"Paper Diagnostics (and others technologies): Simple, Low-Cost Systems"

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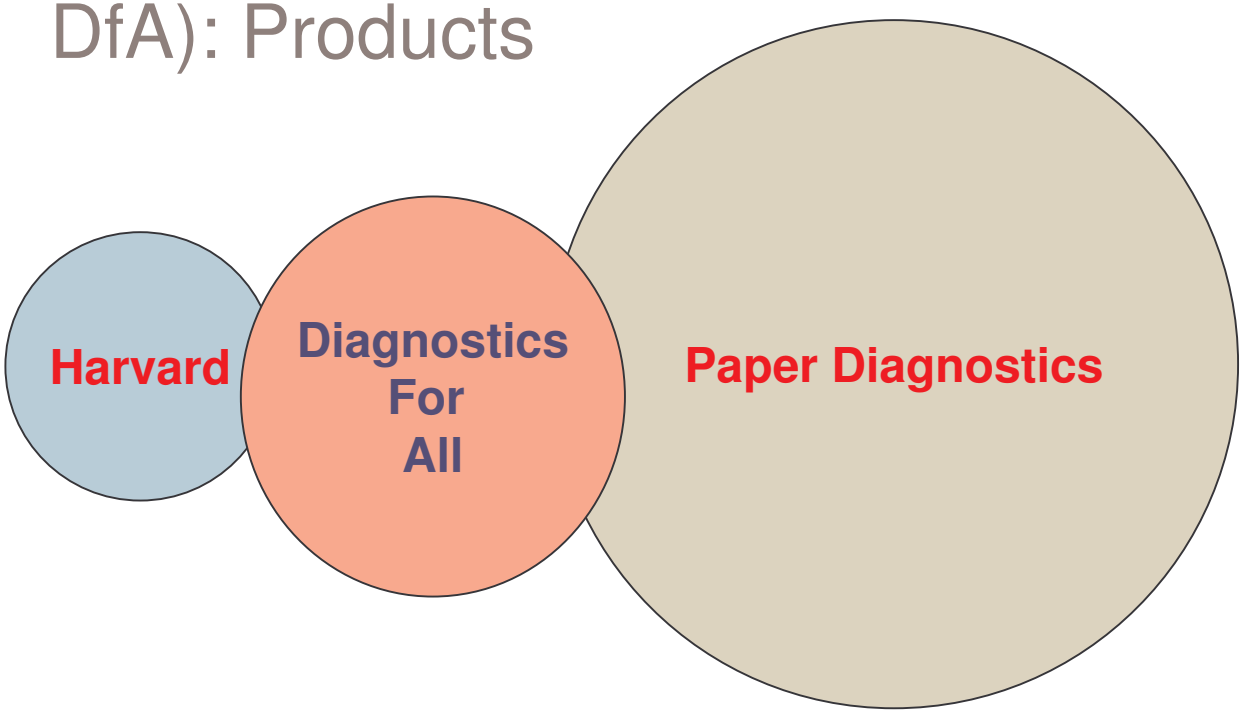
Bill & Melinda Gates Foundation
MF 3 (DARPA; UC Irvine)

Structure

- Harvard group (Gates Foundation): Invention
- Diagnostics for All (501-c-3; Not for Profit Company): Engineering/Premanufacturing Prototypes; Trials; Regulatory Affairs
- Paper Diagnostics (for profit; royalties returned to DfA): Products



So, the Question

- How can we provide diagnostics
  - …at “zero” cost
  - …where there are no doctors or highly trained paramedical personel
  - …and no infrastructure
  - …and not even a shared understanding of “disease”?
  - *High-quality point-of-care results at insignificant cost (at a distance)*

What would we like to know/do?

- Triage: “Fever of unknown origin” (“fever panel”)
- Specifics for detailed diagnosis
  - AIDs; Hepatitis B/C/E; Malaria; Lower respiratory/enteric disease; TB (especially drug resistant)
- Guidance for Treatment:
  - Treatment-limiting drug reactions/Toxicity; Compliance; response. Counterfitting. Delivery/companion diagnostics.
- Many Other Uses
  - Nutrition; Agriculture/Food Safety/Quality; Vaccination Status; Animal/Plant Disease; Water; Surveillance

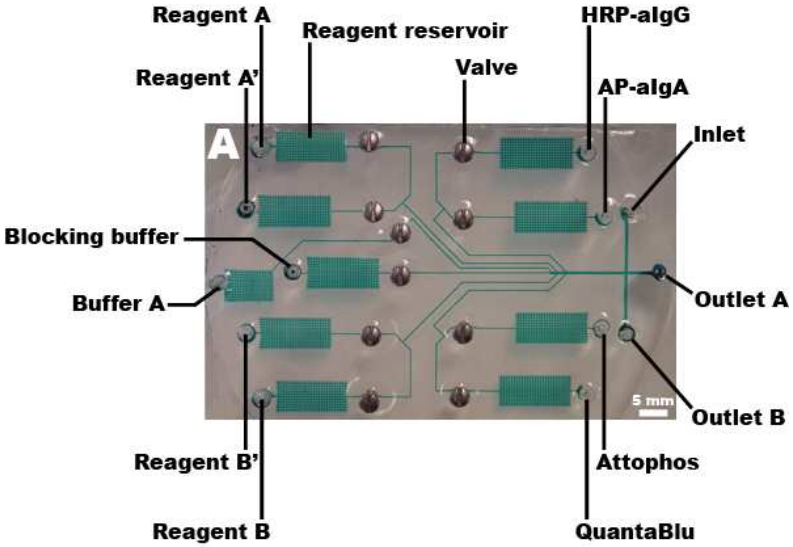
Key Ideas

- Simplicity. Generating medically relevant information as simply (inexpensively, robustly, …) as possible

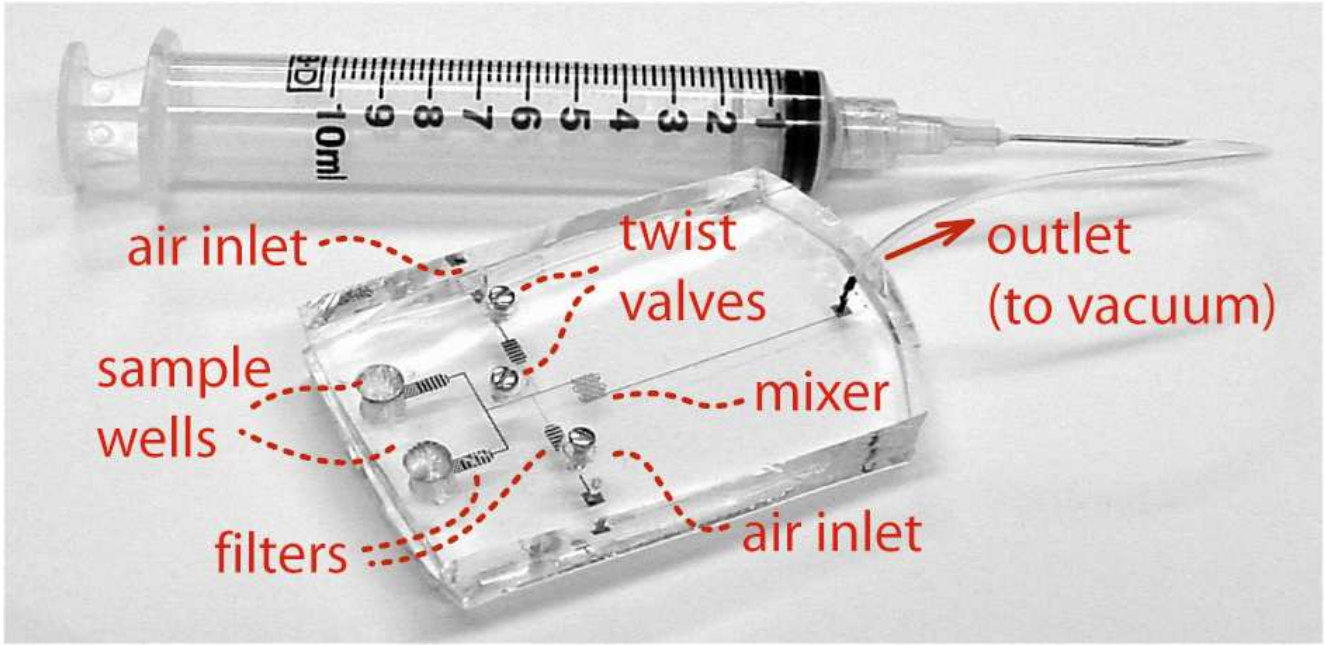
- Changing the Cost Structure for Biomedical Information. Change emphasis from “profitable devices that generate information” to “manipulating abundant, inexpensive information.”

