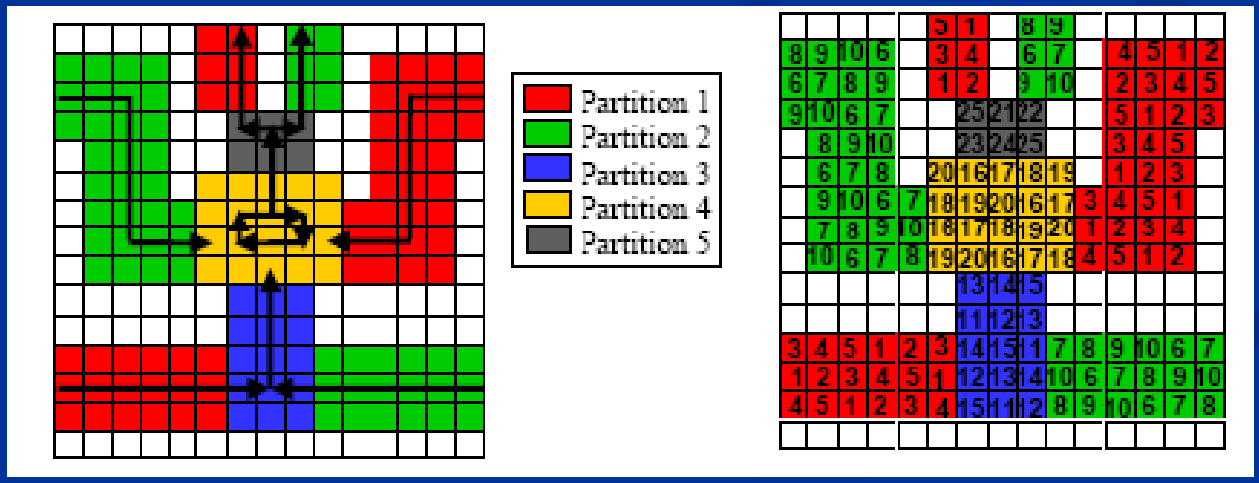
Schedule for a multiplexed bioassay

Step/Time Elapsed (s)	Operation
Step 1 / 0	Sample 2 and Reagent 2 start to move towards the mixer.
Step 2 / 0.8	Sample 2 and Reagent 2 begin to mix together and turn around in the 2×3-array mixer.
Step 3 / 6.0	Sample1 and Reagent 1 start to move towards the mixer Sample 2 and Reagent 2 continue the mixing.
Step 4 / 6.8	Sample 2 and Reagent 2 finish the mixing and product 2 leaves the mixer to optical detection location 2. Sample 1 and Reagent 1 begin to mix in the 2×3-array mixer.
Step 5 / 12.8	Sample 1 and Reagent 1 finish the mixing and product 1 leaves the mixer to the optical detection location 1. Product 2 continues the absorbance detection.
Step 6 / 19.8	Product 2 finishes optical detection and leaves the array to the waste reservoir. Product 1 continues the absorbance detection.
Step 7 / 25.8	Product 1 finishes optical detection and leaves the array to the waste reservoir. One procedure of the multiplexed bioassays ends.



A 15×15 array used for multiplexed bioassays

Partition and pin assignment results for the multiplexed bioassay



Cross-Referencing-Based Design

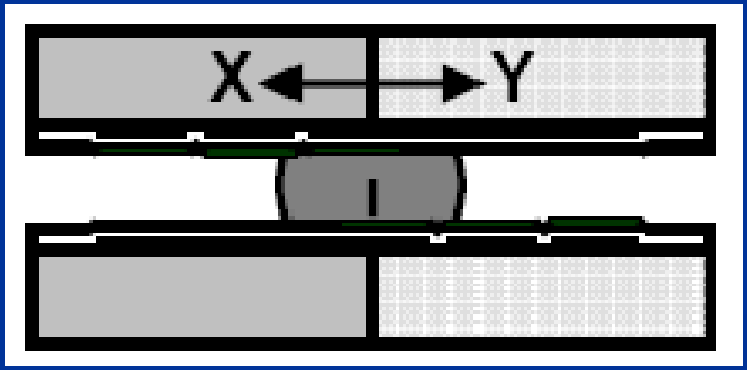
- Orthogonally placed pins on top and bottom plates

