Compilers Without Borders
Repurposing Paper, Plastic, and Household Devices as Computational Substrates

Bill Thies


Microsoft Research
StreamIt: A Language and Compiler for Streaming Applications

- **Key idea:** design language that enables static analysis
  - To improve programmer productivity
  - To enable automatic parallelization

- Project contributions:
  - Language design for streaming [CC'02, CAN'02, PPoPP'05, IJPP'05]
  - Automatic parallelization [ASPLOS'02, G.Hardware'05, ASPLOS'06, MIT’10]
  - Domain-specific optimizations [PLDI'03, CASES'05, MM'08]
  - Cache-aware scheduling [LCTES'03, LCTES'05]
  - Extracting streams from legacy code [MICRO'07]
  - User + application studies [PLDI'05, P-PHEC'05, IPDPS'06, PACT’10]
I hate it when my house is so big, I need two wireless routers.
Microsoft Research India

Photo: Natalie Linnell (courtesy Kentaro Toyama)
Microsoft Research India

Photo: Natalie Linnell (courtesy Kentaro Toyama)
CGNet Swara: A Voice Portal for Citizen Reporting
No handpump in Baiga adivasi village of 25 families, Pls call officers to help...

Naresh Bunkar is visiting Tikarapara mohalla in Mahuamanancha village, Bijarakachhar panchayat Lormi block Mungeli district in Chhattisgarh where adivasi women tell him there is no hand pump in their village of 25 Baiga families. They fetch water from river 1.5 km away. People fall ill due to dirty water. Health center is 15 km away. They complained to officials many times but no one listens. Pls call P.H.E officer@8878832200 and collector@9425280067. Naresh Bunkar@8720822286
What are the Skills of Programming Language and Compiler Writers?
Application / Problem Statement

Computational Resources
Application / Problem Statement

What is important to you?
What are you willing to compromise on?
What are you willing to pay?

Computational Resources

What are you good at?
What are you not good at?
What is cheap or expensive for you?
Microfluidic Chips

- **Idea:** a whole biology lab on a single chip
  - Input/output
  - **Sensors:** pH, glucose, temperature, etc.
  - **Actuators:** mixing, PCR, electrophoresis, cell lysis, etc.

- **Benefits:**
  - Small sample volumes
  - High throughput

- **Applications:**
  - Biochemistry
  - Cell biology
  - Biological computing
Application to Rural Diagnostics

Disposable Enteric Card

PATH, Washington U.
Micronics, Inc.,
U. Washington

Targets:
- E. coli, Shigella,
  Salmonella,
  C. jejuni

DxBox

U. Washington,
Micronics, Inc.,
Nanogen, Inc.

Targets:
- malaria (done)
- dengue, influenza,
  Rickettsial diseases,
  typhoid, measles
  (under development)

CARD

Rheonix, Inc.

Targets:
- HPV diagnosis
- Detection of specific gene sequences
Biology Protocols

Microfluidic Chips
Abstraction Layers for Microfluidics

Protocol Description Language
- architecture-independent protocol description

Fluidic Instruction Set Architecture (ISA)
- primitives for I/O, storage, transport, mixing

Fluidic Hardware Primitives
- valves, multiplexers, mixers, latches

Silicon Analog
- C
- x86
- Pentium III, Pentium IV
- transistors, registers, ...
Abstraction Layers for Microfluidics

Protocol Description Language
- architecture-independent protocol description

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- primitives for I/O, storage, transport, mixing

Contributions
- BioCoder Language
  [J.Bio.Eng. 2010]
- Optimized Compilation
  [Natural Computing 2007]
- Demonstrate Portability
  [DNA 2006]
- Micado AutoCAD Plugin
  [MIT 2008, ICCD 2009]
- Digital Sample Control Using Soft Lithography
  [Lab on a Chip ‘06]

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Implementation: Oil-Driven Chip

