Design and Verification Tools for Continuous Fluid Flow-based Microfluidic Devices

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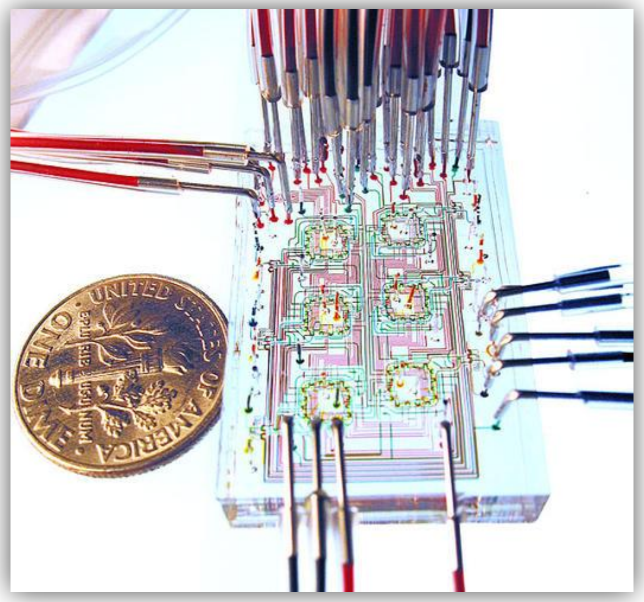
The Future Of Chemistry

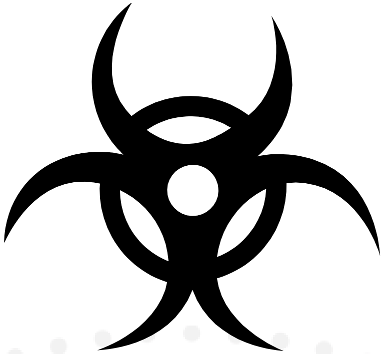
Microfluidics



Miniaturization + Automation

Applications

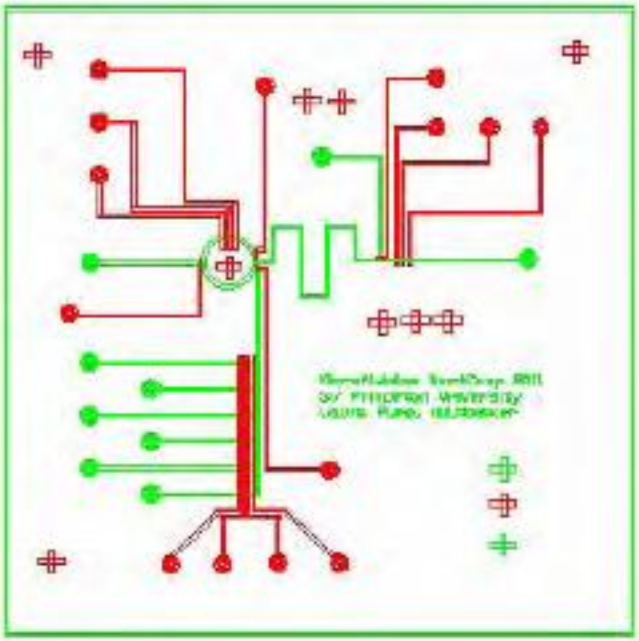
- Biochemical assays and immunoassays
  - Clinical pathology
- Drug discovery and testing
  - Rapid assay prototyping
  - Testing new drugs (via lung-on-a-chip)
- Biochemical terror and hazard detection
- DNA extraction & sequencing



Design of Continuous Fluid-flow LoCs

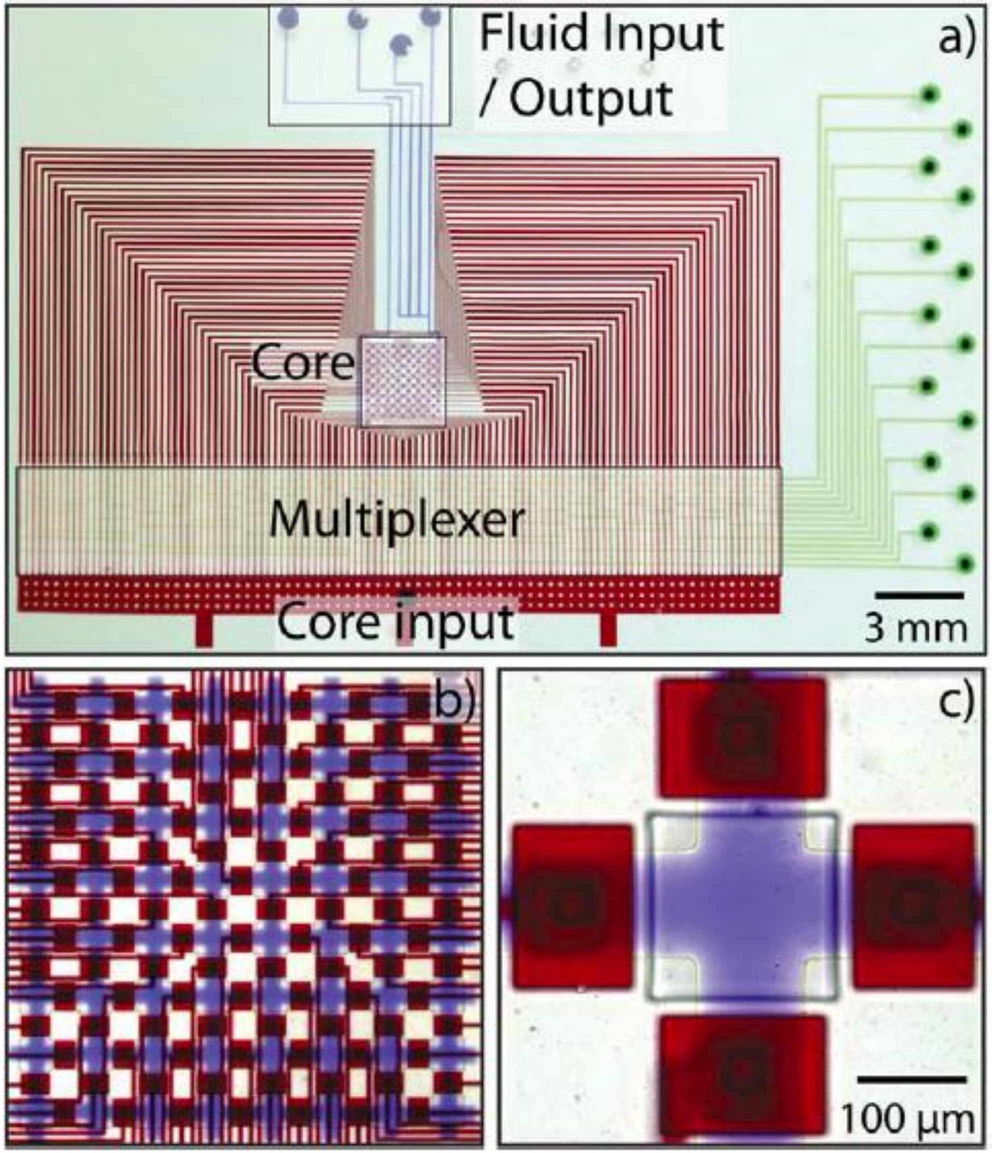
- AutoCAD
  - Draw each layer of the chip manually
  - Akin to transistor-level design of ICs with manual wire routing

- Limited Automation
  - Multi-layer soft lithography
    - [Amin et al., ICCD 2009]
    - [Mihass et al. CASES 2011 & 2012]
  - Capillary dielectrophoresis
    - [Pfeiffer et al. TCAD 2006]
    - [Hsieh and Ho, VLSI Design 2011]
  - This session at ASPDAC 2013