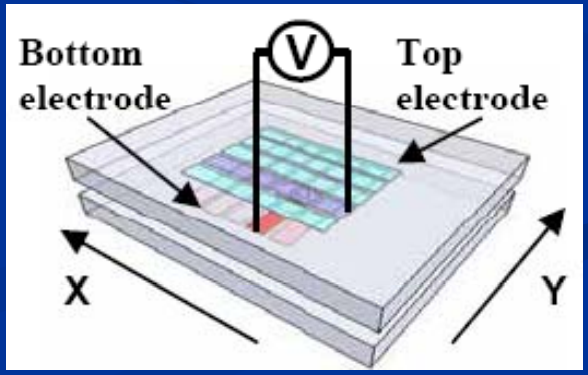
Advantage

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

Disadvantage

Suffers from *electrode interference*



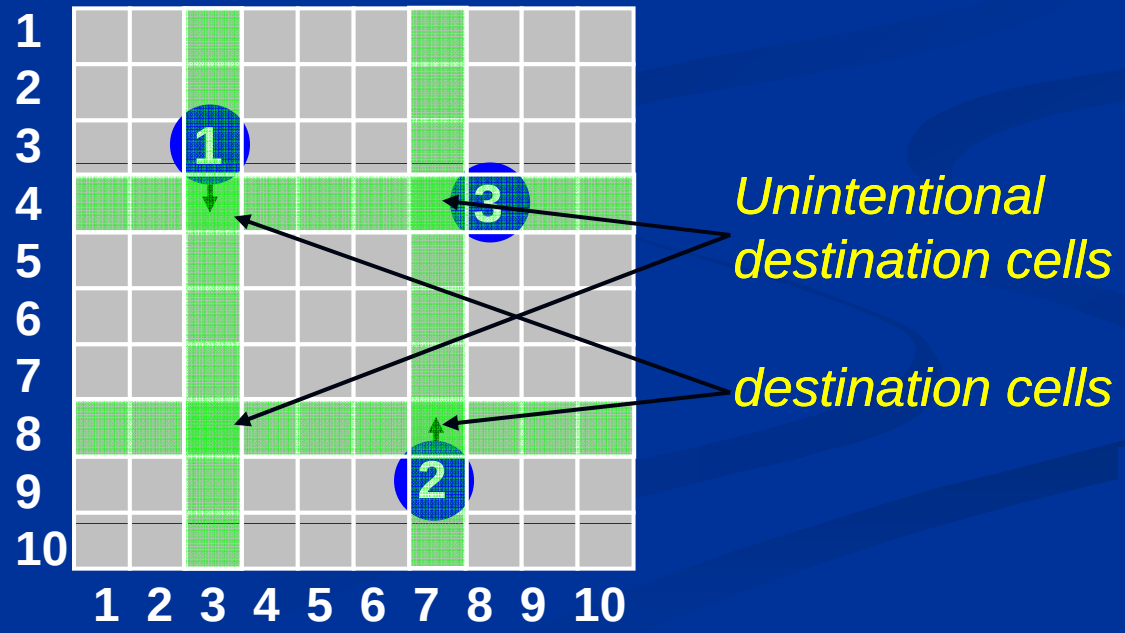


Electrode Interference

- **Unintentional Electrode Actuation**

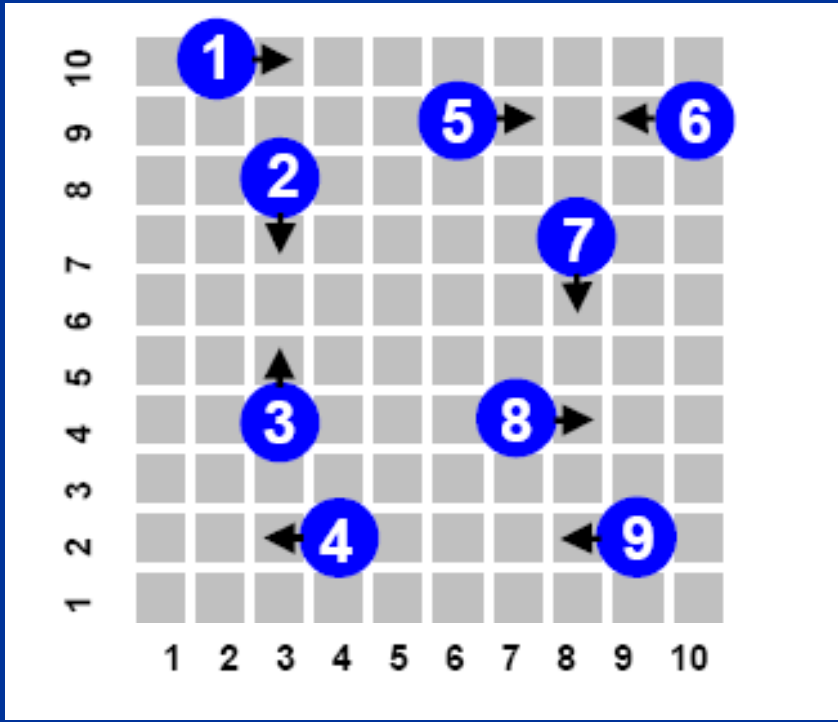
