Fluigi: Microfluidic Design for Synthetic Biology

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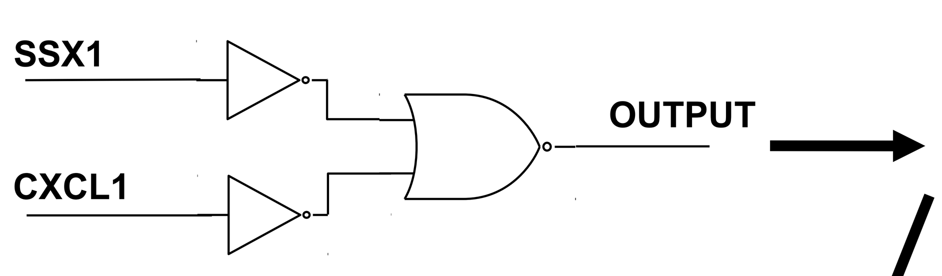
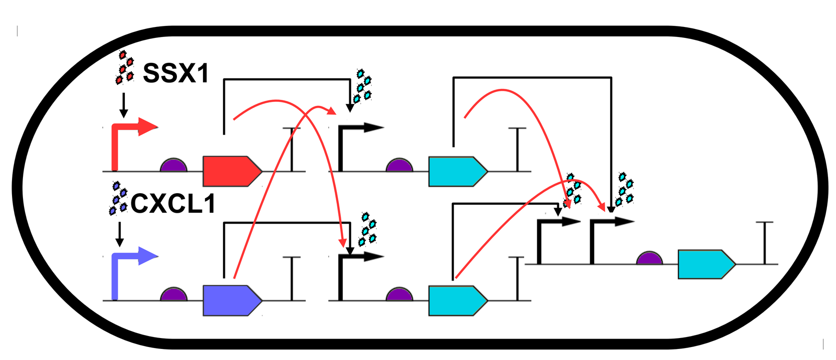
Abstract

Microfluidic technologies provide a reliable and scalable construction of synthetic biological systems by allowing compartmentalization of cells encoding simple genetic circuits and the spatiotemporal control of communication among these cells. We describe a Computer Aided Design (CAD) framework called "Fluigi" for optimizing the layout of genetic circuits on a microfluidic chip, generating the control sequence of the associated signaling fluid valves, and simulating the behavior of the configured biological circuits. We demonstrate the capabilities of Fluigi on a set of Boolean algebraic benchmark circuits found in both synthetic biology and electrical engineering and a set of assay based benchmark circuits, and show the photomasks for fabrication generated by our software for those circuits.

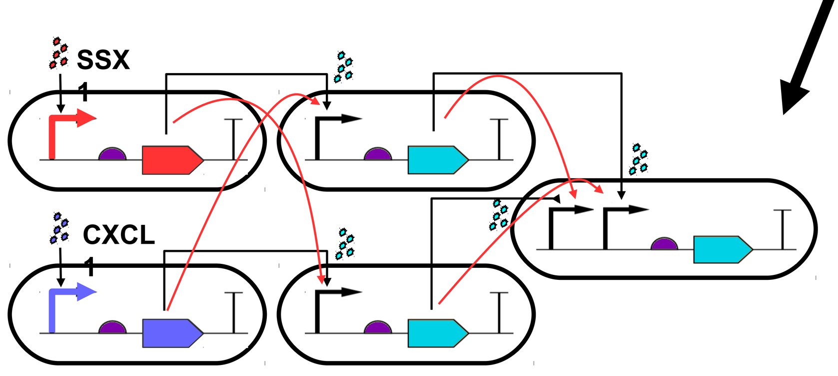
Microfluidics for Distributed Biological Computation