EPFL Programmable Fluidic Device

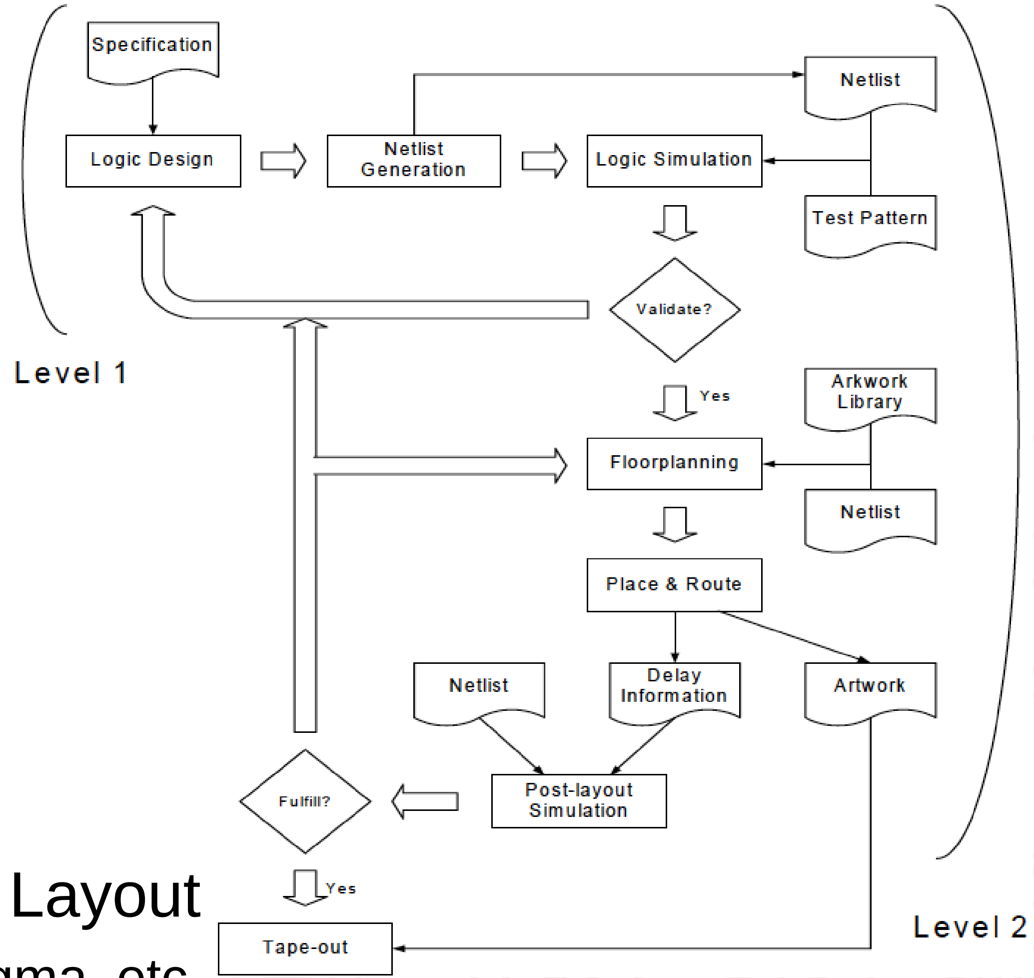
- 918 micromechanical valves
- Multiplexer allows control of micromechanical valves by 21 external solenoid valves
- Design and physical layout took approximately 1 year of postdoc time (personal communication)



[Fidalgo and Maerkl, Lab-on-a-Chip 2010]

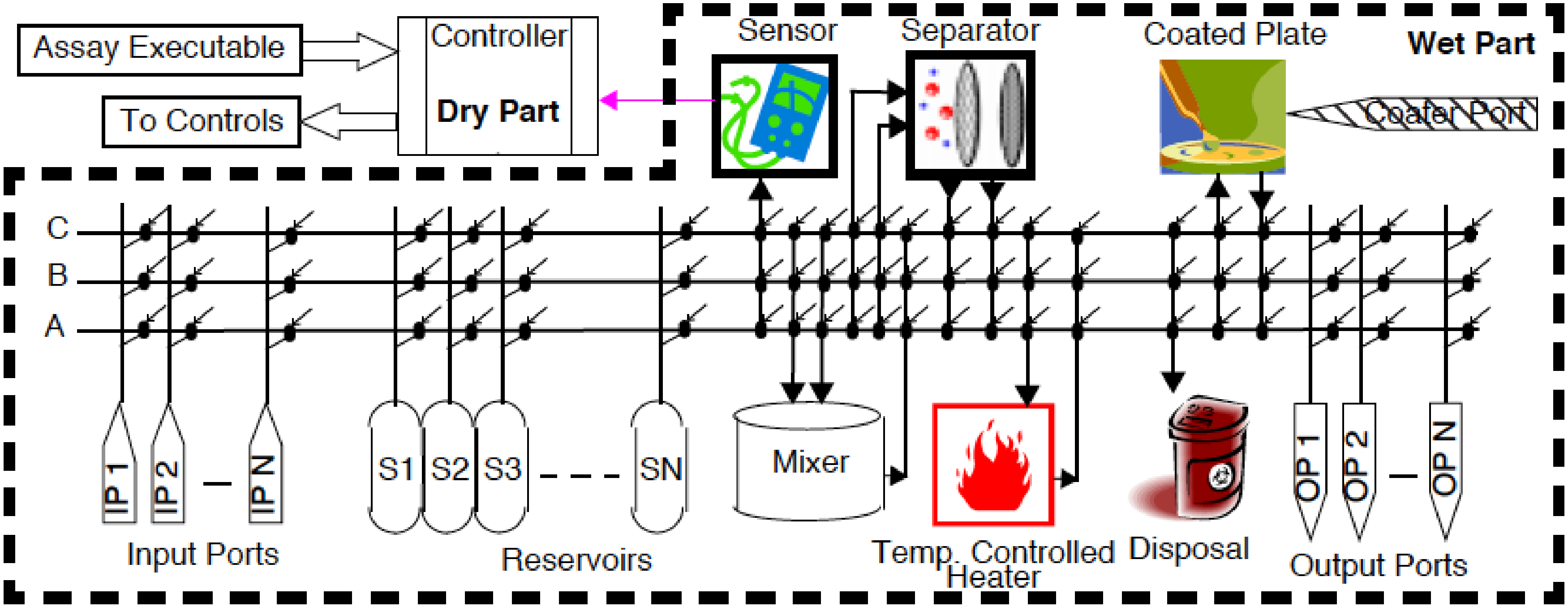
Semiconductor Industry Design Principles

- Hardware Design Languages
  - VHDL
  - Verilog / SystemVerilog
  - SystemC
- Verification
  - User specifies behavioral properties to verify
- Synthesis and Physical Layout
  - Synopsys, Cadence, Magma, etc.
  - Mostly automated, but also support user interaction



Key Observation!