  Selected column and row pins may intersect at multiple electrodes

- **Unintentional Droplet Manipulation**



Efficient Droplet Manipulation Method

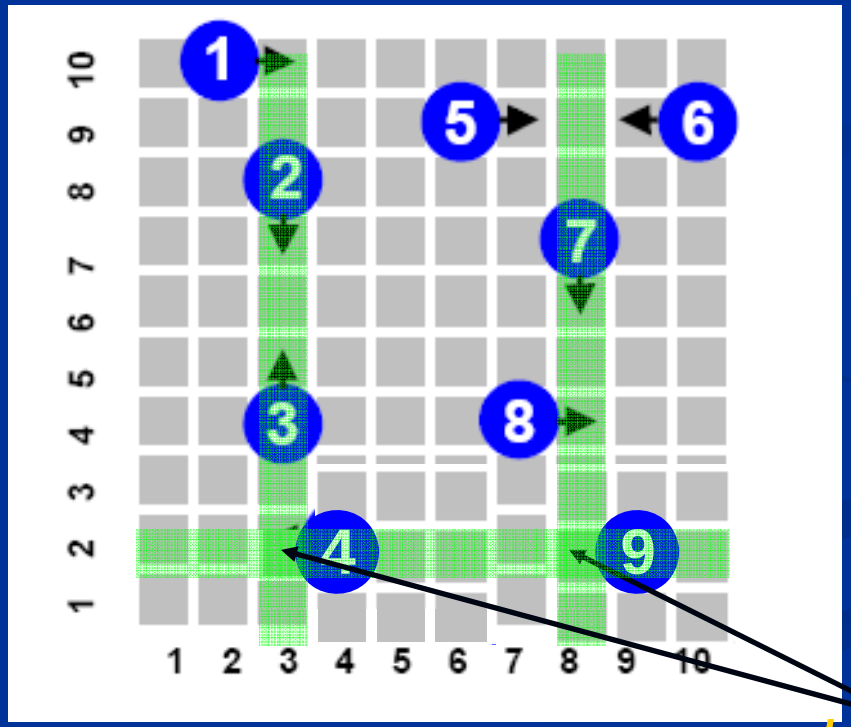
- **Goal**
  - Improve droplet manipulation concurrency on cross-referencing-based biochips.



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.