<table>
<thead>
<tr>
<th></th>
<th>Inputs</th>
<th>Storage Cells</th>
<th>Background Phase</th>
<th>Wash Phase</th>
<th>Mixing</th>
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<tbody>
<tr>
<td>Chip 1</td>
<td>2</td>
<td>8</td>
<td>Oil</td>
<td>—</td>
<td>Rotary</td>
</tr>
</tbody>
</table>
**Implementation: Oil-Driven Chip**

```plaintext
mix (S₁, S₂, D) {
  1. Load S₁
  2. Load S₂
  3. Rotary mixing
  4. Store into D
}
```

<table>
<thead>
<tr>
<th>Inputs</th>
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Implementation 2: Air-Driven Chip

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<thead>
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<th></th>
<th>Inputs</th>
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<td>2</td>
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<td>Oil</td>
<td>—</td>
<td>Rotary</td>
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<tr>
<td>Chip 2</td>
<td>4</td>
<td>32</td>
<td>Air</td>
<td>Water</td>
<td>In channels</td>
</tr>
</tbody>
</table>
Implementation 2: Air-Driven Chip

mix \((S_1, S_2, D)\) {
1. Load \(S_1\)
2. Load \(S_2\)
3. Mix / Store into \(D\)
4. Wash \(S_1\)
5. Wash \(S_2\)
}

<table>
<thead>
<tr>
<th>Inputs</th>
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<th>Mixing</th>
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<td>32</td>
<td>Air</td>
<td>Water</td>
</tr>
</tbody>
</table>
“Write Once, Run Anywhere”

- **Example: Gradient generation**

```java
Fluid yellow = input(0);
Fluid blue = input(1);
for (int i=0; i<=4; i++) {
    mix(yellow, 1-i/4, blue, i/4);
}
```

- **Hidden from programmer:**
  - Location of fluids
  - Details of mixing, I/O
  - Logic of valve control
  - Timing of chip operations

450 Valve Operations
Abstraction Layers for Microfluidics

Protocol Description Language
- architecture-independent protocol description

Fluidic Instruction Set Architecture (ISA)
- primitives for I/O, storage, transport, mixing

Fluidic Hardware Primitives
- valves, multiplexers, mixers, latches

chip 1

chip 2

chip 3
Genetic Control of Surface Curvature

Utpal Nath, Brian C. W. Crawford, Rosemary Carpenter, Enrico Coen*
Material and Methods

\textit{In situ} Hybridization. The methods used for tissue preparation were carried out as described in the Boehringer digoxigenin-nucleic acid detection kit with some modifications. The probe used was digoxigenin-labelling of RNA probes, and \textit{in situ} hybridisation were as described previously (S13).
BioCoder: A High-Level Programming Language for Biology Protocols

In biology publications, can we replace the textual description of the methods used with a computer program?

1. Enable automation via microfluidic chips
2. Improve reproducibility of manual experiments
Example: Plasmid DNA Extraction

I. Original protocol *(Source: Klavins Lab)*

Add 100 ul of 7X Lysis Buffer (Blue) and mix by inverting the tube 4-6 times. *Proceed to step 3 within 2 minutes.*

II. BioCoder code

FluidSample f1 = measure_and_add(f0, lysis_buffer, 100*uL);
FluidSample f2 = mix(f1, INVERT, 4, 6);
time_constraint(f1, 2*MINUTES, next_step);

III. Auto-generated text output

Add 100 ul of 7X Lysis Buffer (Blue).
Invert the tube 4-6 times.
NOTE: Proceed to the next step within 2 mins.
Example: Plasmid DNA Extraction

DNA Miniprep Protocol

Solutions/reagents:
- bacterial culture grown in LB medium
- 7X Lysis Buffer (Blue)
- Neutralization Buffer (Yellow)
- Endo-Wash Buffer
- Zippy™ Wash Buffer
- Zippy™ Elution Buffer
- Zymo-Spin™ II Column