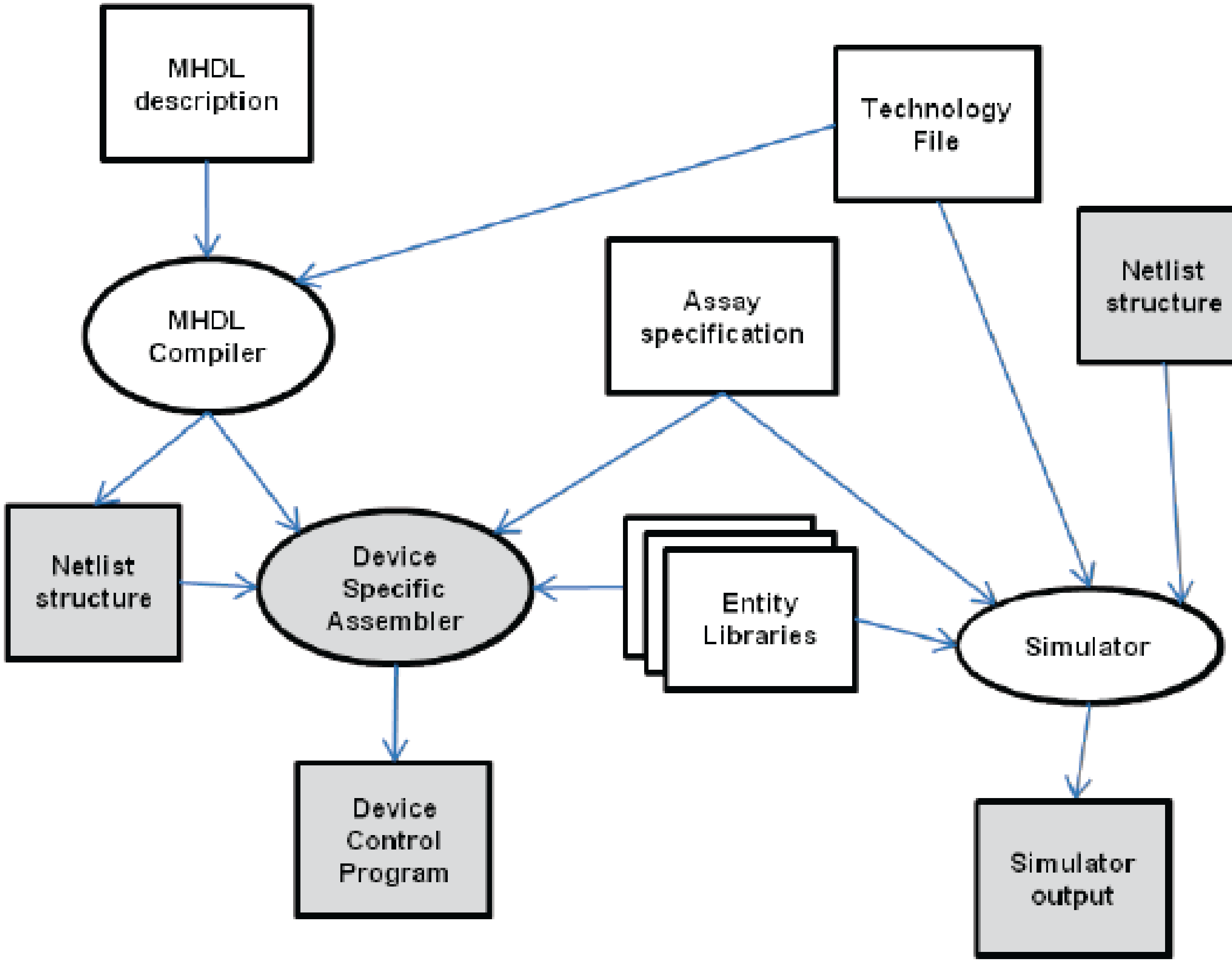
- A typical LoC consists of
  - A collection of "components"
  - Fluidic interconnect between components
  - "Netlist"-like representation



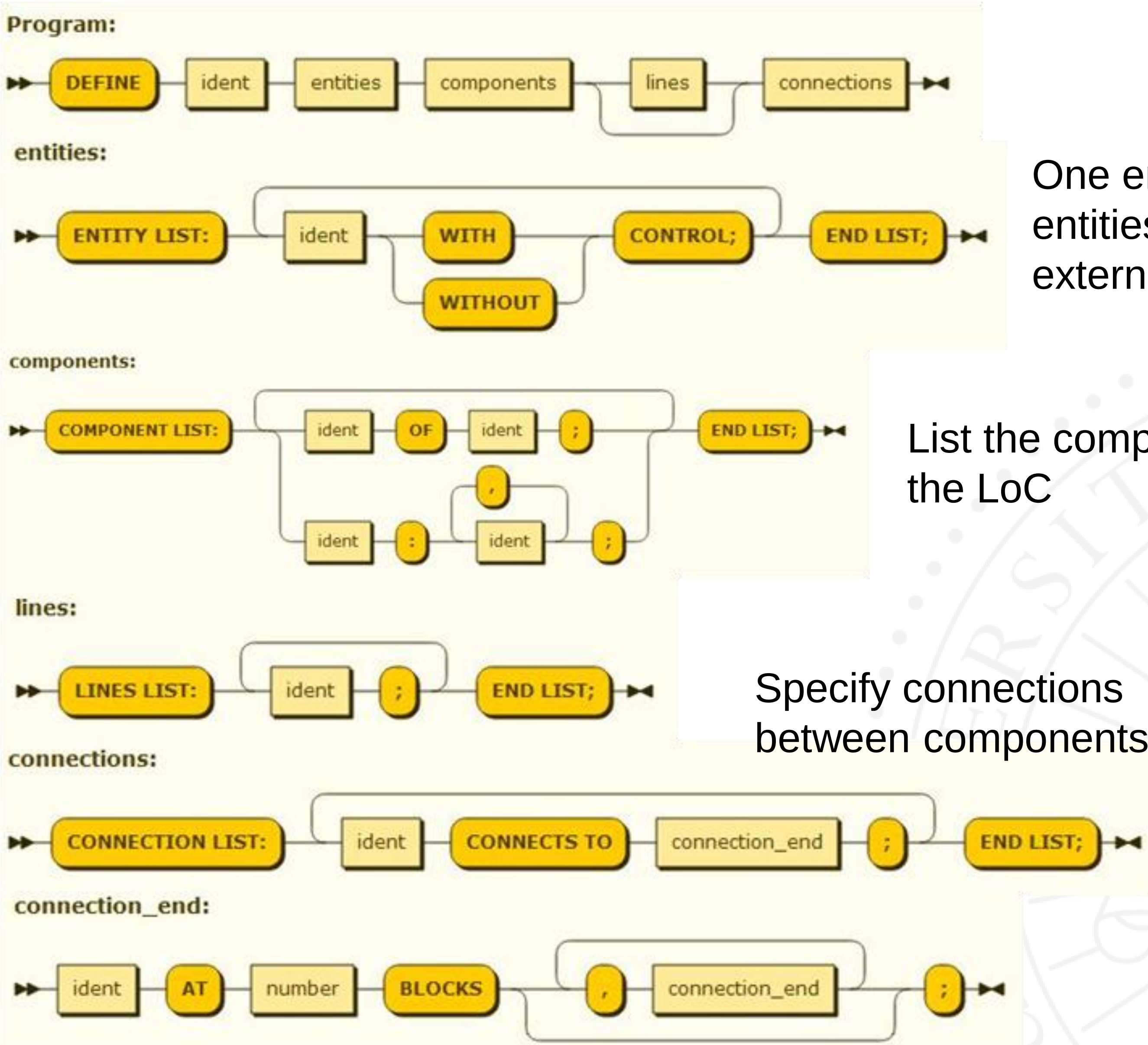
[Amin et al., ISCA 2007]

Our Contributions

- Microfluidic Hardware Design Language (MHDL)
  - Functional Verification, Performance Simulation



MHDL Syntax Diagram



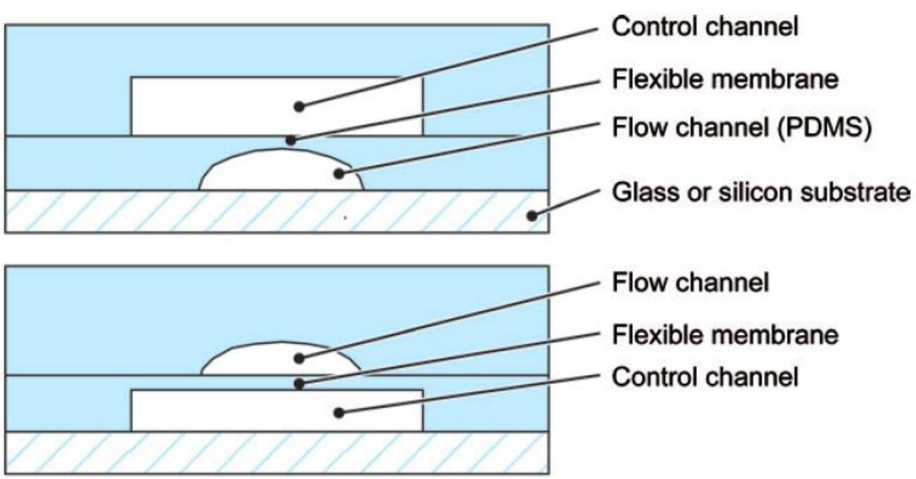
One entity per component; entities may have optional external control