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

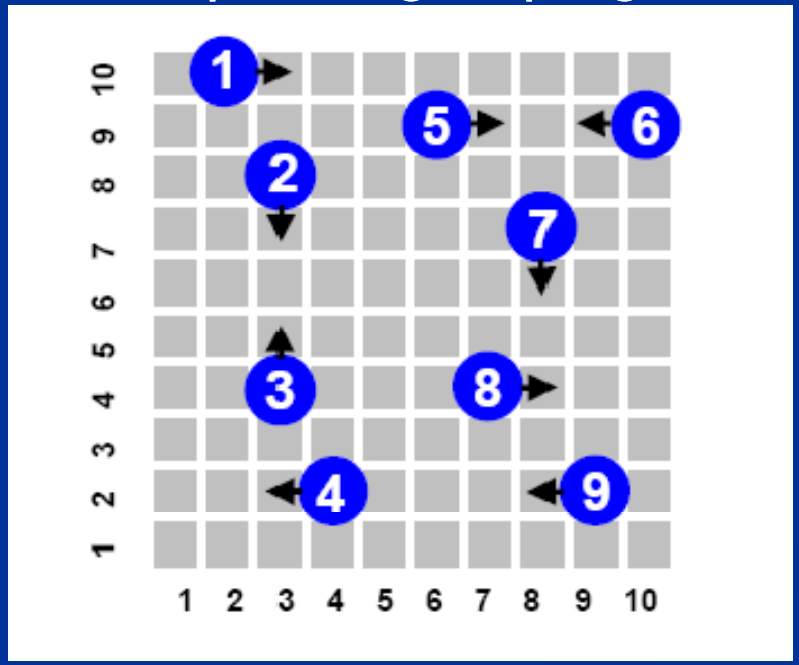
- **Problem formulation**

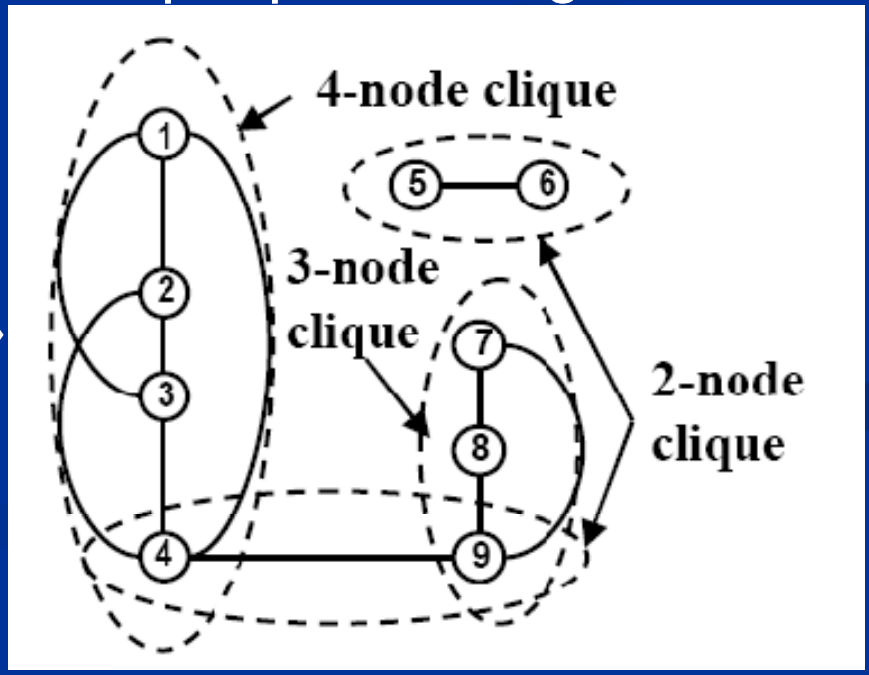
Destination cells → Nodes

Destination cells in one column/row → a Clique

Grouping → Clique partitioning

Optimal grouping → Minimal clique-partitioning





Broadcast Electrode-Addressing

- **Observation**

  "Don't-Cares" in Electrode-Actuation Sequences

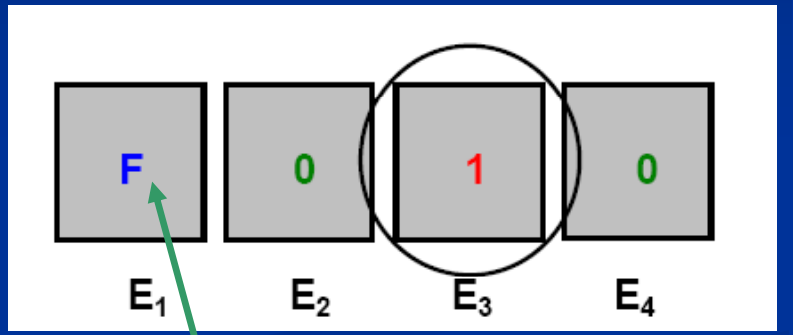
  Electrode control inputs: 3 values

  "1" –- activated