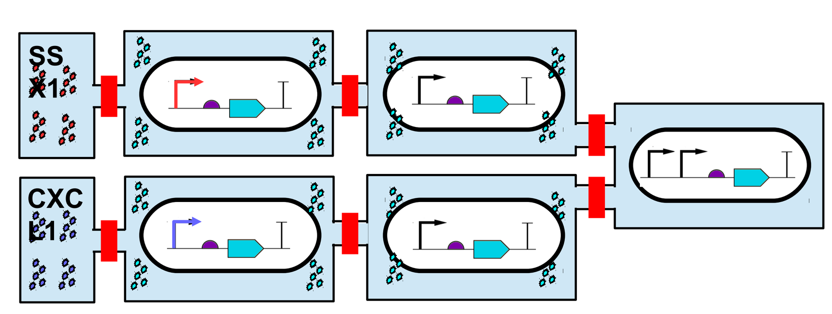
Logic circuit composed of inverters and NOR gates representing the function AND



The same AND gate implemented as genetic circuits in a single cell. Red arcs indicate the cross talk between proteins.



Separating the complex circuit into multiple cells will not eliminate issues caused by crosstalk.



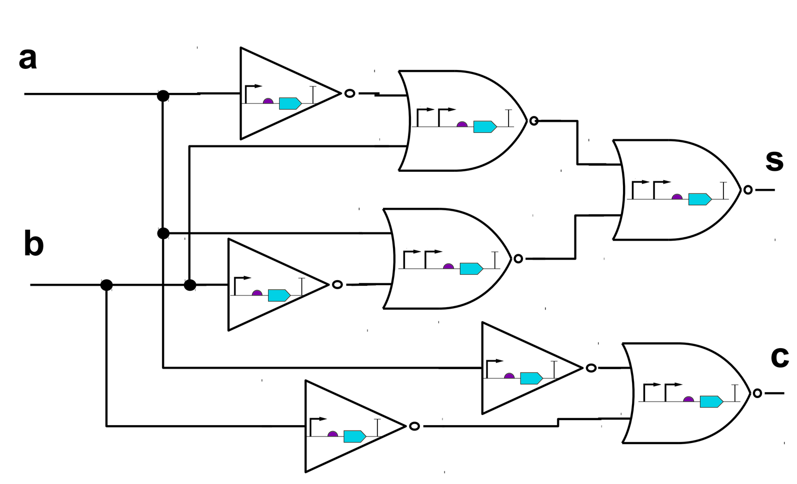
Compartmentalization by microfluidic chambers will allow for precise application of input molecules to the circuit and potentially eliminated crosstalk.

Automated Design Flow

1. Obtain function from input file

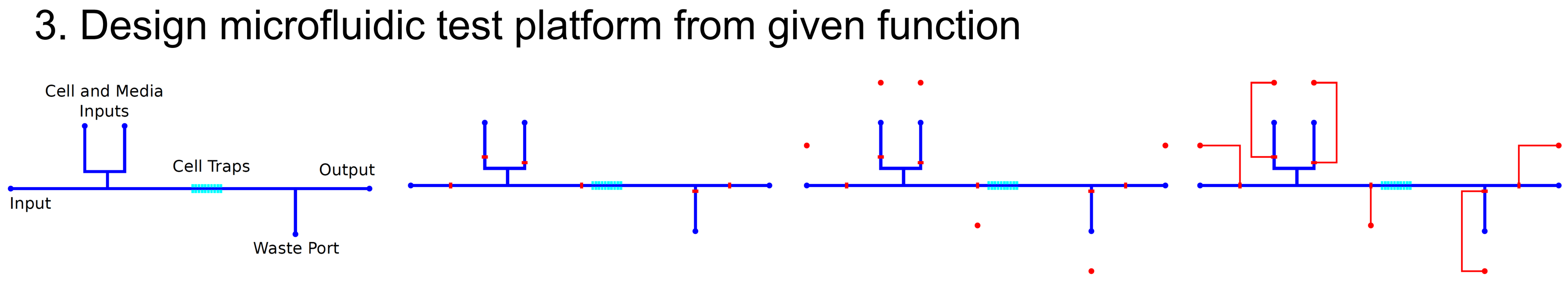
```
module half_adder (a, b,
      sum, carry );
input  a;
input  b;
output sum;
output carry;
assign sum = a^b;
assign carry = a&b;
endmodule
```