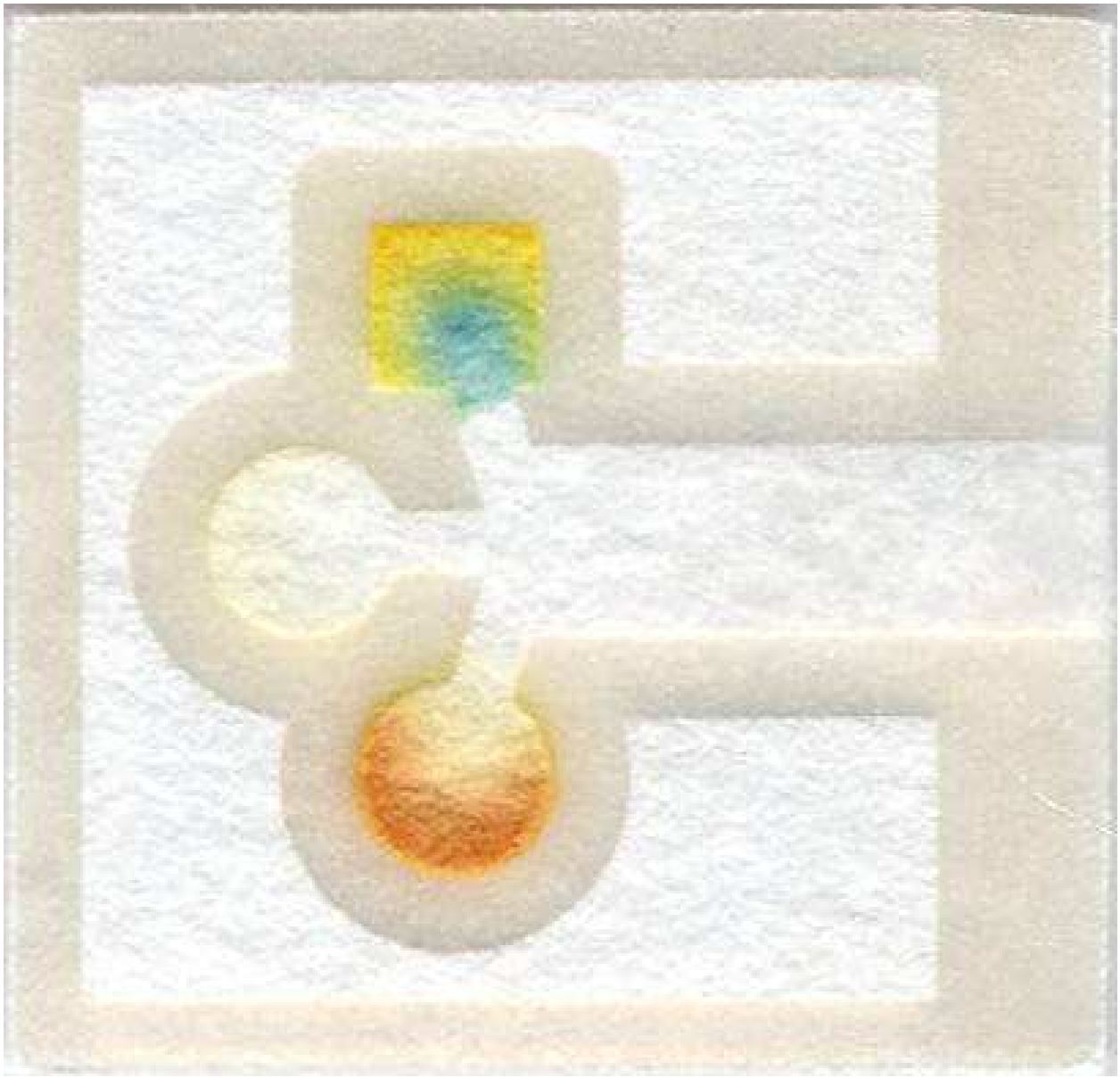
A Resource Allocation Issue: What Kinds of Tests/Assays?

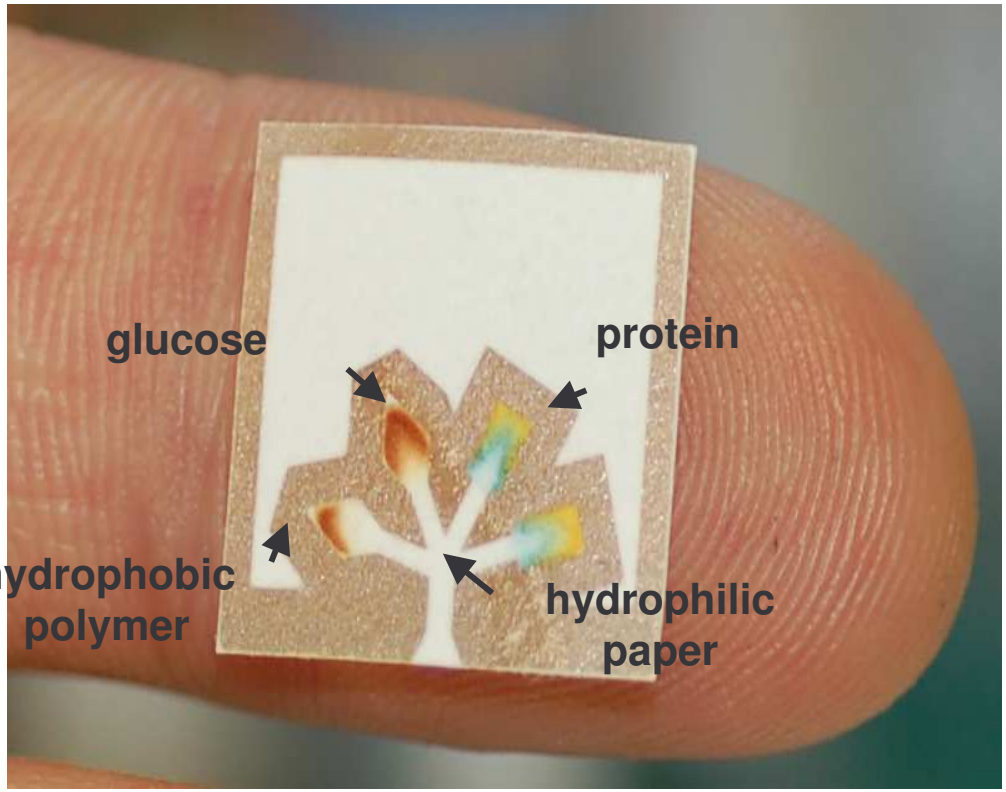
- Metabolic Assays (enzymes, metabolites, ..: Glc, electrolytes, AST, ASP,
- Immunoassay (ELISA…)
- Nucleic Acids (DNA, mRNA, ..;)
- Cells (Malaria, rare cells)
- Tissues and 3D Cell Culture
- Organism (sleep/awake, depression, TBI)



"Simple" microfluidics: PDMS and Soft Lithography






glucose
protein
hydrophobic
polymer
hydrophilic
paper

“An ideal diagnostic test is ASSURED (affordable, sensitive, specific, user-friendly, rapid, equipment-free, and delivered to those who need it).”