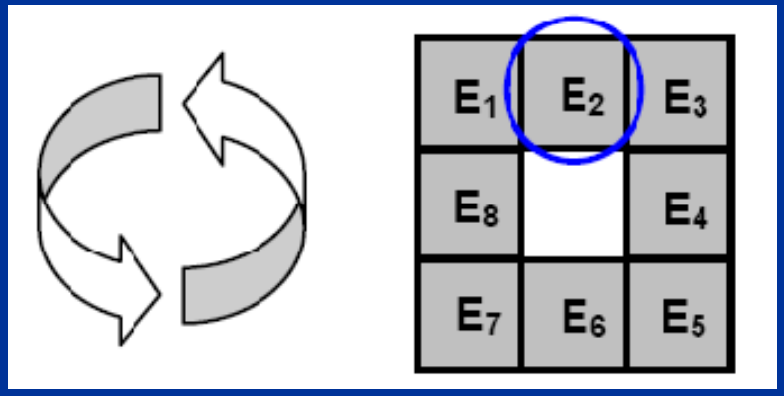
  "0" –- deactivated

  "x" –- can be either "1" or "0"

  Therefore, activation sequences can be combined by interpreting "x"



Floating electrode



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

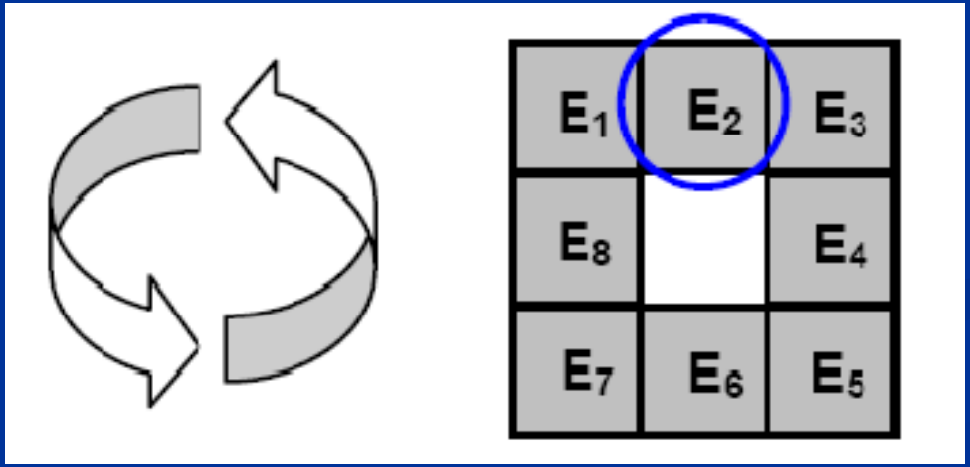
Electrode Addressing Based on Clique Partitioning in Graphs

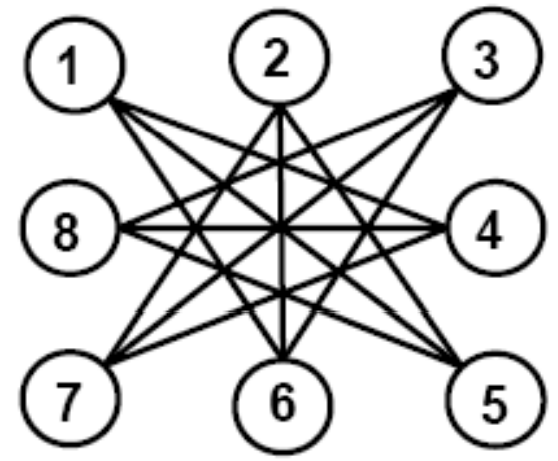
- **Idea**
  - Combining compatible sequences to reduce # of control pins
- **Clique-partitioning-based method**