Equipment:
- Centrifuge
- Microfuge

Steps:
1. Measure out 600 μl of bacterial culture grown in LB medium into a 1.5ml reaction tube.
2. Add 100 μl of 7X Lysis Buffer (Blue).
   Invert the tube 4-6 times.
   NOTE: Proceed to the next step within 2 mins.
3. Add 350 μl of Neutralization Buffer (Yellow).
   Vortex the mixture for a few secs.
BioCoder Language Primitives

• Declaration / measurement / disposal
  - declare_fluid
  - declare_column
  - measure_sample
  - measure_fluid
  - volume
  - discard
  - transfer
  - transfer_column
  - declare_tissue

• Combination / mixing
  - combine
  - mix
  - combine_and_mix
  - addto_column
  - mixing_table

• Centrifugation
  - centrifuge_pellet
  - centrifuge_phases
  - centrifuge_column

• Temperature
  - set_temp
  - use_or_store
  - autoclave

• Timing
  - wait
  - time_constraint
  - store_until
  - inoculation
  - invert_dry

• Detection
  - ce_detect
  - gas_chromatography
  - nanodrop
  - electrophoresis
  - mount_observe_slide
  - sequencing
Standardizing Ad-Hoc Language

• Need to convert qualitative words to quantitative scale

• Example: a common scale for mixing
  – When a protocol says “mix”, it could mean many things
  – Level 1: tap
  – Level 2: stir
  – Level 3: invert
  – Level 4: vortex / resuspend / dissolve

• Similar issues with temperature, timing, opacity, …
# Benchmark Suite

## Protocols

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<tr>
<th>Protocol Description</th>
<th>Source</th>
<th>TOTAL INSTR.</th>
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</thead>
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<td>CTAB DNA Plant Miniprep (Utpal Nath Lab)</td>
<td>Academic Laboratory</td>
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<td>2ab Assembly Protocol (Douglas Densmore)</td>
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<td>DNA Miniprep (Eric Klavins Lab)</td>
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<td>Ligation (Eric Klavins Lab)</td>
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<tr>
<td>Protein in situ localization (Utpal Nath Lab)</td>
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<td>Restriction Digestion (Eric Klavins Lab)</td>
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<td>Alkaline lysis with SDS - miniprep (Mol. Cloning)</td>
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<td>Knight colony PCR</td>
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<td>Knight in vitro transcription</td>
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<td>Maxiprep of plasmid DNA from E.coli</td>
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<td>Restriction Digest (Richard Lab)</td>
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<td>Separation based sensing of neurotransmitter</td>
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<td>Size selective DNA precipitation</td>
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<td>Small-scale plasmid isolation - Maxiprep</td>
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<td>Small-scale plasmid isolation - Miniprep</td>
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<td>Studier lysate prep</td>
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<td>Transformation inoue</td>
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<td>Transforming chemically competent cells</td>
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<td>Yeast DNA prep</td>
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<td>AllPrep RNA protein protocol (Qiagen)</td>
<td>Commercial Kit</td>
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<td>DNA sequencing by capillary elec. (App. Biosystems)</td>
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<tr>
<td>Miniprep (Qiagen)</td>
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<td>Plasmid purification high yield (Qiagen)</td>
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<tr>
<td>Plasmid purification standard (Qiagen)</td>
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</table>

**65 protocols**

**5800 LOC**
Example: PCR

repeat thermocycling
Example: Molecular Barcodes

Preparation

+ PCR (2)
Example: DNA Sequencing

Preparation

PCR

Analysis
Validating the Language

- **Eventual validation: automatic execution**
  - But BioCoder more capable than most chips today
  - Need to decouple language research from microfluidics research

- **Initial validation: human execution**
  - In collaboration with Prof. Utpal Nath’s lab at IISc
  - Target Plant DNA Isolation, common task for summer intern

![Diagram showing the process from Original Lab Notes to Execution in Lab](Diagram)

*Biologist is never exposed to original lab notes*

- To the best of our knowledge, first execution of a real biology protocol from a portable programming language
Growing a Community
Growing a Community

One step 'miniprep' method for the isolation of plasmid DNA

plasmid miniprep

All 'miniprep' methods reported so far for the isolation of plasmid DNA involve multiple pipetting, extraction, centrifugation and changes of minifuge tubes. For screening large number of samples, they are therefore cumbersome, time consuming and not economical.