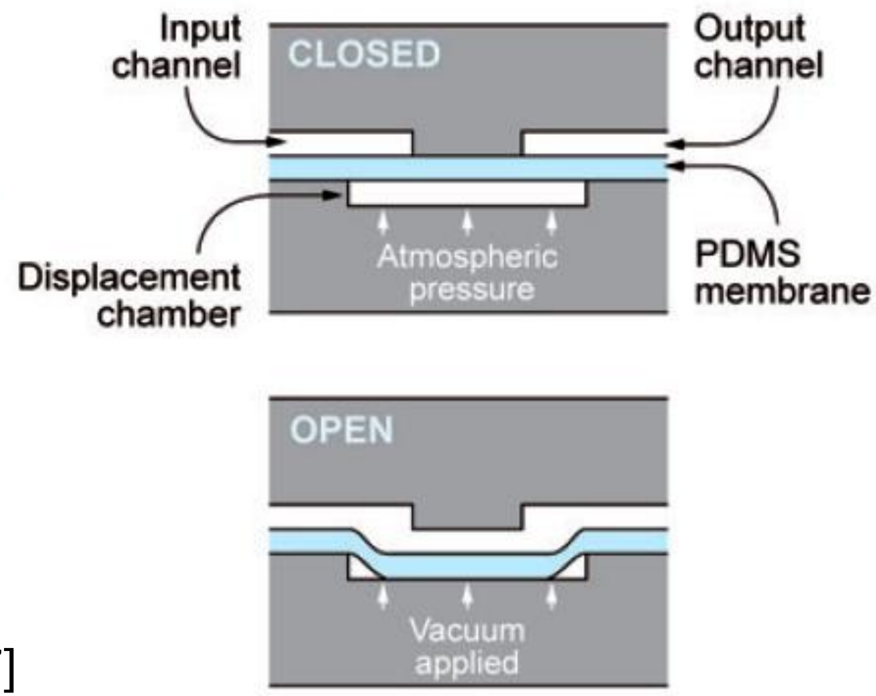
List the components in the LoC

Specify connections between components

MHDL Design Challenges

- Engineers will continually invent new components
  - Extensible component libraries are necessary
- Technological (in)compatibility between components
  - Must be part of component/library specification

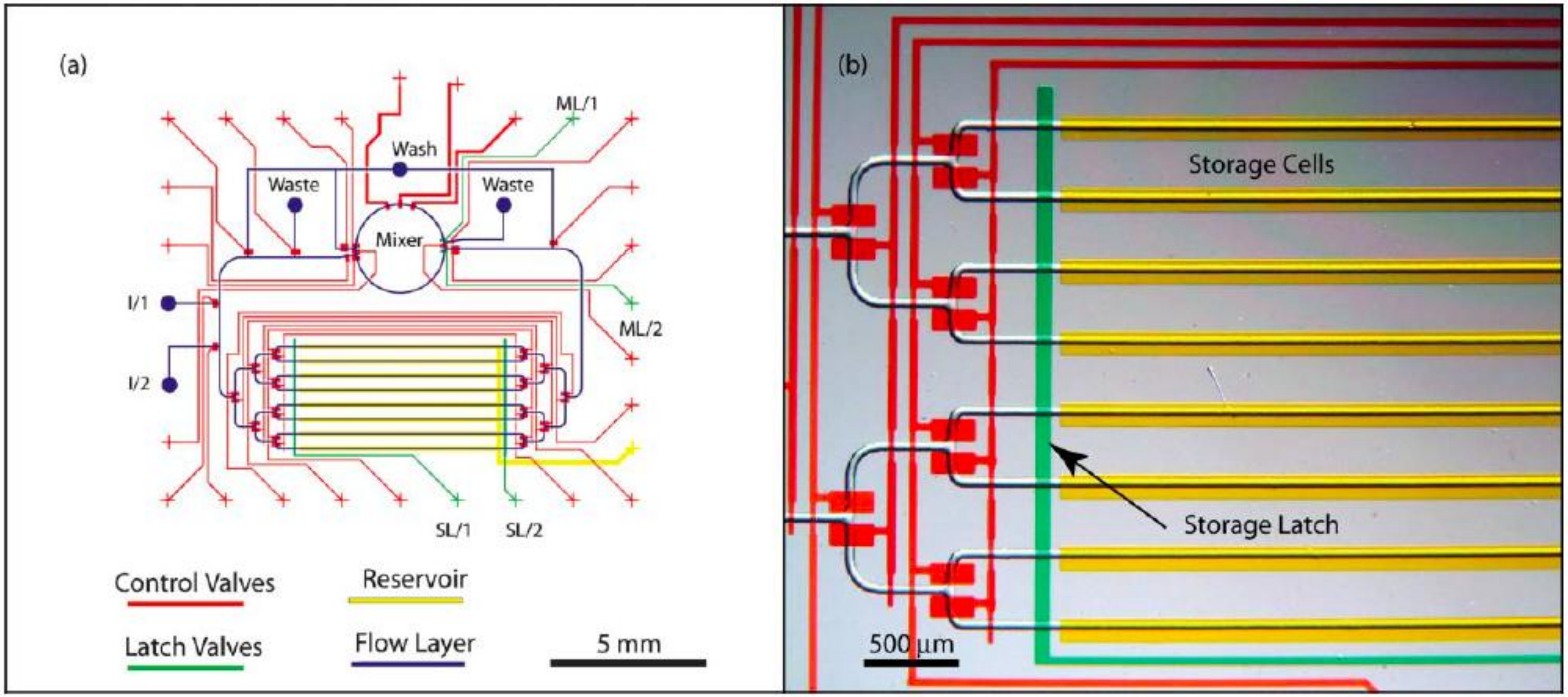




[Melin and Quake,
Annu. Rev. Biophys. Biomol. Struct. 2007]