  Electrodes → Nodes

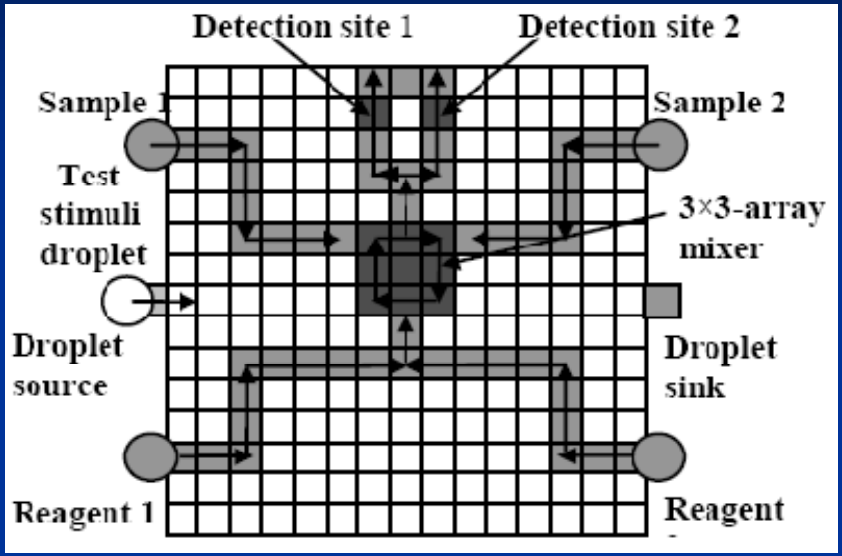
  Electrodes with compatible activation sequences → a clique

  Optimal combination → Minimal clique-partitioning

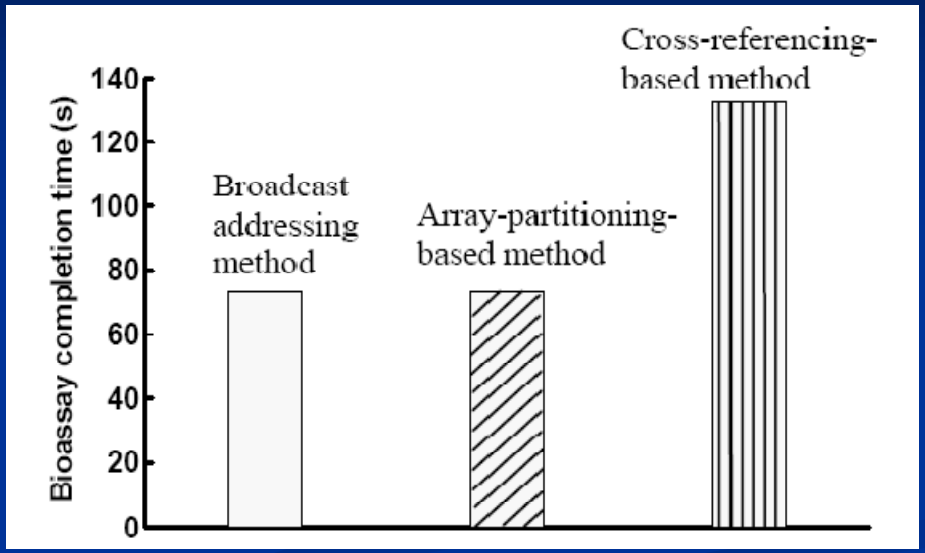




Addressing Results



A biochip target execution of a multiplexed assay



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*

Conclusions

- High concurrency can be achieved on pin-constrained lab-on-chip using a number of methods
  - Partitioning of the array based on droplet-movement patterns
  - Grouping of droplet movements based on clique partitioning
  - Exploiting flexibility in electrode-actuation sequences
- Array partitioning:
  - Specific to target application, number of pins determined such that there is no impact on assay completion time
- Clique partitioning in cross referencing:
  - Independent of target application, number of pins is fixed, and goal is to minimize impact on assay completion time
- Broadcast addressing:
  - Specific to target application, number of pins determined such that there is no impact on assay completion time
- Growing interest and ongoing work in CAD for digital microfluidic lab-on-chip: University of Texas (Austin), National Taiwan University, Penn State University, Rennsselaer Polytechnic University, etc.