— World Health Organization

lateral flow tests

dip sticks

Solid Wax Printing

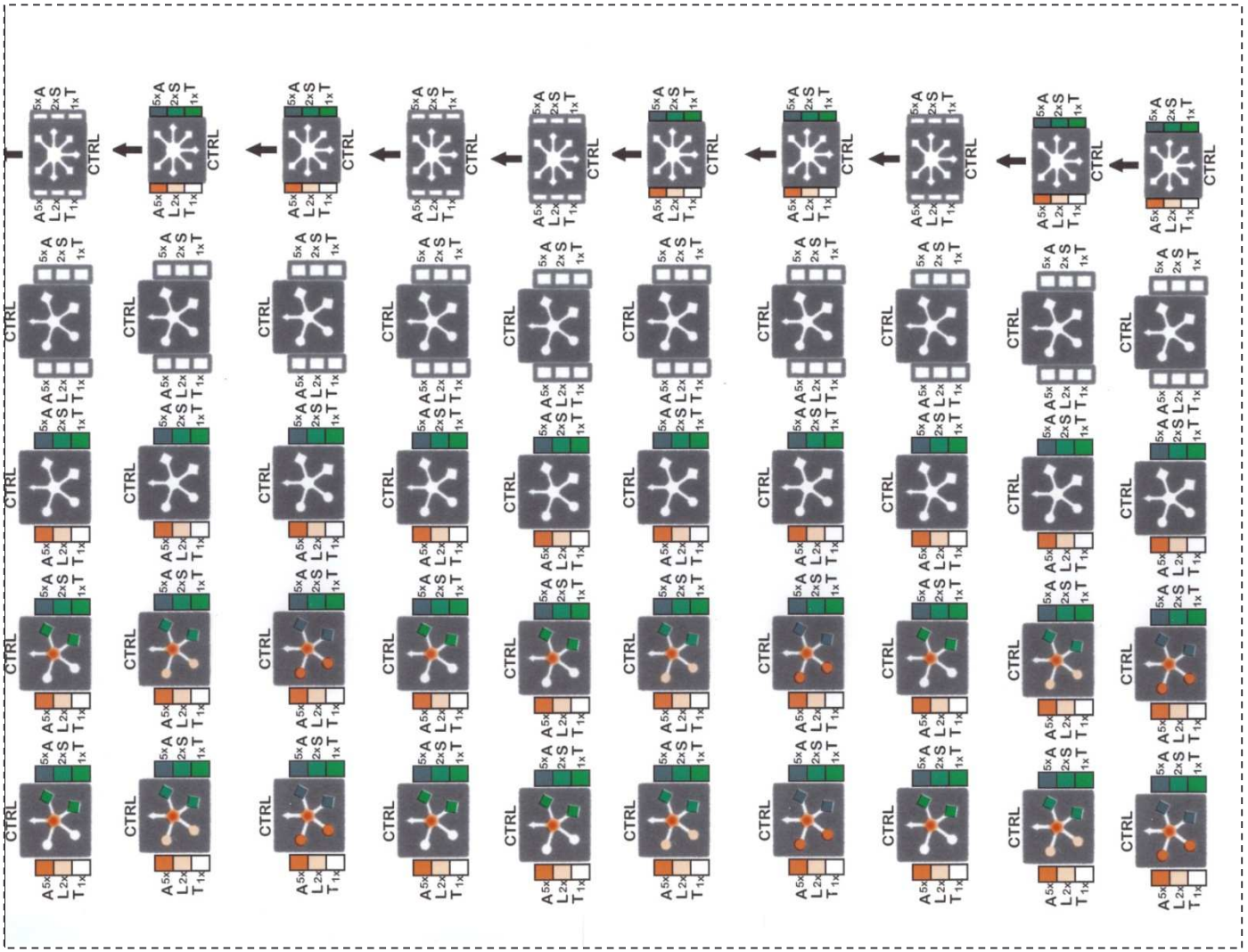
1. Design

2. Print

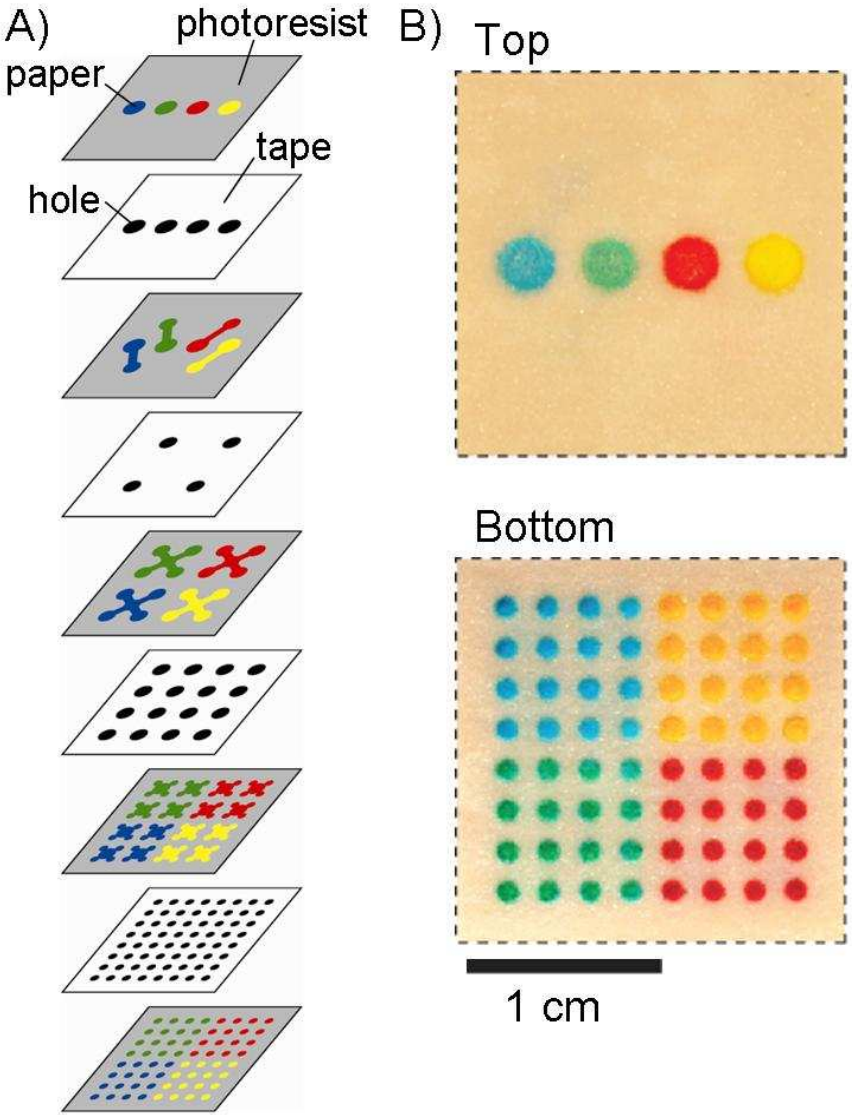
3. Melt

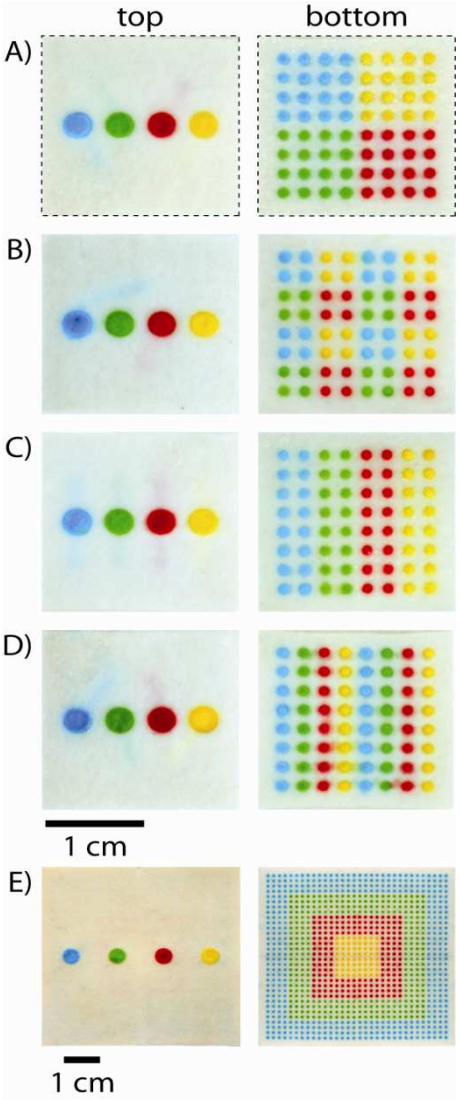
Inexpensive Large Scale Printing

Cost of printing ~ 5 cents/ page ~ 0.1 cents/device



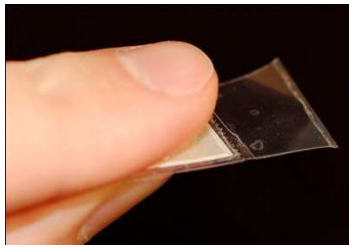
3D Paper Microfluidic Devices



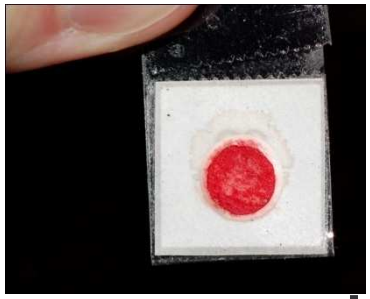


Liver Function Tests

prick finger



gently squeeze device



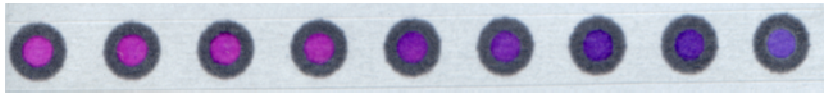
blood on filter

plasma (with liver function tests)

LFT Development – Diagnostics For All

Visual distinction

AST

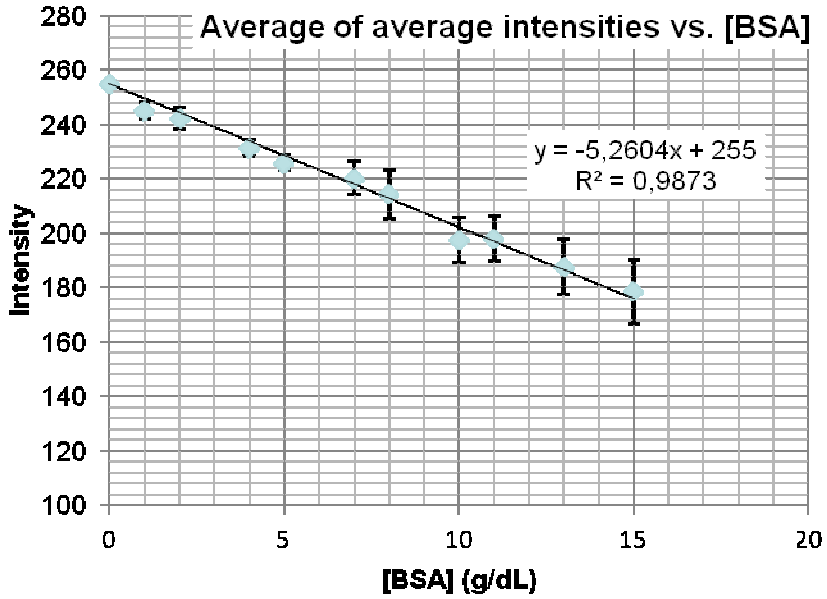


390 305 190 145 74 50 25 0 U/L

10x 5x 2x Normal

Protein

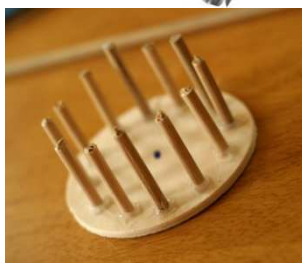
Quantitative readout

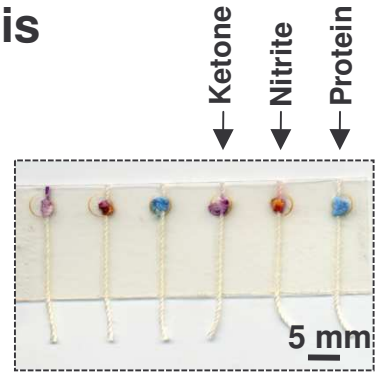


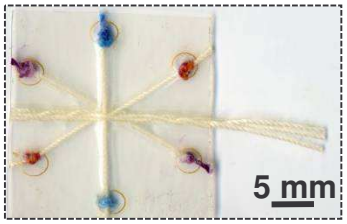
DFA

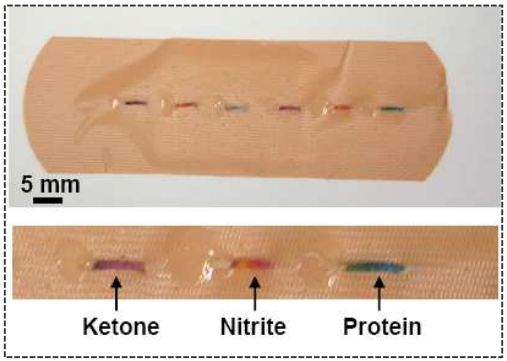
Thread as a Matrix for Biomedical Assays