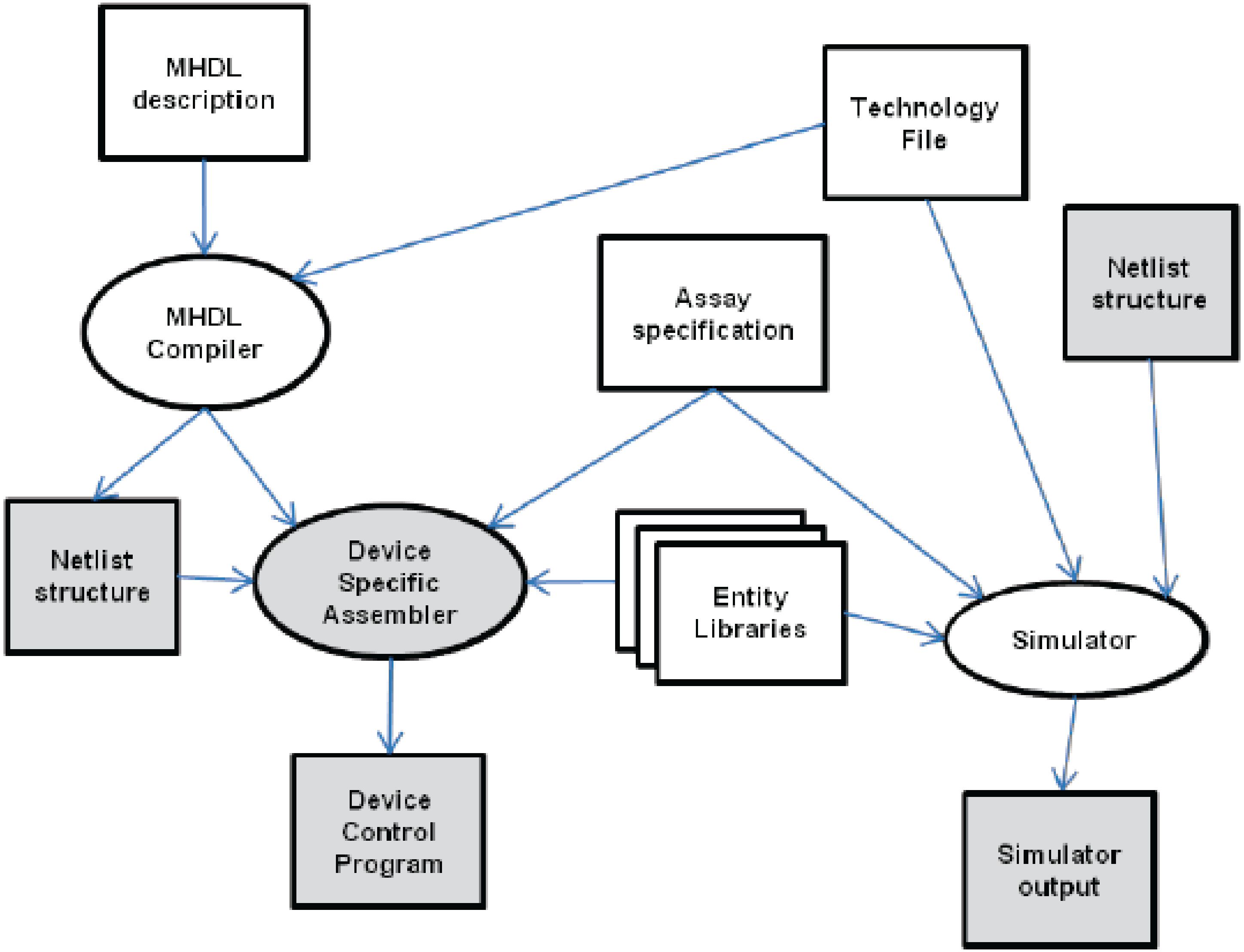
Components, Sub-components

- Mixer
  - 3 valves + input/output control
- Memory
  - Multiplexer, Demultiplexer



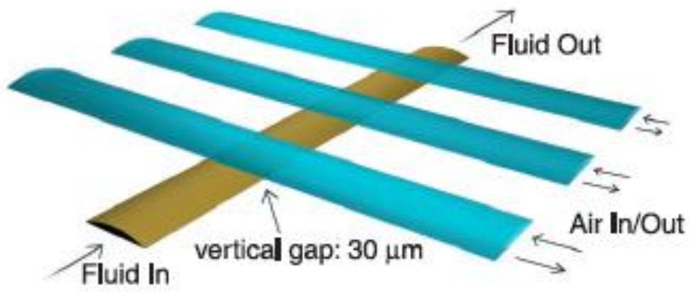
[Urbanski et al., Lab-on-a-Chip 2006]

Design Flow (Revisited)

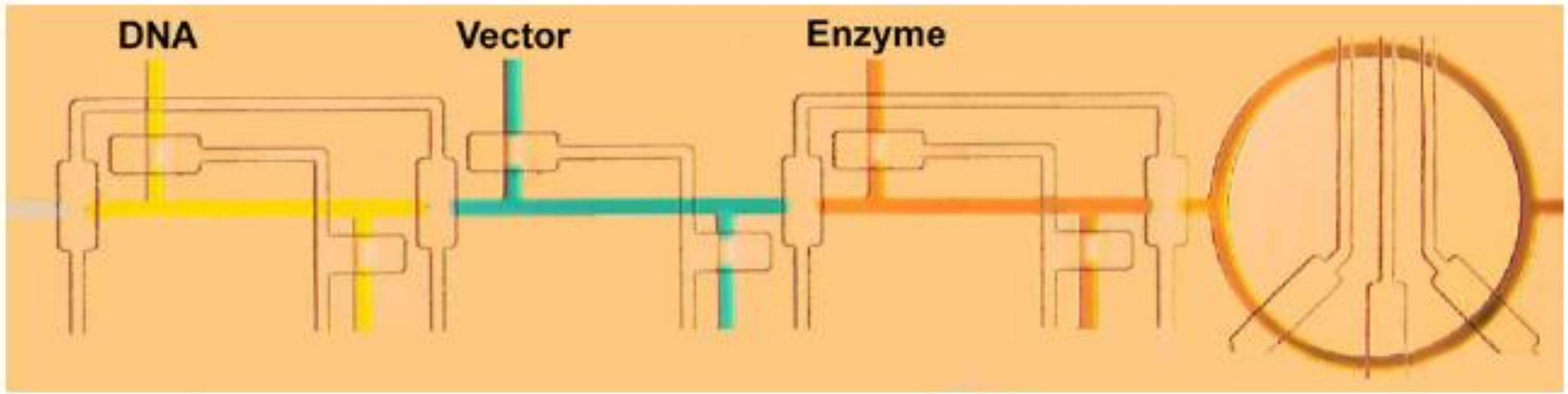


Machine and Assembly Languages

- The control inputs to the components that compose an LoC form a machine language
  - Electrical control: inputs are Boolean
  - Solenoid (pressure) control: inputs are real-valued

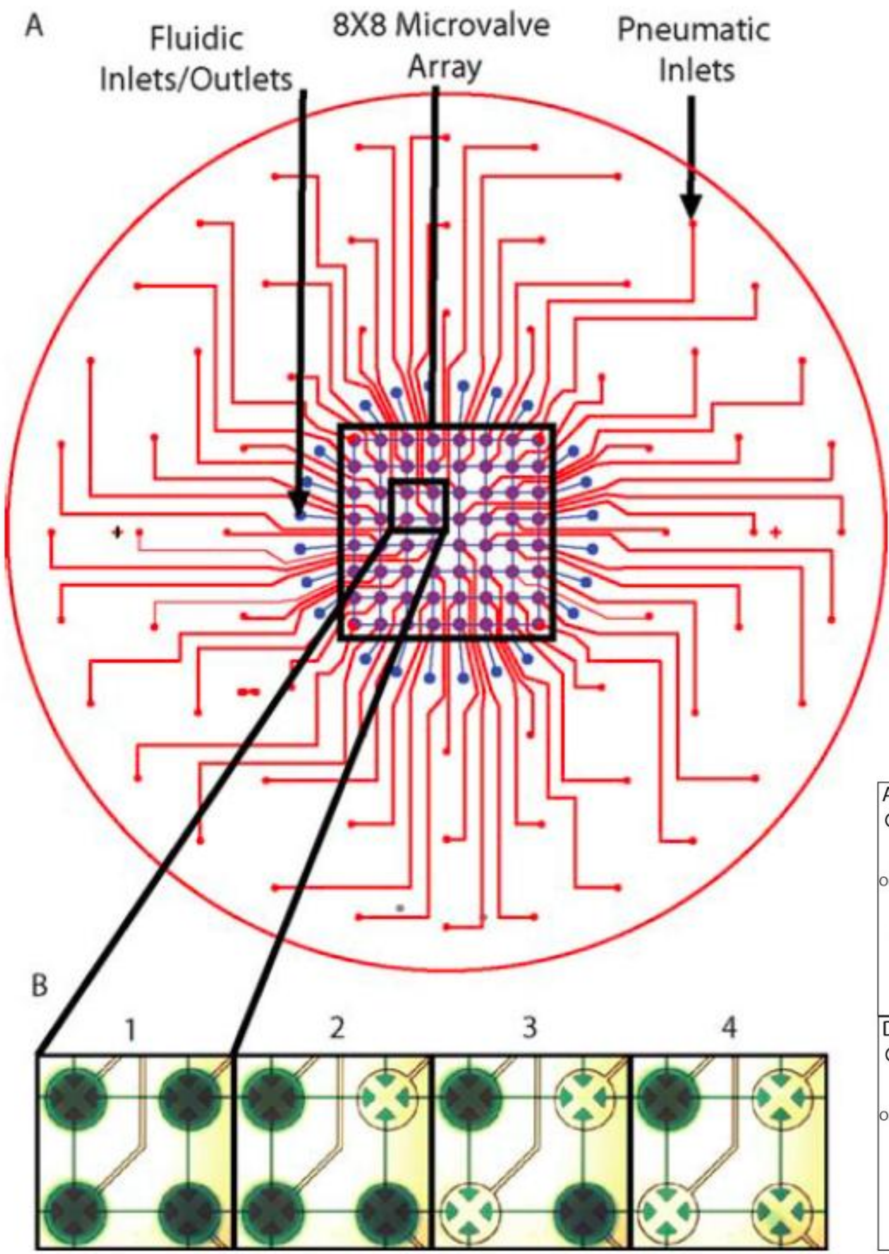


[Unger et al., Science 2000]