a	b	s	c
0	0	0	0
0	1	1	0
1	0	1	0
1	1	0	1



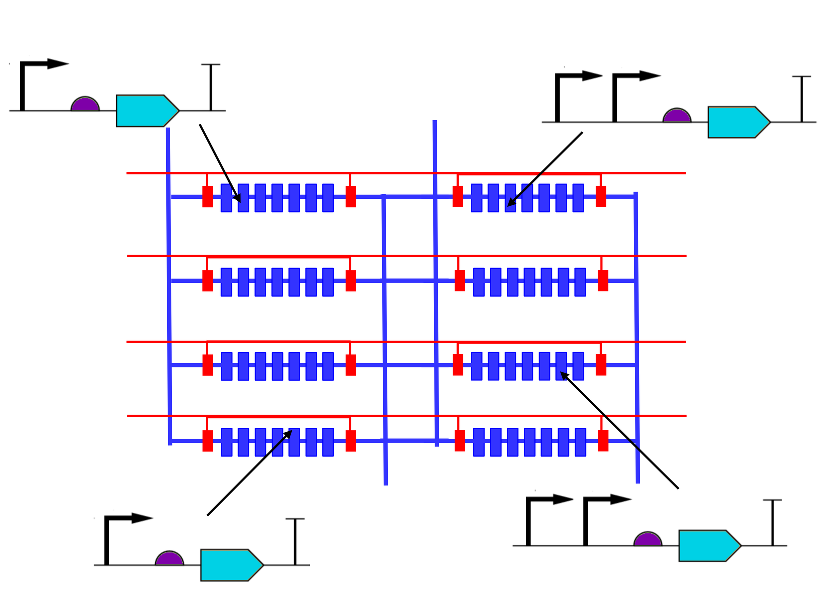
2. Construct function from devices in library or registry