Urinalysis

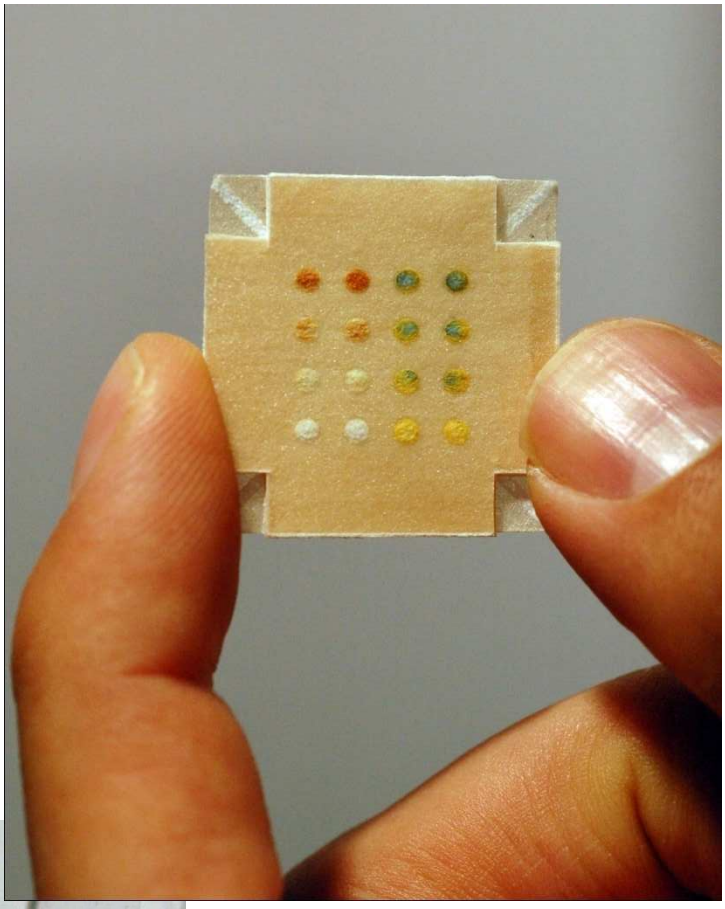


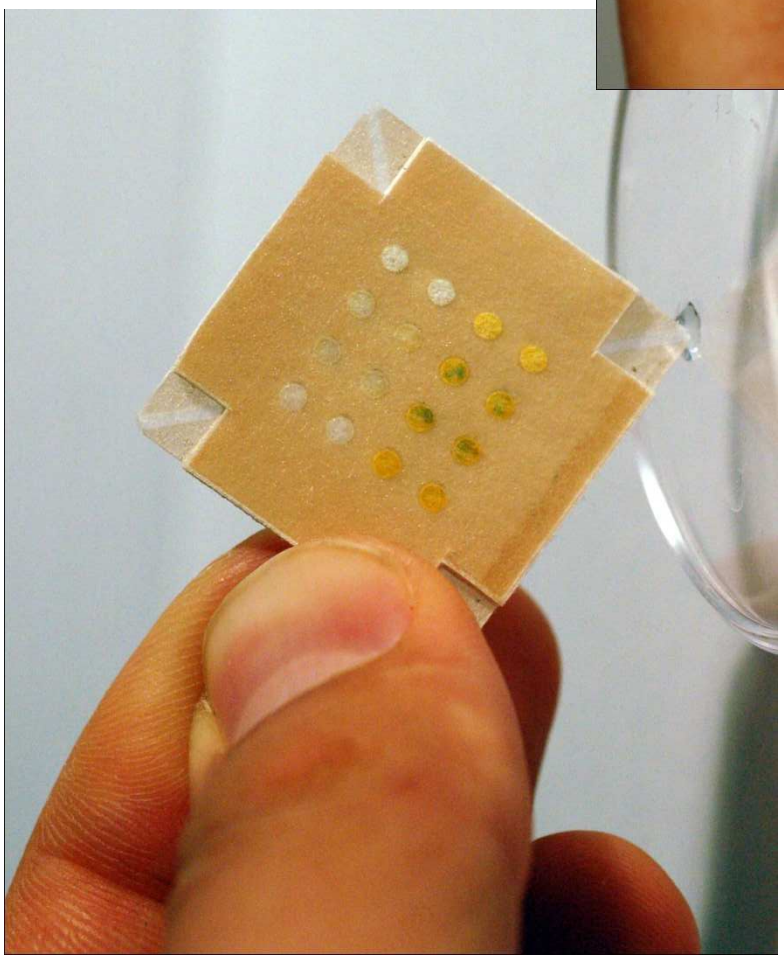




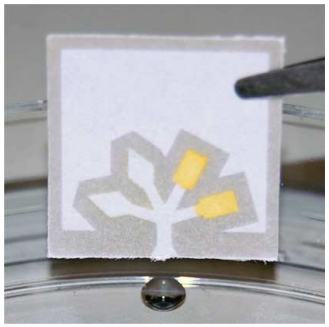


1. Fabricate devices without lab equipment.
2. Small sample volumes (~1 µl per thread).
3. Rapid (minutes)



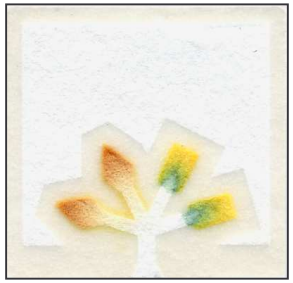


Quantitative Assays and Telemedicine



Dip device into sample

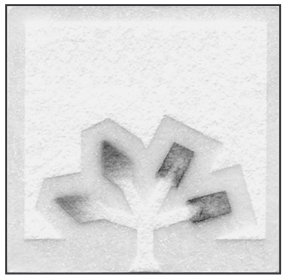
Device wicks sample into test zones

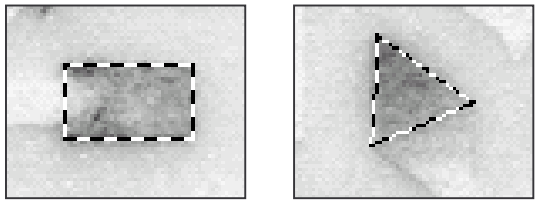


1 cm

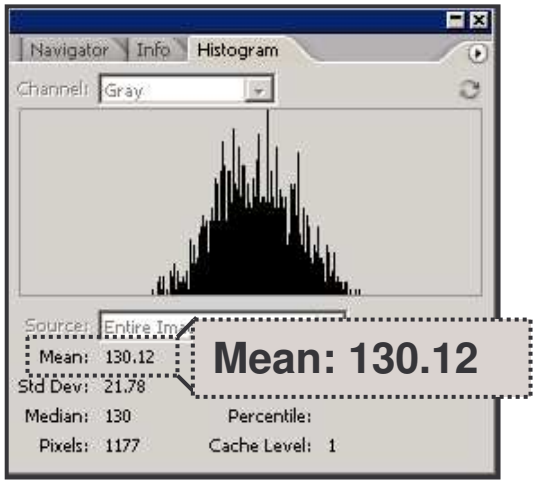
Color develops for each assay