The technical report below by Chowdhury, K. (1991) is a very fast, simple and one step 'miniprep' procedure. The quality and quantity of DNA obtained by using this procedure is similar to those obtained by the other commonly used procedures of Sarghini et al. (1) or Birboim and Doly (2). According to this procedure, the bacterial culture is directly extracted with a mixture of phenol-chloroform-isooamyl alcohol and the liberated DNA is precipitated with isopropanol. This method is now being used routinely in our laboratory for isolating plasmids up to 12kb in size. A detailed description of the method is presented below:

1. Take 0.5ml of overnight E coli culture in a microtube. We routinely grow our cells in standard M13 bacteriological media supplied by Merck, Germany.
2. Add 0.5ml of phenol-chloroform-isooamyl alcohol (25:24:1). The phenol was saturated with TE (10mM Tris, 7.5, 1mM EDTA) prior to mixing with chloroform and isooamyl alcohol.
3. Mix by vortexing at the maximum speed for 1 minute. Alternatively, vortex for 10 seconds and then transfer to microfuge for 5 minutes.
4. Spin at 12,000g for 5 minutes. During the spin, prepare microfuge tubes with 0.5ml of isopropanol. After the spin, remove carefully about 0.45ml of the upper aqueous phase leaving the interphase undisturbed and add it to the isopropanol. Mix well and spin immediately at 12,000g for 5 minutes. Addition of salt and cooling is unnecessary.
5. Pour off the supernatant, add carefully 0.5ml of 70% ethanol to the side of the tube, pour off. Repeat the washing once more. Vacuum dry the pellet and suspend in 100ul/ml RNAase. About 5-10ul of this DNA can now be cleaved with appropriate restriction enzyme(s) for analysis.

References

Additional Notes
- Sterile LB broth works very well in this protocol
- In step 1, one can pipette 1.5ml of broth spin the microtube, decant 1ml and leave behind 500ul to resuspend the pellet and continue as from step 2. This maximizes the total yield of plasmid.

BioStream version

Following is the One step 'miniprep' method for the isolation of plasmid DNA protocol in BioStream, a high-level programming language for expressing biology protocols. What you see here is the auto-generated text output of the protocol that was coded up in BioStream (see Source code). More information about BioStream can be found on my home page. Feel free to mail me your comments/suggestions Vaishnavi

Text Output

One step 'miniprep' method for the isolation of plasmid DNA protocol

Source Code

One step 'miniprep' method for the isolation of plasmid DNA protocol - source code
Growing a Community

One step 'miniprep' method for the isolation of plasmid DNA protocol

Solutions/reagents:
- overnight E. coli culture
- phenol : chloroform : isooamyl alcohol(25:24:1)
  (phenol saturated with TE(10mM Tris, 7.5, 1mM EDTA) prior to mixing with chloroform and
  isooamyl alcohol)
- isopropanol
- 70% ethanol
- 100 µl/µl RNase

Equipment:
- Centrifuge
- Flasks of appropriate volumes
- Sterile 1.5-ml microcentrifuge tubes