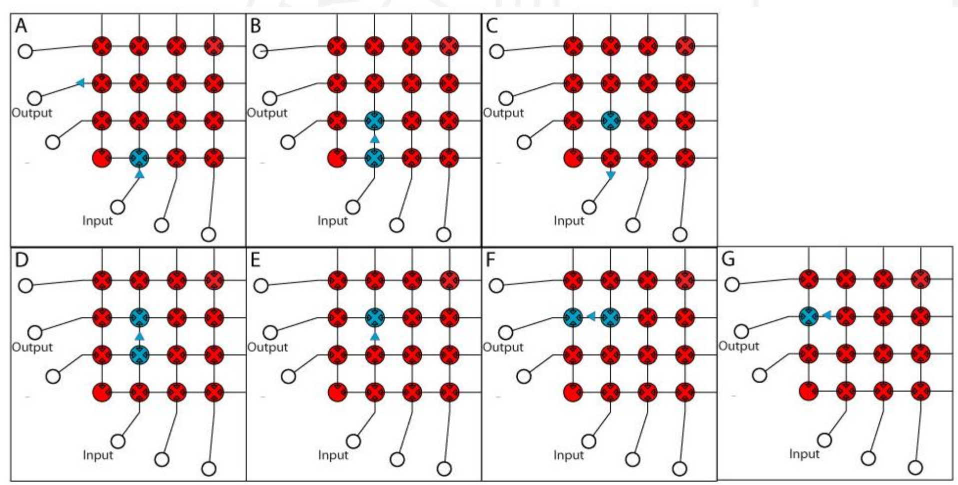
[Hong et al., J. Physics: Condensed Matter, 2006]

Machine and Assembly Languages



- A vector of control values is like a machine language instruction
  - A sequence of vectors forms a machine language program

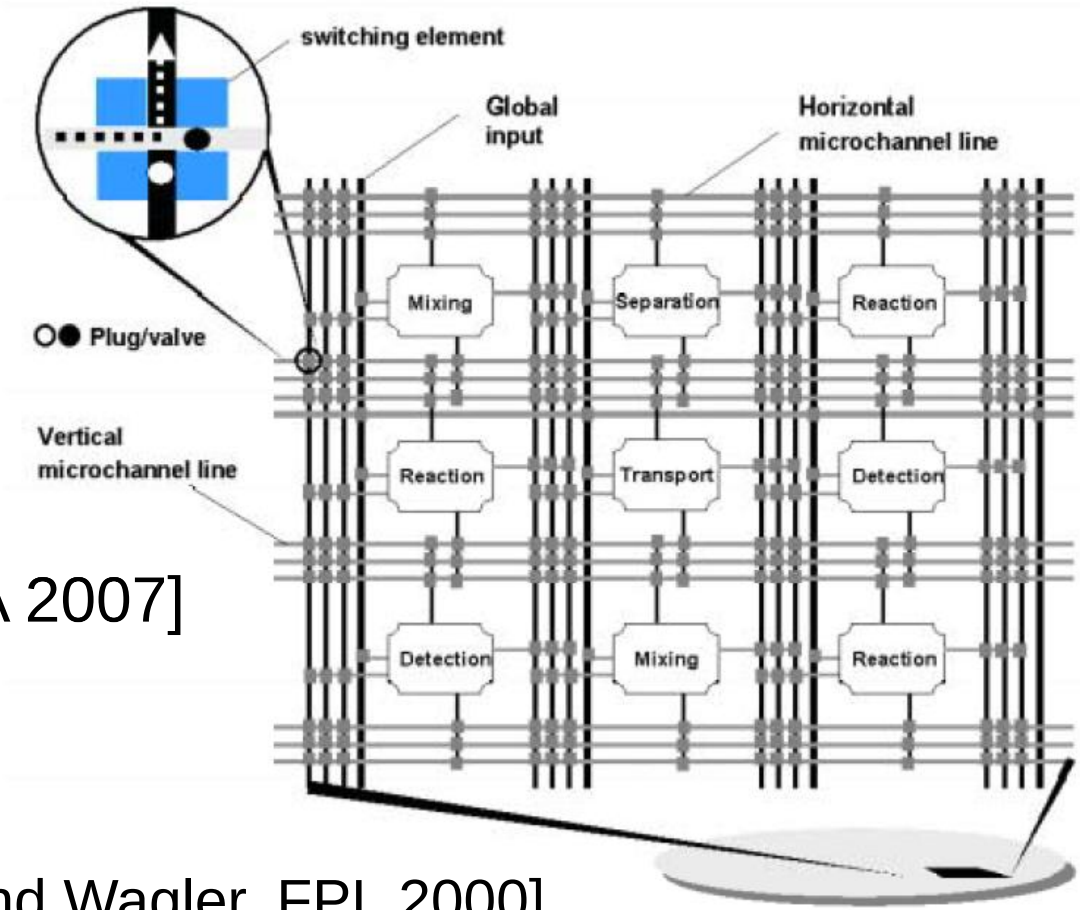
[Jensen et al., Lab-on-a-Chip 2010]