Scan or photograph the device

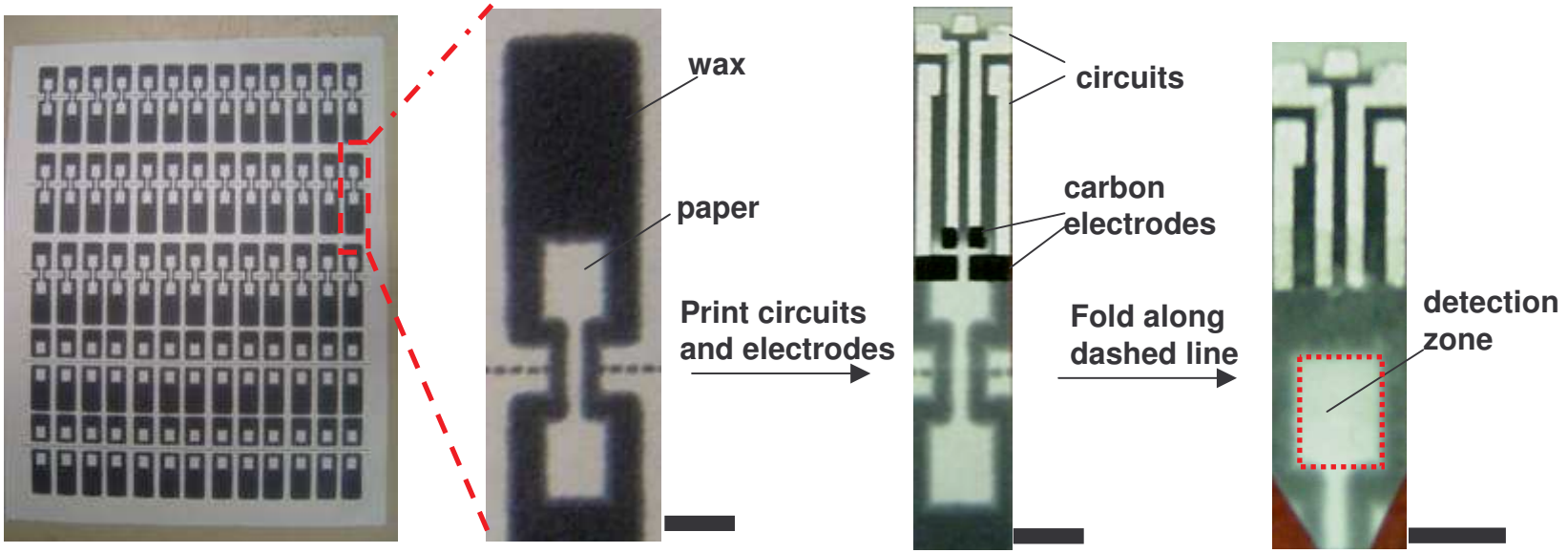




Select test zones and record mean intensity using Adobe®Photoshop®

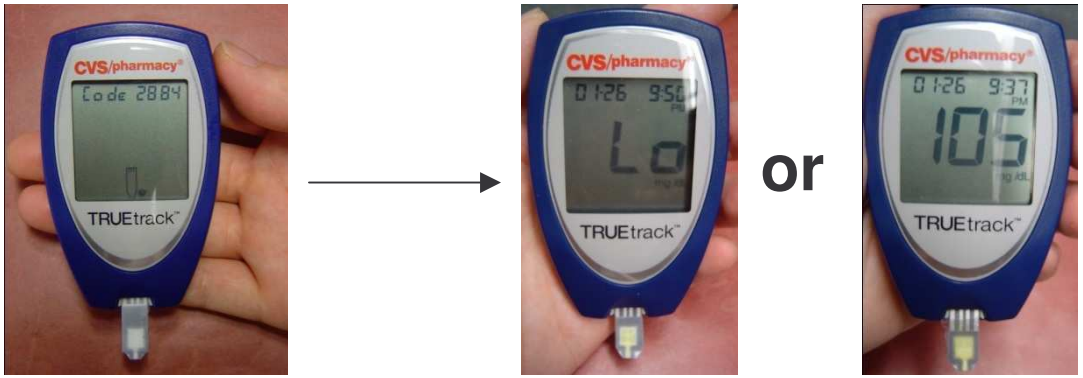


Glucometers as electrochemical readers for low-cost diagnostics



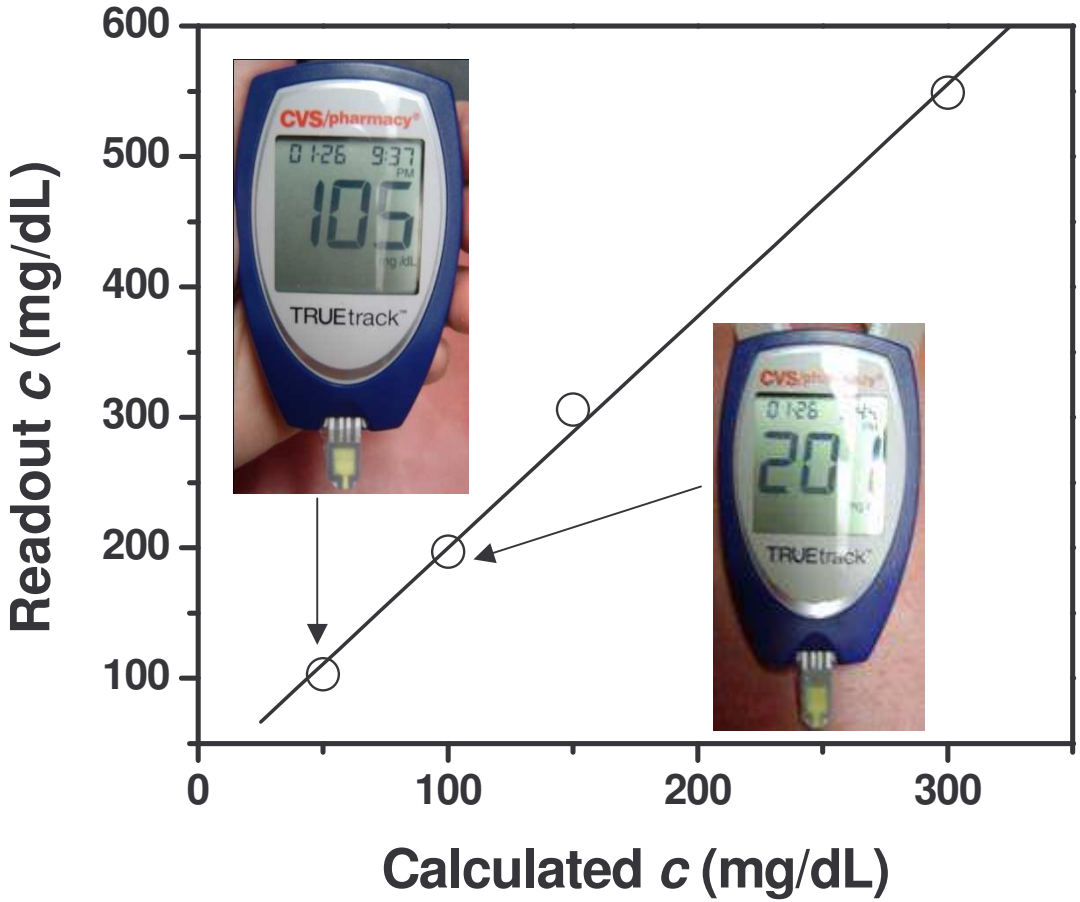
Wax-printed device

Screen-printed electrodes/circuits



Glucometers as electrochemical readers

Calibration of the glucometer for paper-based device



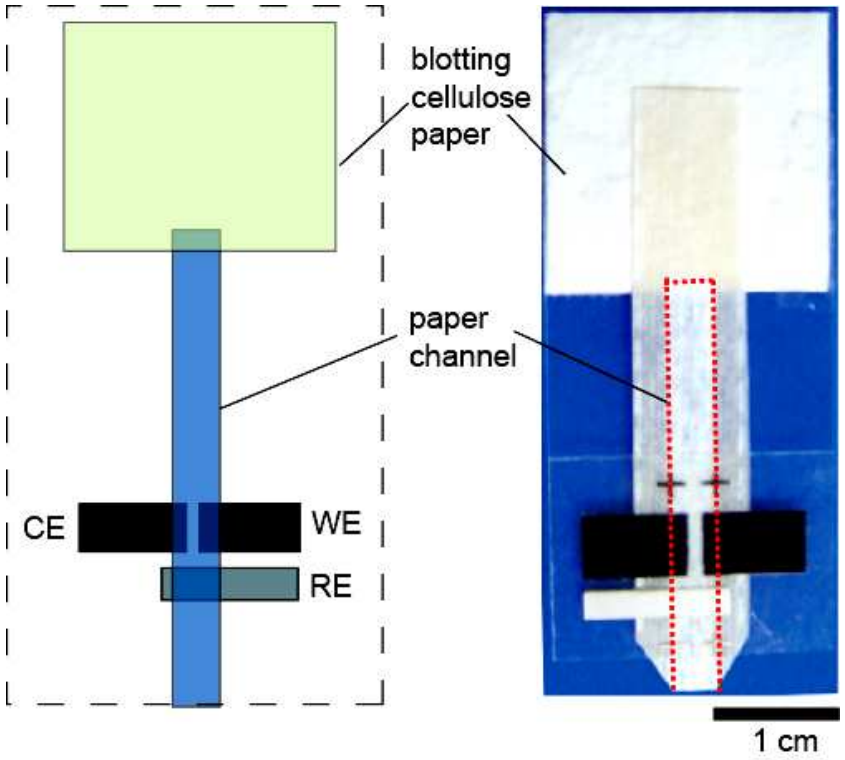
Calibration curve for the analysis of glucose