Steps:
1. Measure out 0.5 ml of overnight E. coli culture into a sterile 1.8-ml microcentrifuge tube.
   We routinely grow our cells in 'standard' bacteriological media supplied by Merck, Germany.
2. Add 0.5 ml of phenol : chloroform : isooamyl alcohol(25:24:1).
3. Vortex the mixture for 1 min.
   Vortex at maximum speed.
   Alternatively, vortex for 10 seconds and then transfer to an overhead mixer or an over-the-top rotator for 5 minutes.
4. Centrifuge at a speed of 12000 Xg for 5 mins at room temperature.
5. Meanwhile:
   Set aside a fresh sterile 1.5-ml microcentrifuge tube. Call it Tube I.
   Measure out 0.5 ml of isopropanol into Tube I.
6. Measure out 0.45 ml of top aqueous phase obtained after centrifugation into Tube I.
   Vortex the mixture for a few secs.
   Centrifuge at a speed of 12000 Xg for 5 mins at room temperature, gently aspirate out the supernatant and discard it.
   Addition of salt and cooling is unnecessary.
7. Add 0.5 ml of 70% ethanol.
   Add ethanol carefully to the side of the tube.
   Discard solution.
8. Repeat Step 7.
   Add 100 µl/µl RNase to solution.
   Resuspend the pellet by vortexing by shaking vigorously.
   About 5-10µl of this DNA can now be cleaved with appropriate restriction enzyme(s) for analysis.
Future Work

• **Backends for BioStream**
  – Generate graphical protocol
  – Generate a microfluidic chip to perform protocol

• **Reliability and troubleshooting**
  – Verify that protocol is safe, correct, obeys timing constraints
  – If protocol fails, automatically suggest troubleshooting routine

• **Building a knowledge base**
  – Encode experimental results in addition to protocols
  – Search for a protocol based on input/output relationship
  – Revision control for biology protocols
Part 2: Education
Classroom Environment in India
Classroom Environment in India

- Total Schools: 1.4 M
- Rural Schools: 1.2 M

Source: DISE 2012-2013, ASER 2013
Classroom Environment in India

- Total Schools: 1.4 M
- Rural Schools: 1.2 M

Source: DISE 2012-2013, ASER 2013
Classroom Environment in India

- **Schools:**
  - **Rural Schools:** 1.2M
  - **Toilet for Girls:** 53%
  - **3rd Graders Reading Level 1 Text:** 40%
  - **3rd Graders Subtract 2-Digit #s:** 26%
  - **Has a Computer:** 20%

Source: DISE 2012-2013, ASER 2013
Some photos courtesy Nithya Sambasivan
Wikipedia

Household Devices
(TV, DVD player, ...)

DVD Player as a Programmable Device

- 16 general-purpose 16-bit registers
  - (No heap/stack)
- Virtual machine instructions
  - Arithmetic - Comparison - Branch/Jump - Timing
  - (No indirect jump)
- Display:
  - Pre-built MPEG-2 videos with mask and highlight layers
- Constrained and specialized internal organization
5,500 articles from Schools-Wikipedia.org on TV-DVD

Make a selection or wait for help:

① Search  ② Title Index
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Make a selection or wait for help:

① Search  ② Title Index
5 Close, Brian
6 Clothing
7 Cloud
8 Club Band, Sgt. Pepper's Lonely Heart
9 cluster, Globular
10 cluster, Open
11 cluster, Tone
12 Coal
13 Coal Tit
14 Cobalt
15 Cobra
16 Coccinellidae
5 Close, Brian
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8 Club Band, Sgt. Pepper's Lonely Heart
9 cluster, Globular
10 cluster, Open
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13 Coal Tit
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15 Cobra
16 Coccinellidae
Cloud

Wikipedia. Related subjects: Climate and the Weather

A cloud is a visible mass of droplets or frozen crystals floating in the atmosphere above the surface of the Earth or another planetary body. A cloud is also a visible mass attracted by gravity (clouds can also occur as
Cloud

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Stratocumulus perlucidus clouds, as seen from an aircraft window.
Cloud