3. Design microfluidic test platform from given function

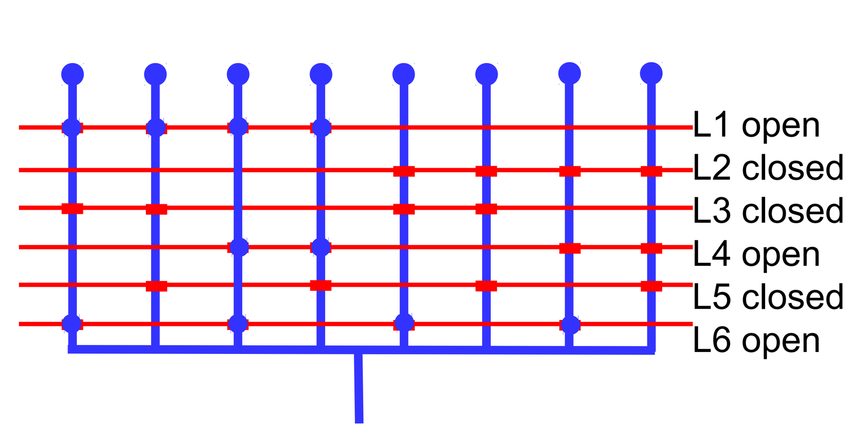


A. Layout flow layer B. Place valves on control layer C. Place control ports D. Route control layer

E. Generate photomasks



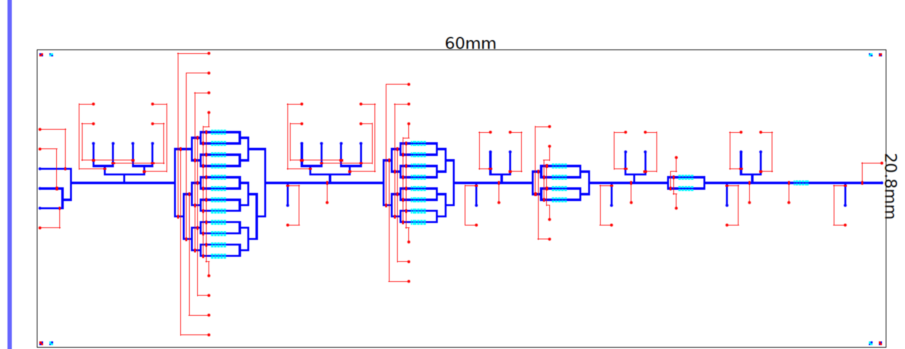
4. Assign cells to locations in chip



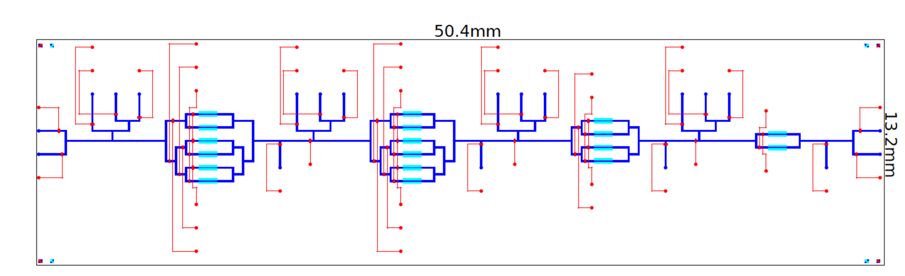
5. Generate valve control patterns

Sample Microfluidic Devices Made With Fluigi

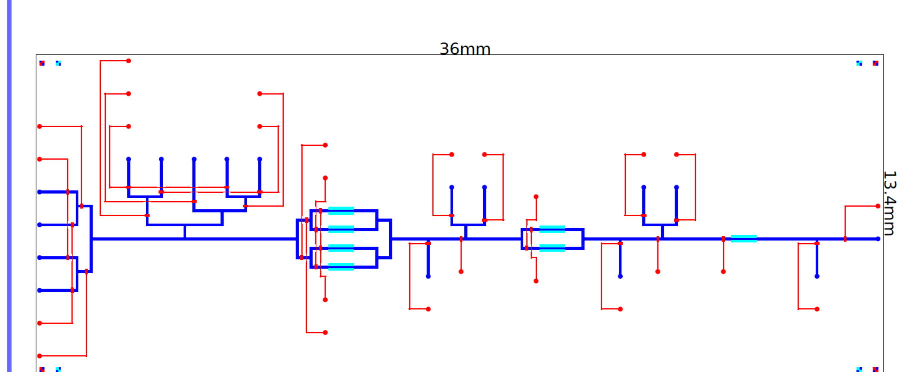
Circuit	Number of Stages	Average Unoptimized Control Lines	Average Optimized Control Lines	Average Control Line Reduction	Length (mm)	Width (mm)
Logic Functions						
AND4	3	26	26	0.00%	36.0	13.4
XOR3	5	54	48	11.11%	60.0	20.8
ADDER	4	41	41	0.00%	50.4	13.2
8-3 ENC3	3	48	41	14.58%	48.0	20.8
XOR4	7	97	77	20.62%	89.4	24.0
Non-logic Functions						
Oscillator	3	17	17	0.00%	29.4	8.8
Assay	3	49	46	6.12%	54.8	17.4