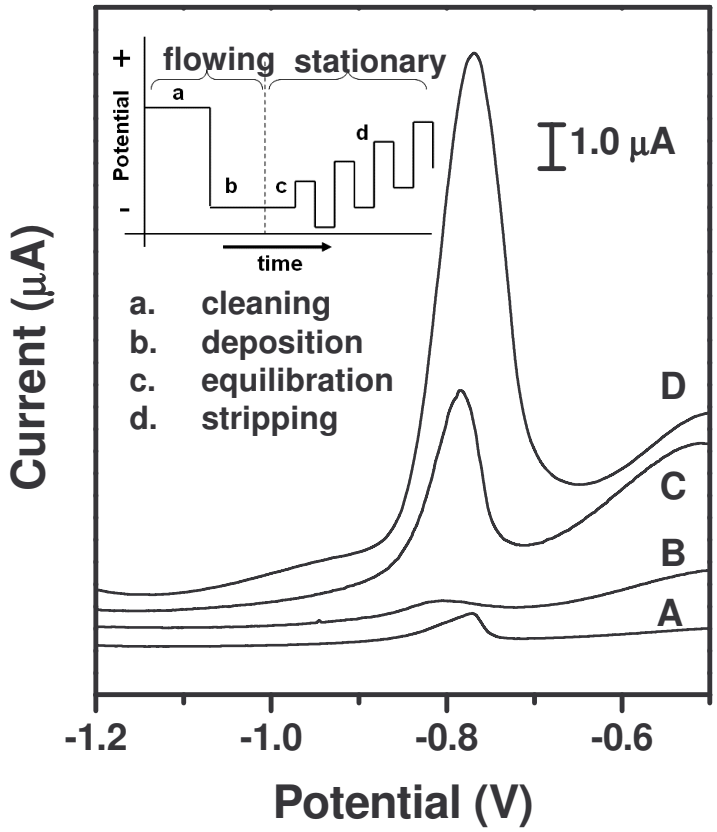
Slope: 1.78

$c_{real} = c_{read}/1.78$

Other analytes in progess: Lactate, cholesterol, phenolic compounds

Hydrodynamic μPED for the Analysis of Heavy Metal Ions



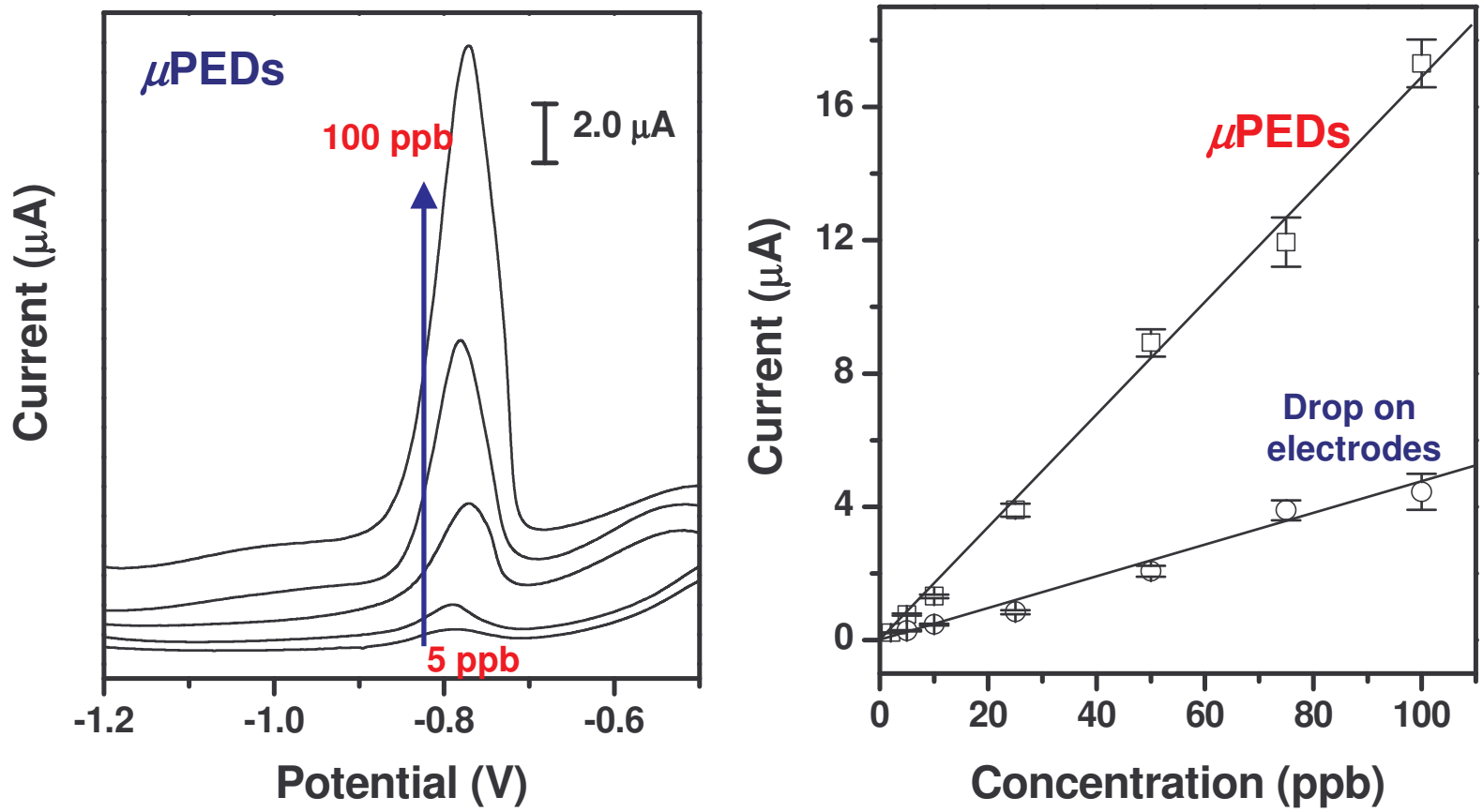


- Simple, low-cost, and portable
- Do not require extra instruments
- Reusable

Analysis of Pb(II) in a mixture of Pb(II) and Zn(II)

A) A drop placed on electrodes
B) Stagnant μPEDs
C) Hydrodynamic μPEDs (120s)
D) Hydrodynamic μPEDs (360s)

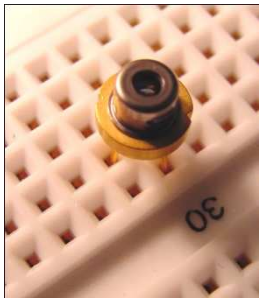
Hydrodynamic μPED for the Analysis of Heavy Metal Ions