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attracted by gravity (clouds can also occur as masses of material in interstellar space, where they are called interstellar clouds and nebulae.) The branch of meteorology in which clouds are studied is nephology. On Earth the condensing substance is typically water vapor, which forms small droplets or ice crystals, typically 0.01 mm in diameter. When surrounded by billions of other droplets or crystals they become visible as clouds. Dense deep clouds exhibit a high reflectance (70% to 95%) throughout the visible range of wavelengths: they thus appear white, at least from the top. Cloud droplets tend to scatter light efficiently, so
attracted by gravity (clouds can also occur as masses of material in interstellar space, where they are called interstellar clouds and nebulae.) The branch of meteorology in which clouds are studied is nephology. On Earth, the forming substance is typically water vapor, which forms small droplets or ice crystals, typically 0.01 mm in diameter. When surrounded by billions of other droplets or crystals they become visible as clouds. Dense deep clouds exhibit a high reflectance (70% to 95%) throughout the visible range of wavelengths: they thus appear white, at least from the top. Cloud droplets tend to scatter light efficiently, so
Crystal

Wikipedia. Related subjects: Materials science
In chemistry, mineralogy, and materials science, a crystal is a solid in which the constituent atoms, molecules, or ions are packed in a regularly ordered, repeating pattern extending in all three spatial dimensions.
Crystal

Wikipedia. Related subjects: Materials science

In chemistry, mineralogy, and materials science, a crystal is a solid in which the constituent atoms, molecules, or ions are packed in a regularly ordered, repeating pattern extending in all three spatial dimensions.
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Key Challenge: Addressing A Large Number of Menus

“I am not familiar with another customer trying to create a disc with the maximum number of menu allowable in the DVD specification.”

— Scenarist Support
Key Challenge: Addressing A Large Number of Menus

[T4E 2012]

ButtonHandler → Register := Value; jump Label

16 registers! 16 bits very constrained
Children’s Books on TV-DVD [ICTD 2010]

$0.50 for 1 book in print

$0.50 for 10,000 books on DVD

Wikipedia Subset on TV-DVD [CHI 2011]
Clickers for Classroom Polling

+ Pedagogical benefits
– Very expensive
Is There a Cheaper Solution?

Audience Polling

At Most One Electronic Device
qCards: Low-Cost Audience Polling Using Computer Vision
Polling an Audience of 300
[UIST 2012]

90% of people captured
98% of those captured accurately
Polling an Audience of 1,800
Part 3: Public Health
The Problem of Medication Adherence

- WHO: In developed countries, 50% having chronic disease take medication as directed
- In US, non-adherence causes:
  - $300 billion annual cost to healthcare system
  - 10% of hospital admissions
  - 23% of nursing home admissions
- Globally, non-adherence claims millions of lives and poses threat of untreatedable diseases

Extensively Drug-Resistant Tuberculosis (XDR-TB)

Countries Notifying At Least One Case by the End of 2013
TB Control Strategy in India: Directly Observed Therapy (DOTS)
Electronic Pillboxes: Effective but Very Costly

Vitality Glowcap
$99 + $15 / month

Clinical trial shows significant improvement in adherence to hypertension medication (2012)
Is There a Cheaper Solution?

Pill-in Hand Adherence Monitoring

Common Supplies
(Incl. basic mobile phones)
99DOTS: Real-Time Adherence Tracking at Very Low Cost
Adherence

**Wednesday, January 14, 2015**
2 of 51 patients have responded today

Mark dose taken

RNTCP Program

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Deployments in Treatment Programs

Enrolled 80 patients and counting

- Across public and private programs
- In five urban and rural sites
- High acceptance by all partners
Support of Key Stakeholders
Compilers Without Borders

- Biology Protocols
- Microfluidic Chips
- Audience Polling
- Pill-In-Hand Adherence
- Wikipedia
- Household Devices
- One Electr. Device
- Common Supplies
Future Directions

• Crowdsourcing
• Compiling to living systems
• Personalized education
• More microfluidics
• Problem discovery
Thank you