Programming Language, Type System, and Compiler Design for Cyber-physical Digital Microfluidic Biochips: Automating Programmable Biochemistry at the Microfluidic Scale

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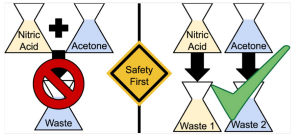
BioScript: Programming Language for Digital Microfluidics

Digital microfluidic devices are typically programmed in a manner akin to writing machine code – BioScript enables high-level programmability of EWoD LOCs featuring real-time feedback via integrated sensing. It features a chemical safety type system based on union types, preventing accidental unsafe chemical interactions.

T-Mix

$$\frac{\Gamma, X \vdash x_1 : \cup\overline{Mat_i} \qquad \Gamma, X \vdash x_2 : \cup\overline{Mat_j} \qquad \Gamma, X \vdash t : \mathbb{R} \quad \textit{interact-abs}(Mat_i, Mat_j) \subseteq \Gamma(x) \text{ for each } i \text{ and } j}{\Gamma, X \vdash x := \textbf{mix}\ x_1\ \textbf{with}\ x_2\ \textbf{for}\ t, X \setminus \{x_1, x_2\} \cup \{x\}}$$

(a)



(c)

```
1  step_1 = mix 10uL of acetic_acid
2       with 10uL of tetrahydrofuran
3  step_2 = mix step_1 with
4               10uL of water
5  step_3 = mix step_2 with
6               10uL of acetonitrile
7  heat step_3 at 20C for 12h
```

(b)

```
1  step_1 = mix
       hydroxylamine_hydrochloride with
       toluene
2  heat step_1 at 105C for 24h
```

(d)

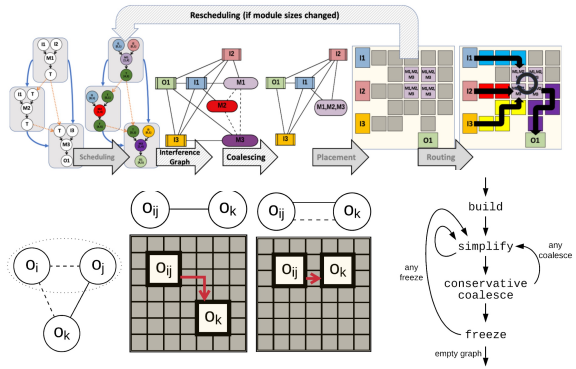
BioScript's type system prohibits unsafe mixtures (a), causing an unsafe method for synthesizing acetaminophen to fail (b), while allowing a safe method (d). The type system has been adapted to prevent unsafe chemical storage and disposal (c).

$t ::=$		Terms:
|	$x \in X$	Variable
|	$t_1 \oplus t_2$	Math operation
|	detect *module* on x for t	Detect
|	$v \in \mathcal{V}$	Value
$v ::=$		Values:
|	*mat*	Material value
|	r	Real number
|	n	Natural number
module ::=		
|	$\text{module}_1, .., \text{module}_n$	Sensor module(s)
$s ::=$		Statements:
|	$i; s$	Sequencing
|	skip	Skip
$i ::=$		instructions :
|	$x := t$	Assignment
|	$x :=$ mix x_1 with x_2 for t	Mixing
|	$(x_1, .., x_n) :=$ split x into n	Splitting
|	if t then s_1 else s_2	Conditional
|	while t s	Loop
$T ::=$		Union Types:
|	$\cup\overline{S}$	Union type
|	V	Type variables
$S ::=$		Scalar types:
|	$Mat_1 \mid .. \mid Mat_n$	Material types
|	$\mathbb{R}$	Real number
|	$\mathbb{N}$	Natural number
$\Gamma ::=$		Context:
|	$\emptyset$	Empty context
|	$\Gamma, x : T$	Variable type binding
X		Set of variables x
C		Constraints

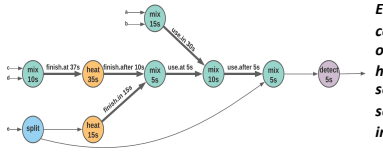
BioScript's Syntax

Optimizing Digital Microfluidic BioChip Compilation

Modern digital microfluidic platforms are severely resource-constrained, and the protocols they execute have precise timing constraints that must be adhered to; complex chemical protocols (especially those featuring multiple execution paths) can be synthesized on these devices by exploring the tradeoffs between instruction parallelism and mix operation latency. Timing expectations are annotated at the language level to enforce these as constraints during compilation.



Compilation updated to include optimizing steps that affect scheduling, placement and routing. Coalescing the interference graph of the schedule allows dependent operations to be optimally placed to reduce routing; rescheduling mix latencies provides spatial resource-availability adjustments.



Execution graph with timing constraints between operations; an efficient heuristic and optimal ILP scheduler solve the updated scheduling problem that includes timing constraints.

Broader Impacts (Society):

- Lower the barrier for entry for microfluidic practitioners
- Increased productivity for researchers in the biological sciences
- Programmable/automated screening for drug discovery applications

Broader Impacts (Education/Outreach):

- 8 PhD students supervised by the PI
- 35 undergraduate participants
  - 8 women; 6 Black or Latino
  - 5 papers with undergraduate co-authors
- "BioHack" Hackathon at UCR

Broader Impacts (Commercial and Scientific Applications):

- DNA Sequencing (Microsoft, Oxford Nanopore, Sharp, AQDrop)
- Neonatal Screening (Baebies)
- Neuromorphic Behavior (UT Knoxville)

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