Machine and Assembly Languages

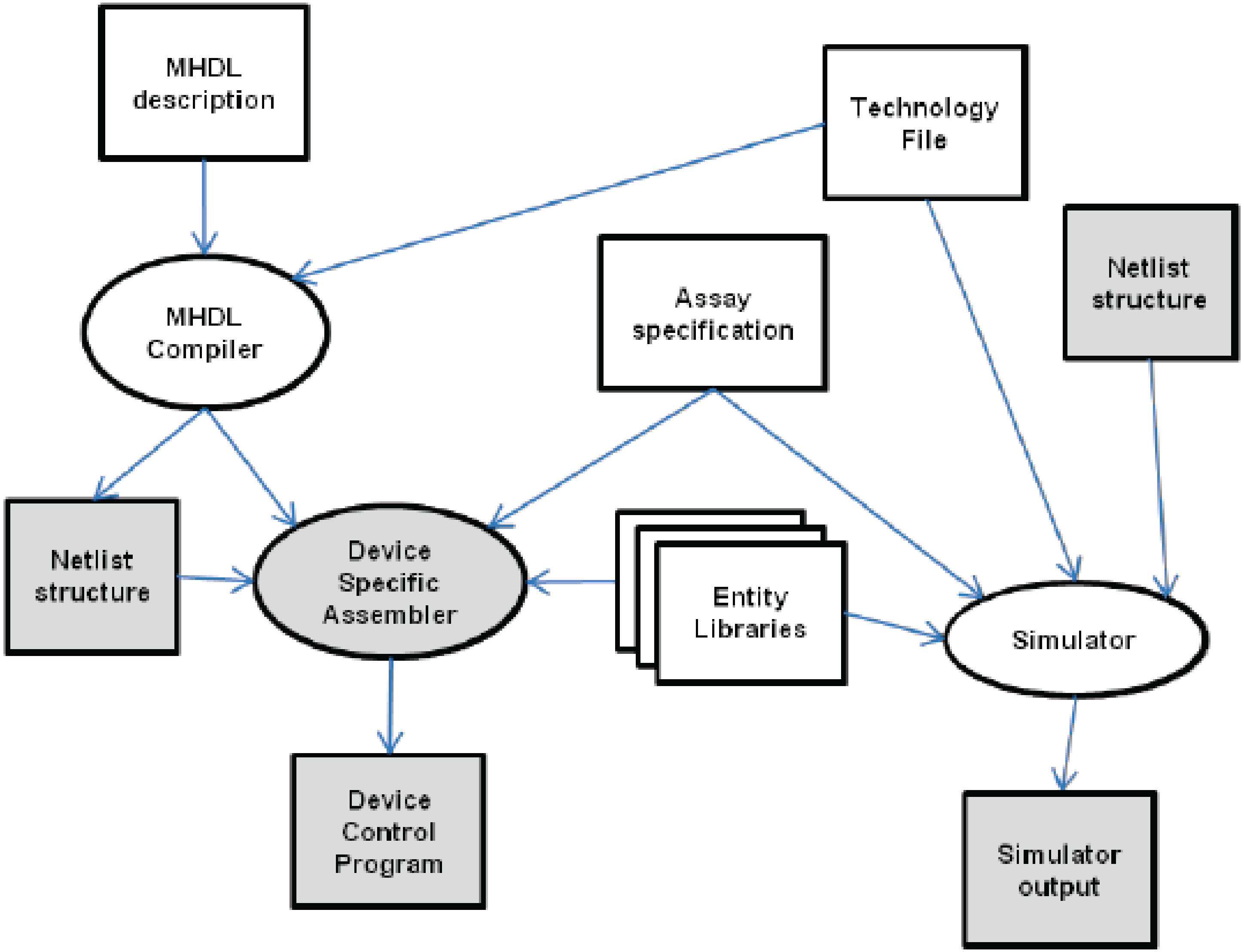
- Automatically derive human-readable assembly language from the netlist/machine language
  - Turn each component on/off (etc.)
  - Fluid transfers

- Generalizes the notion of a fluidic instruction set like AquaCore [Amin et al., ISCA 2007]



[McCaskill and Wagler, FPL 2000]

Design Flow (Revisited)



Device-Specific Assembler

- Inputs
  - Netlist representation of an LoC
  - Assembly language assay specification
- Functional verification
  - Can the netlist execute the assay?
    - Is there a component to execute each operation?
    - Are all required fluid transfers possible?
- Output: Device Control Program
  - Sequence of control vectors to execute the assay

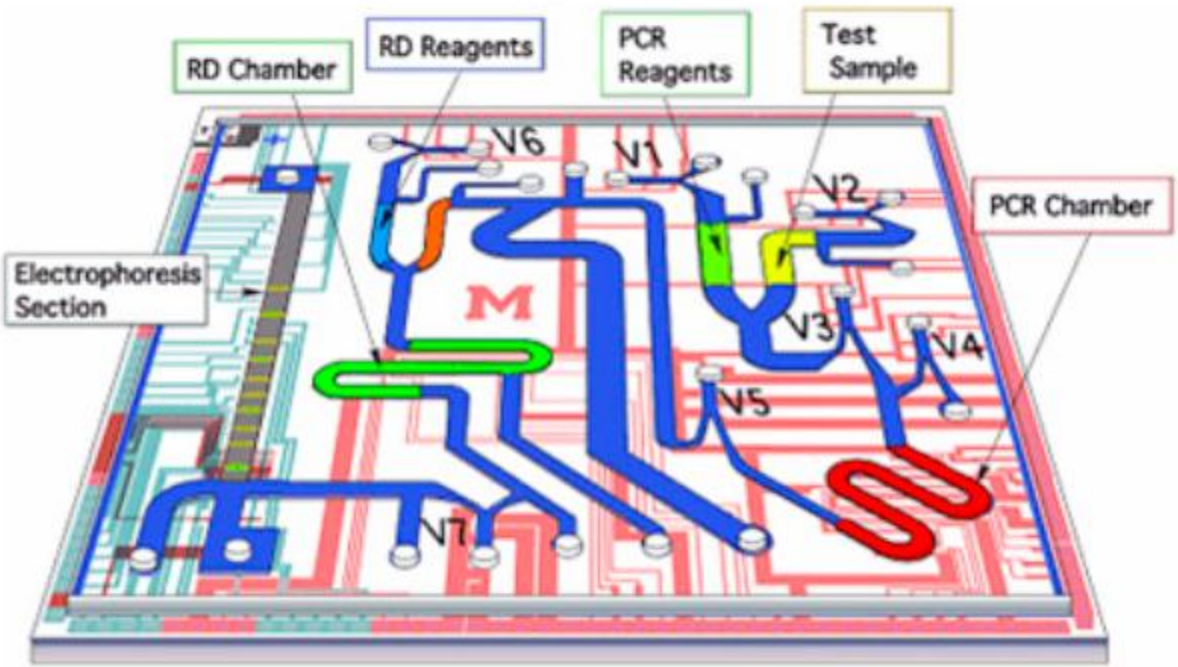
Simulation

- Performance Evaluation (Latency)
  - Assay specification (e.g., MIX for 30s)
  - Fluid transfer overhead

    - Hagen-Poisseuile Equation: $T = V/Q$
      - V: Volume of fluid to transfer
      - Q: Volumetric flow rate

    - Volumetric Flow Rate: $Q = \Delta P \pi d^4 / 128 \mu L$
      - ΔP: Pressure drop
      - μ: Fluid viscosity
      - d: Channel diameter – not known until after physical layout
      - L: Channel length – not known until after physical layout
        - Absent layout information, the user can specify d and L

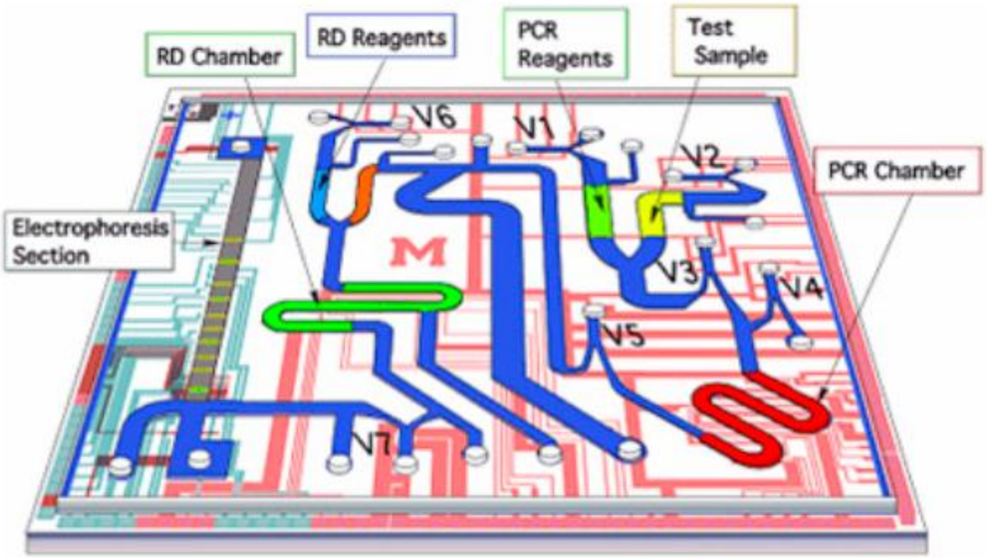
Example: Influenza Detection



[Pal et al., Lab-on-a-Chip 2005]

The thermocycling protocol applied to the device consists of 92 degrees C for 30s, and then 35 cycles of the following: 92 degrees C for 5s, 55 degrees C for 10s, and 72 degrees C for 20s, and finally 72 degrees C for 60s, for a total cycling time of 22 minutes. A portion of the PCR product (~60nl) is subsequently subjected to a restriction endonuclease digestion within the same device. The restriction digest reaction is performed at 37 degrees C for 10 min.