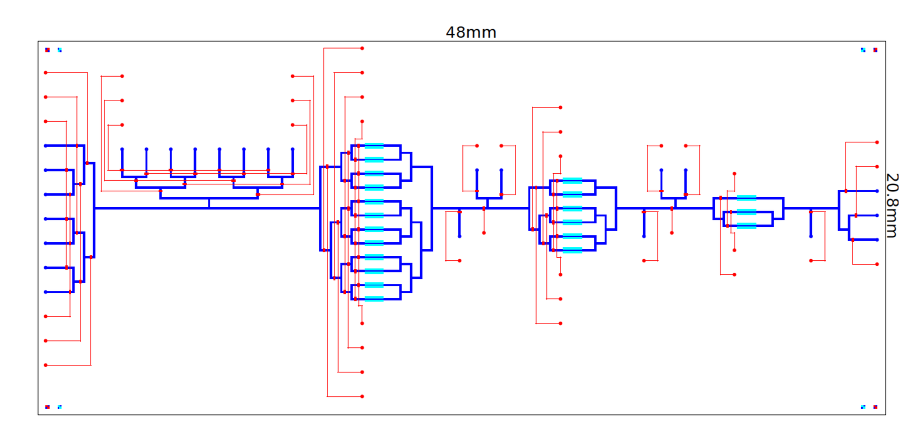
3 Input XOR



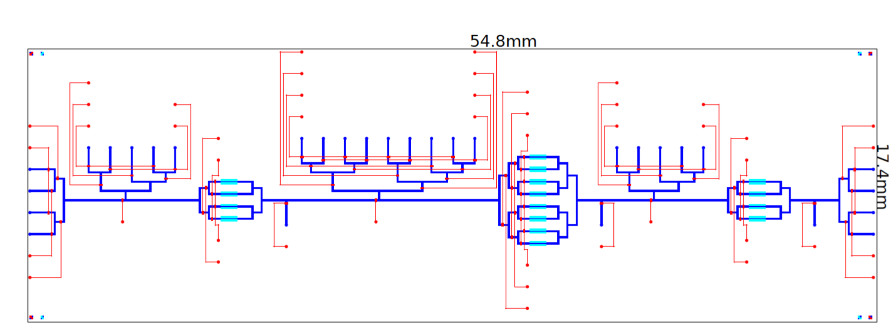
Half Adder



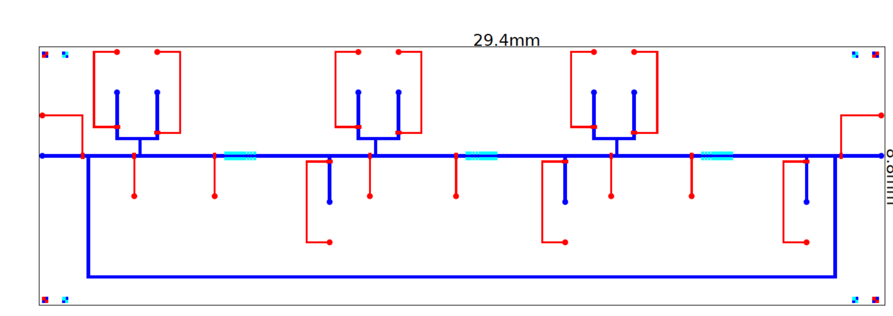
4 Input AND



8-3 Decoder



3 Stage Assay



Oscillator with feedback

Discussion and Future Work

- New architecture for microfluidics based on the placement of genetic circuits in discrete chambers for distributed biological computation
- Fluigi as a framework for a design flow going from a behavioral input file to a chip level behavioral simulation.
- Demonstrate Fluigi on all two and three input boolean functions and four specific example circuits. Added features to allow for specification of 3 stage assay devices and feedback of signals.
- Next milestone is to fabricate a chip using the photomask generated by Fluigi and demonstrate control of the fluid flow through the generated control code.
- Future work includes optimization of valve and control port placement and assignment, further development of additional benchmark circuits for synthetic biology applications, and integration with control software for monitoring biological behavior.
- The integration of microfluidics and synthetic biology has the capability to increase the scale of engineered biological systems for applications in cell-based therapeutics and biosensors, and produce new rapid prototyping platforms for the characterization of genetic devices.

Acknowledgements

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