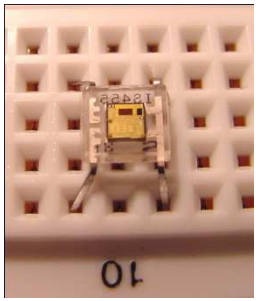


Limit of detection of Pb(II): 1.0 ppb

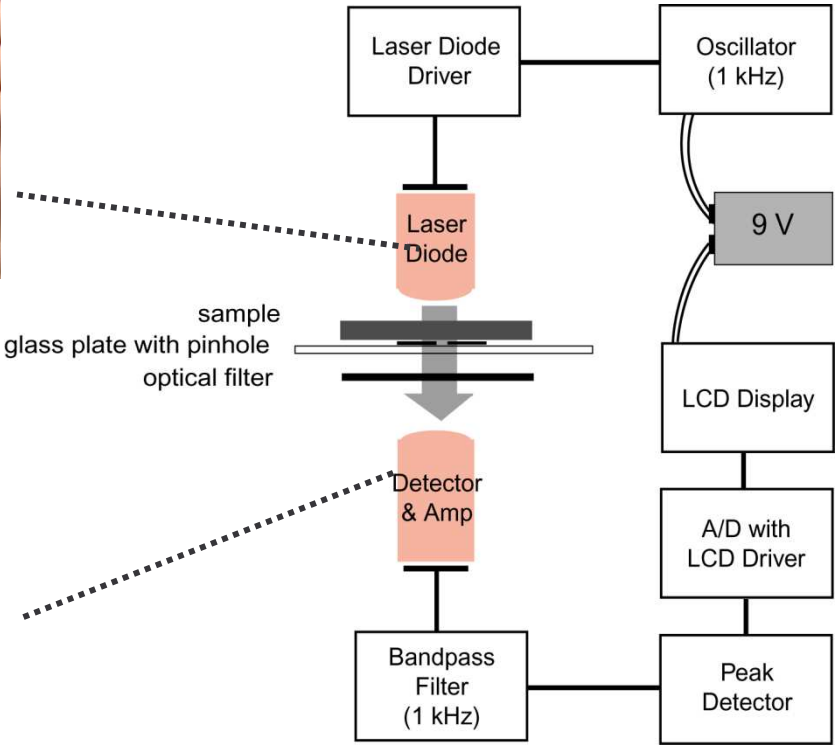
Sensitivity: 0.17 μA·ppb^{-1}

Signal detection:
battery-powered, frequency-modulated detector



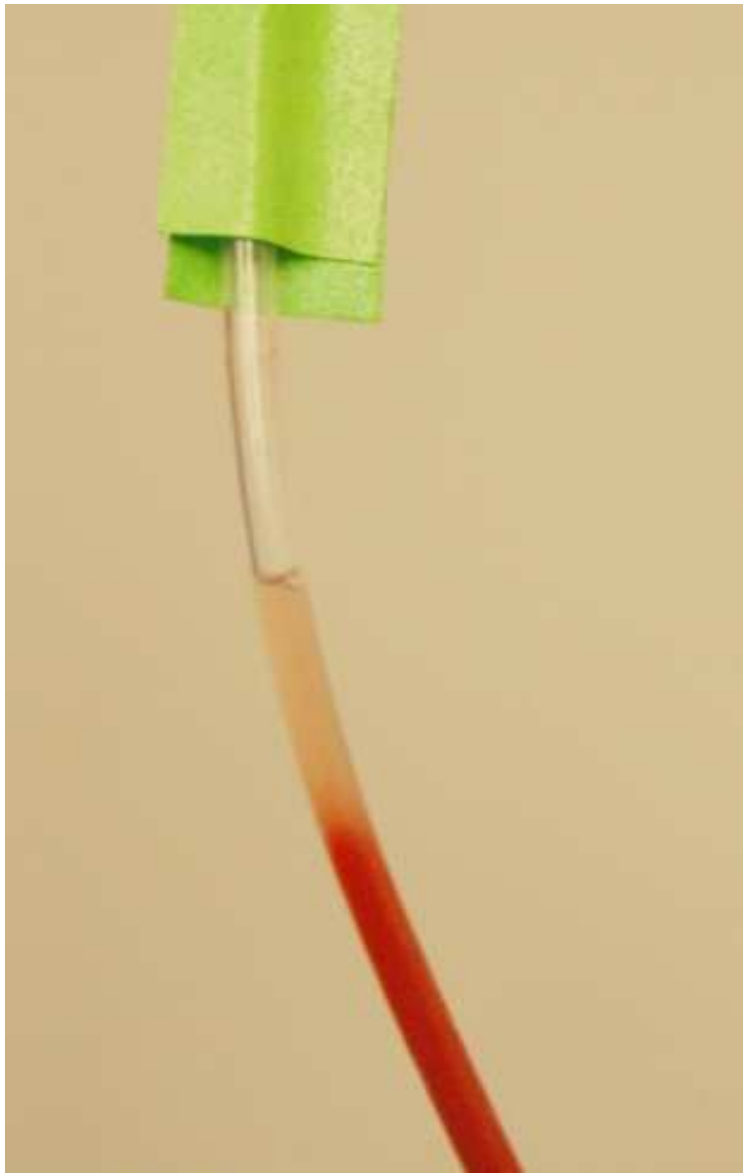


4 mm



cost of components < $50

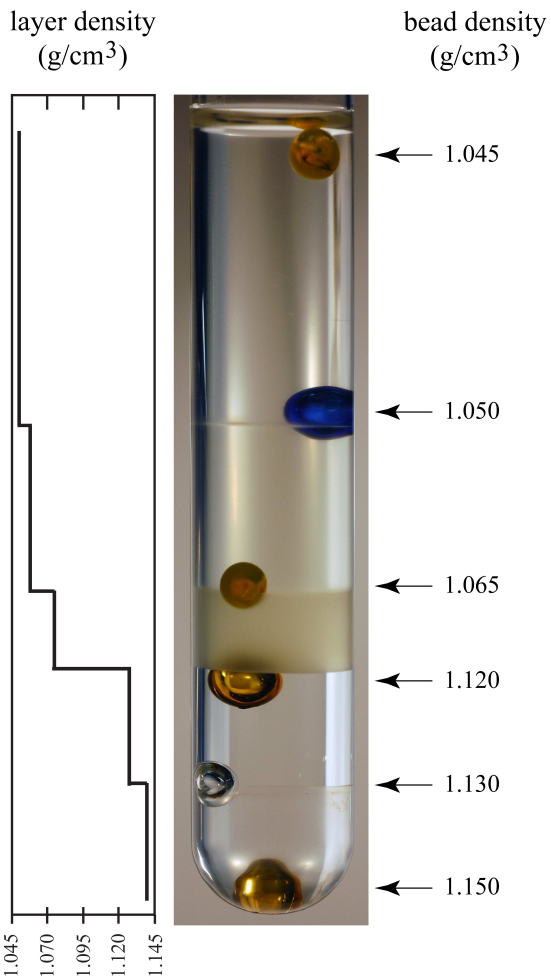
Eggbeater as Centrifuge

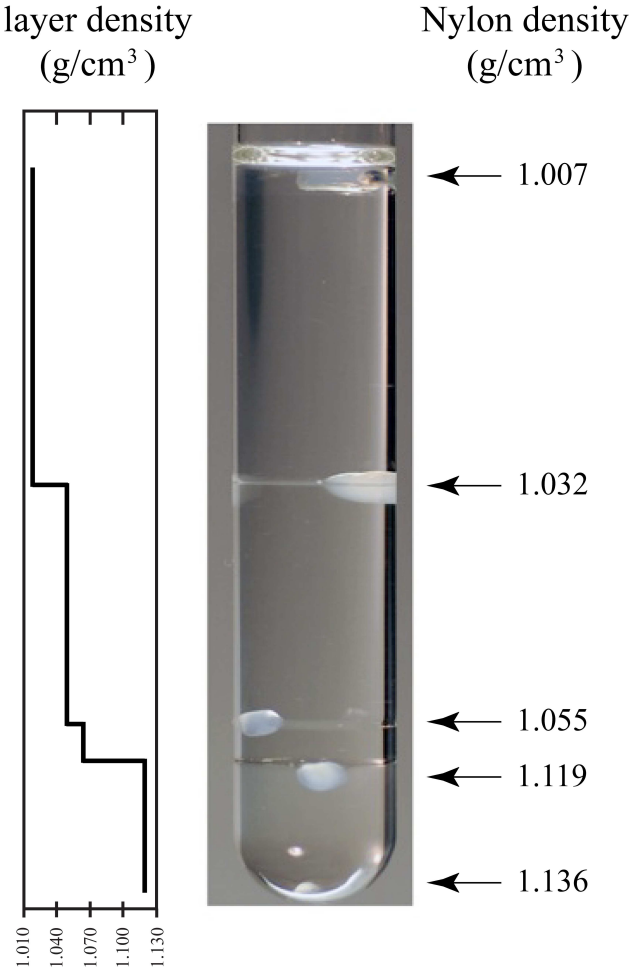


Aqueous Multiphase Polymer Systems

use in density-based separations

interfaces between phases define steps in density that are useful
to separate and collect objects based on density

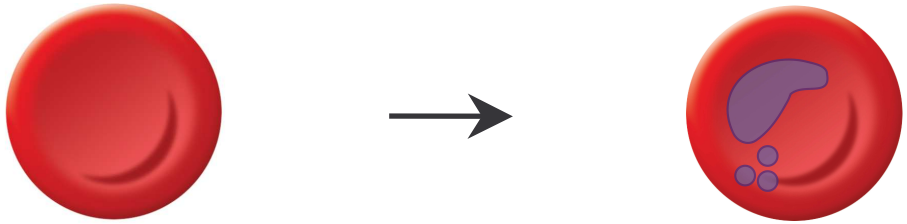




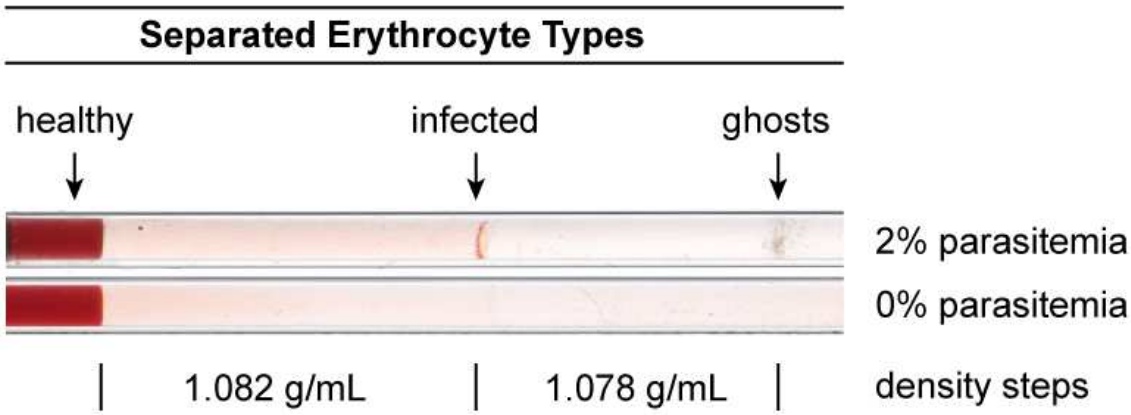
Density-Based Cell Separation as a Diagnostic *malaria*

healthy erythrocytes
ρ = 1.082 – 1.090 g/mL

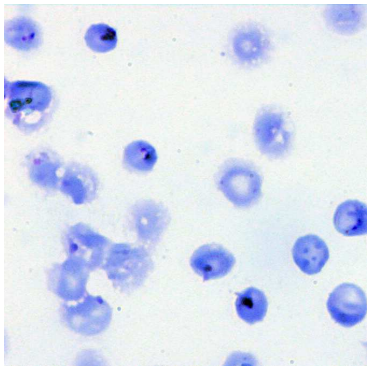
parasitized erythrocytes
ρ = 1.075 – 1.080 g/mL