Example: Influenza Detection

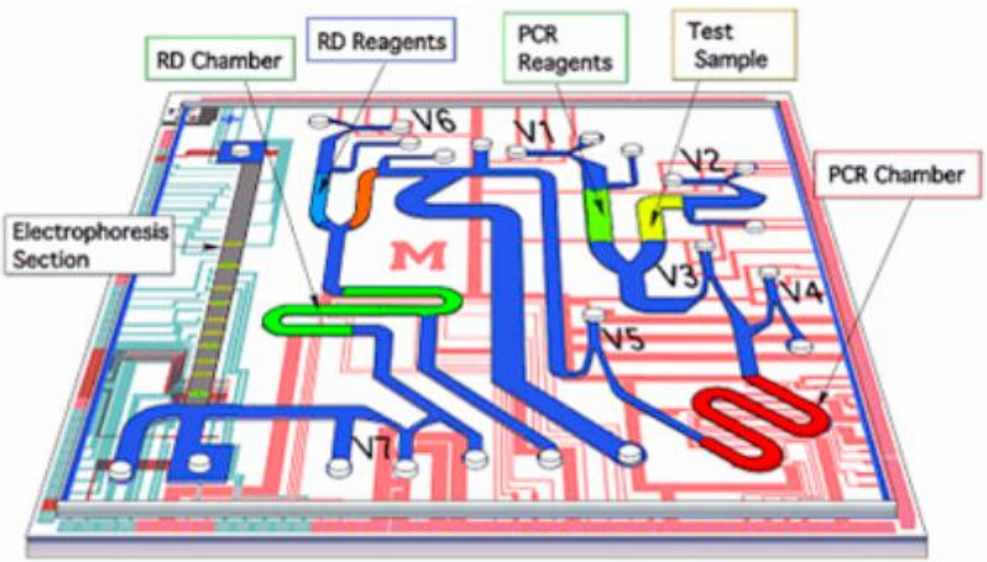


[Pal et al., Lab-on-a-Chip 2005]

<u>Influenza Detection LoC MHDL Specification</u>

```
define flu_diagnoses:
   entity list:
      storage without control;
      valve with control;
      mixer with control;
      electrophoresis with control;
      PCR with control;
      RDR with control;
      Exhaust with control;
   end list;
   component list:
      valve: V1,V2,V3,V4,V5,V6,V7,A4,A6,B2,RDvalve;
      PCR_chamber of PCR: RD_chamber of RDR;
      Electrophoresis_section of electrophoresis;
      B3 of exhaust;
      Storage: L1,L2,L3,PCR_product,B1B4;
   end list;
   connection list:
      L1 connects to V1 at 10 blocks;
      V1 connects to V3 at 100 blocks;
      L2 connects to V2 at 10 blocks;
      V2 connects to V3 at 120 blocks;
      V3 connects to V4 at 40 blocks;
      V4 connects to PCR_chamber at 40 blocks;
      PCR_chamber connects to V5 at 40 blocks;
      V5 connects to A4 at 110 blocks;
      A4 connects to PCR_product at 10 blocks;
      PCR_product connects to A6 at 10 blocks;
      A6 connects to RDvalve at 50 blocks;
      L3 connects to V6 at 10 blocks;
      V6 connects to RDvalve at 100 blocks;
      RDvalve connects to RD_chamber at 10 blocks;
      RD_chamber connects to V7 at 30 blocks;
      V7 connects to B1 at 10 blocks;
      B1 connects to B2 at 20 blocks;
      B2 connects to electrophoresis_section at 10 blocks;
      electrophoresis_section connects to B4 at 10 blocks;
      B2 connects to B3 at 10 blocks;
   end list;
end define;
```

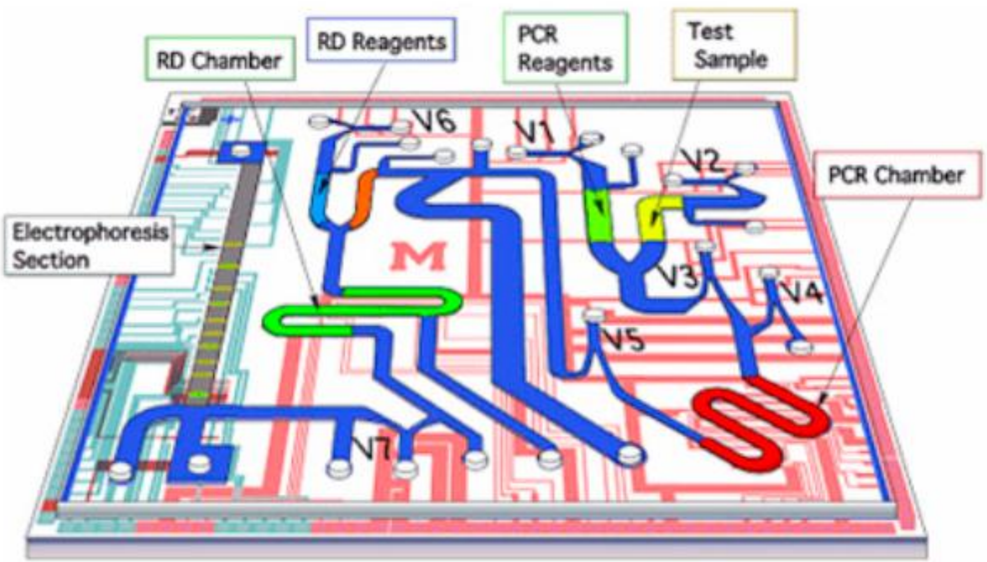
Example: Influenza Detection



[Pal et al., Lab-on-a-Chip 2005]

```
load flu_diagnoses
assay flu diagnoses

fill L1,PCR_Reagents,240,.0008
fill L2,DNA,600,.0008
fill L3,RDReagents,500,.0008
fill B4,ReproGel,100,.0008

moveper PCR_chamber,L1,100
moveper PCR_chamber,L2,100

heat PCR_chamber,30,92

repeat loop 35 times
   heat PCR_chamber,5000,92
   heat PCR_chamber,10000,55
   heat_PCR_chamber,20000,72
end loop

heat PCR_chamber,60000,72

moveper PCR_product, PCR_chamber,50
moveper RD_chamber,L3,100
moveper RD_chamber,PCR_product,100

digest RD_chamber,600000,37
moveper B1,RD_chamber,50

moveper electrophoresis_section,B1,100
moveper electrophoresis_section,B4,100
separate electrophoresis_section,600000

moveper B3,electrophoresis_section,100
flush B3
```

Example: Influenza Detection



[Pal et al., Lab-on-a-Chip 2005]

/* Execution Trace */
L1 is filled with 240 cubic microns of PCR Reagents
L2 is filled with 600 cubic microns of DNA
L3 is filled with 500 cubic microns of RDReagents
B4 is filled with 100 cubic microns of ReproGel

Moved 240 cubic microns from L1 to PCR_chamber
L1->L1V1(65.2229)->V1(0)->V1V3(326.115)->V3(0)->
V3V4(130.446)->V4(0)->PCR_chamber
L1 is now empty
PCR_chamber now contains 240 cubic microns of
PCR_Reagents
Time: 891 ms
...

/* Remaining Fluids */
PCR_chamber contains 300 cubic microns of DNA
RD_chamber contains 150 cubic microns of DNA

/* Statistics Tracking */

Total Valve Actuation Time:	2400ms
Total Time in Lines:	2380.64ms
Total Transfer Time:	5224ms
Total Time in Components:	2.48507e+06ms
Total Time:	2.49049e+06ms
Total Number of Valve Actuations:	17

Conclusion and Future Work

- Continuous Fluid Flow LoC Specification
  - Technology-independent MHDL language
  - Verification and simulation framework

- Machine Language LoC Interface
  - Automatically derive human-readable assembly
  - Human specifies assay in assembly

- Future Work
  - Compile high-level language to assembly
  - Physical design flow(s)