loss of density caused by parasite metabolism of hemoglobin



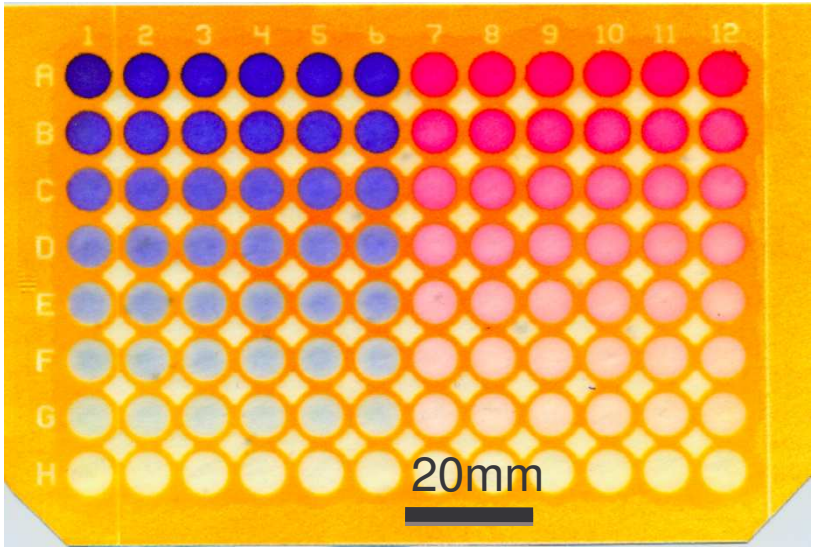
at interface

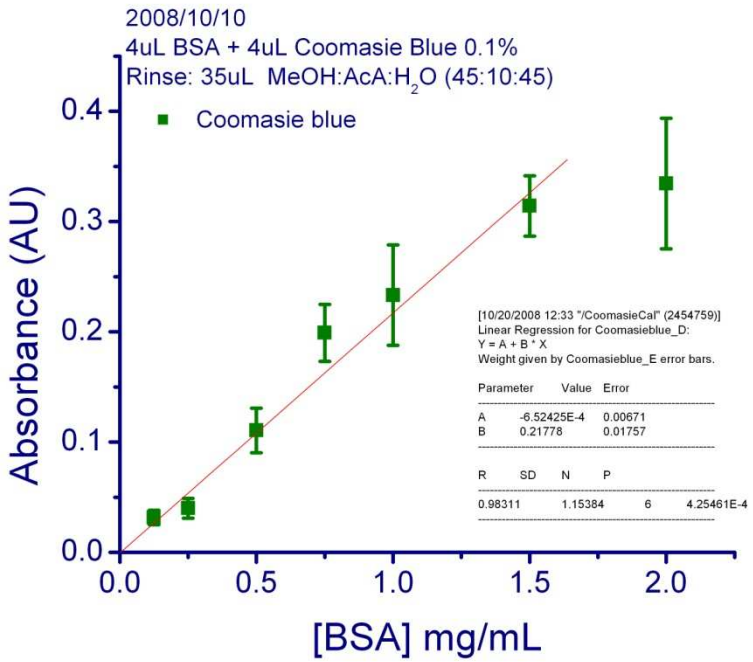


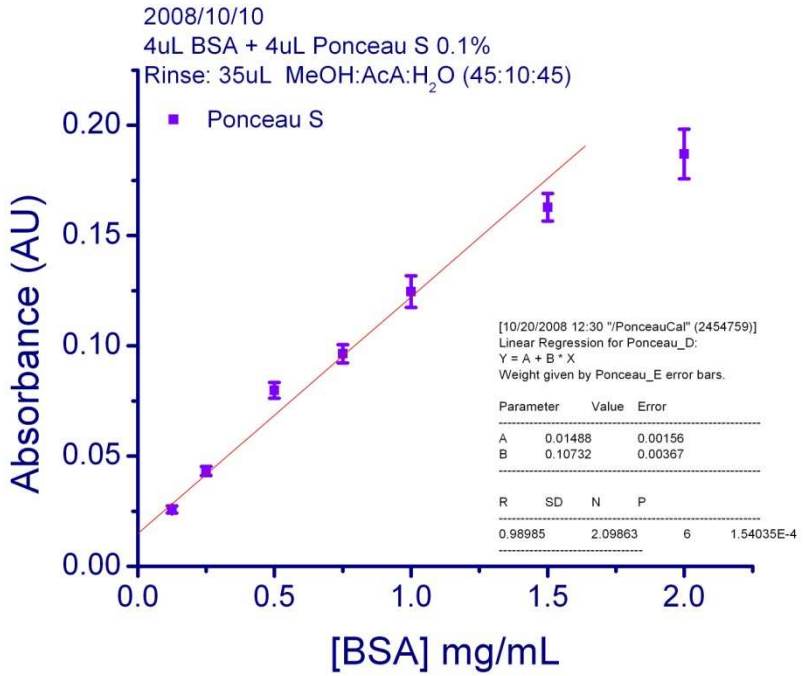
all intact cells contain parasites

Bioassays in 96-Zone Paper Plates Using Microplate Readers

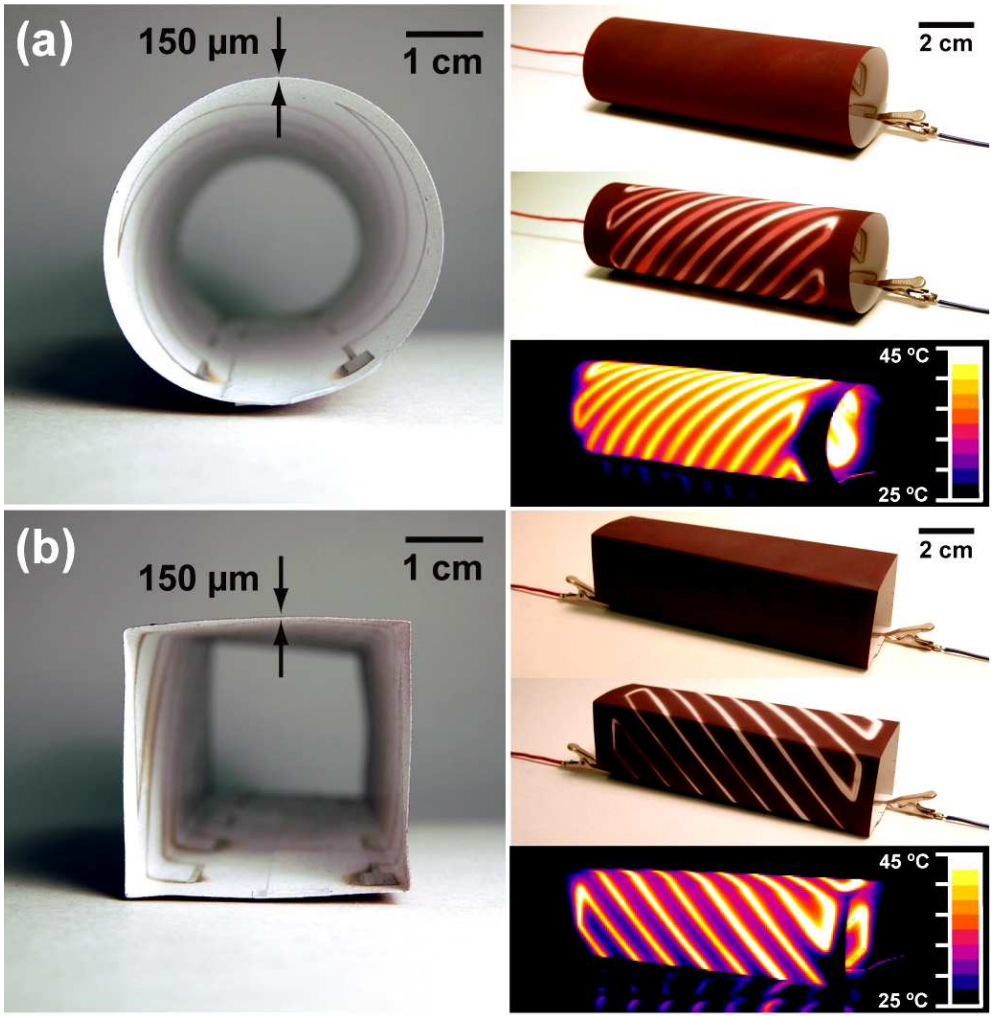
- Total Protein Assays:
  - Ponceau-S
  - Bradford





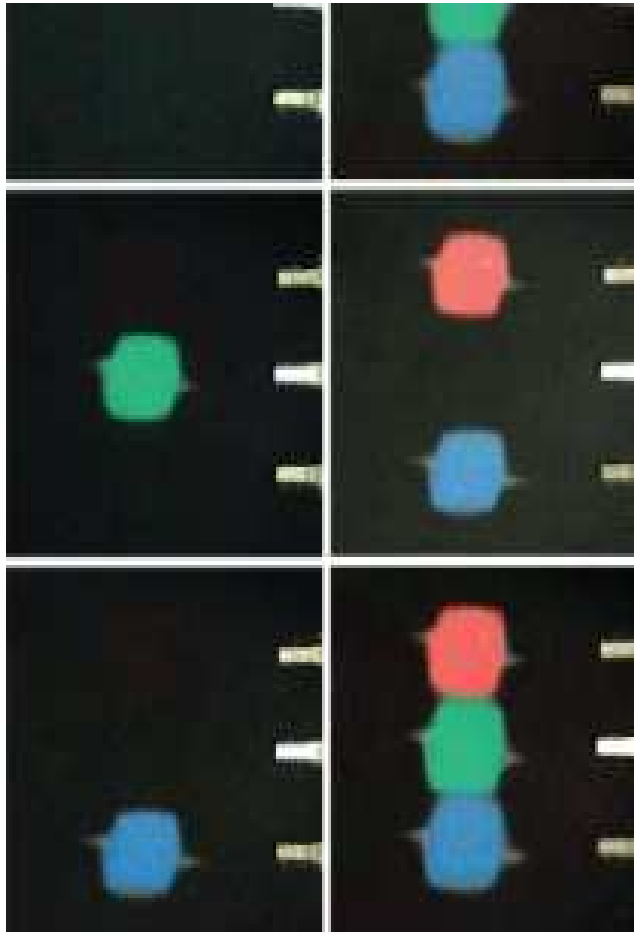


Thermochromic Displays on Paper



- Cost <$0.10/m^2 in materials
- Thin (100 µm), flat, lightweight (<20 mg/cm^2).
- Can be folded, rolled, twisted, and creased.

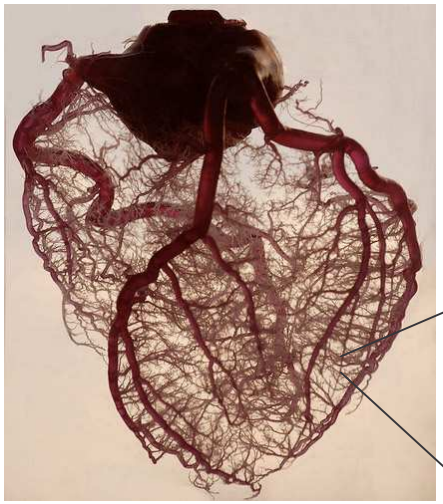
Thermochromic Displays

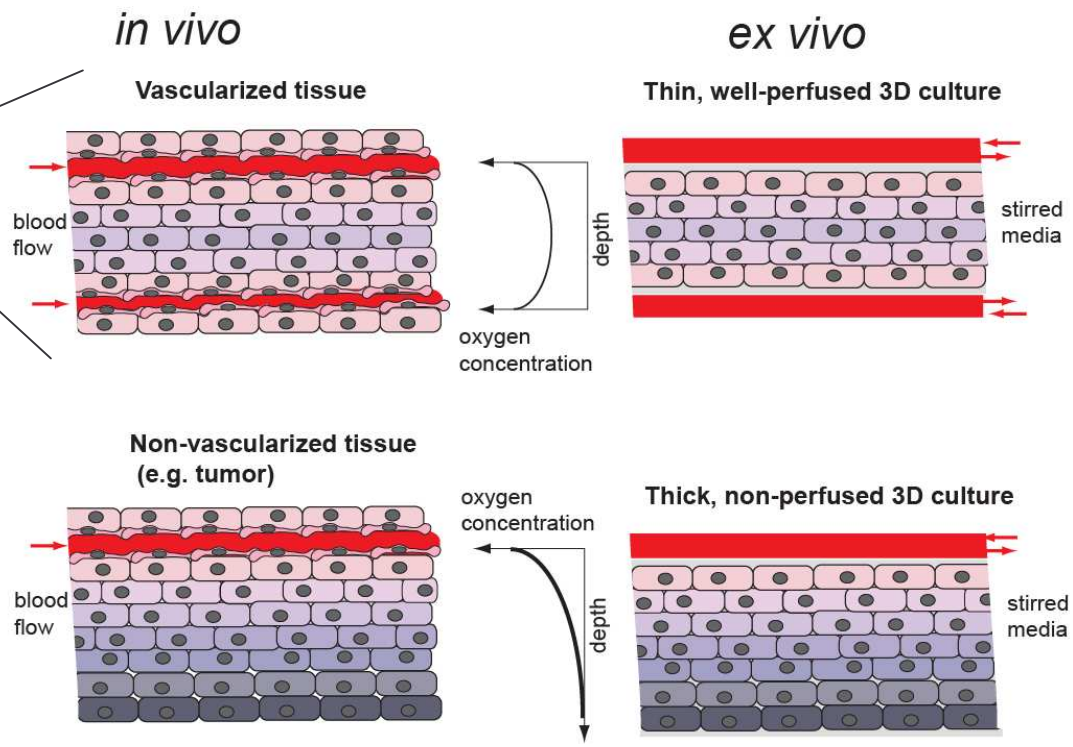


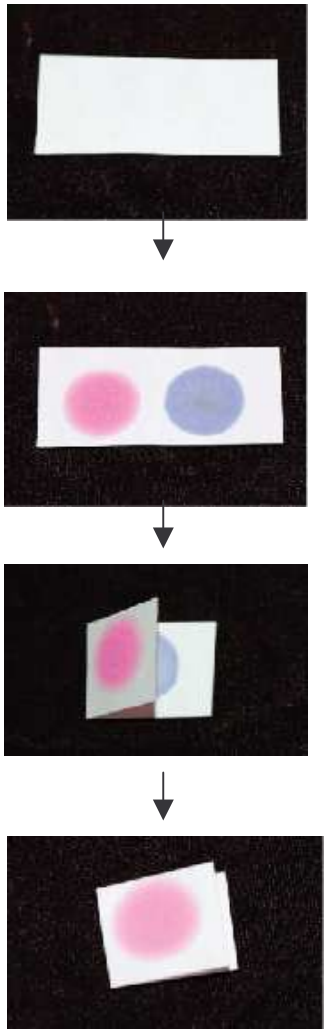
- Andres Martinez
- Scott Phillips
- Sergey Shevkoplyas
- Emanuel Carrilho
- Chao-Ming Chen
- Zhihong Nie
- Meital Reches
- Frederique Deiss
- Kat Mirica
- Charlie Mace

- Diagnostics for All
  - Una Ryan CEO

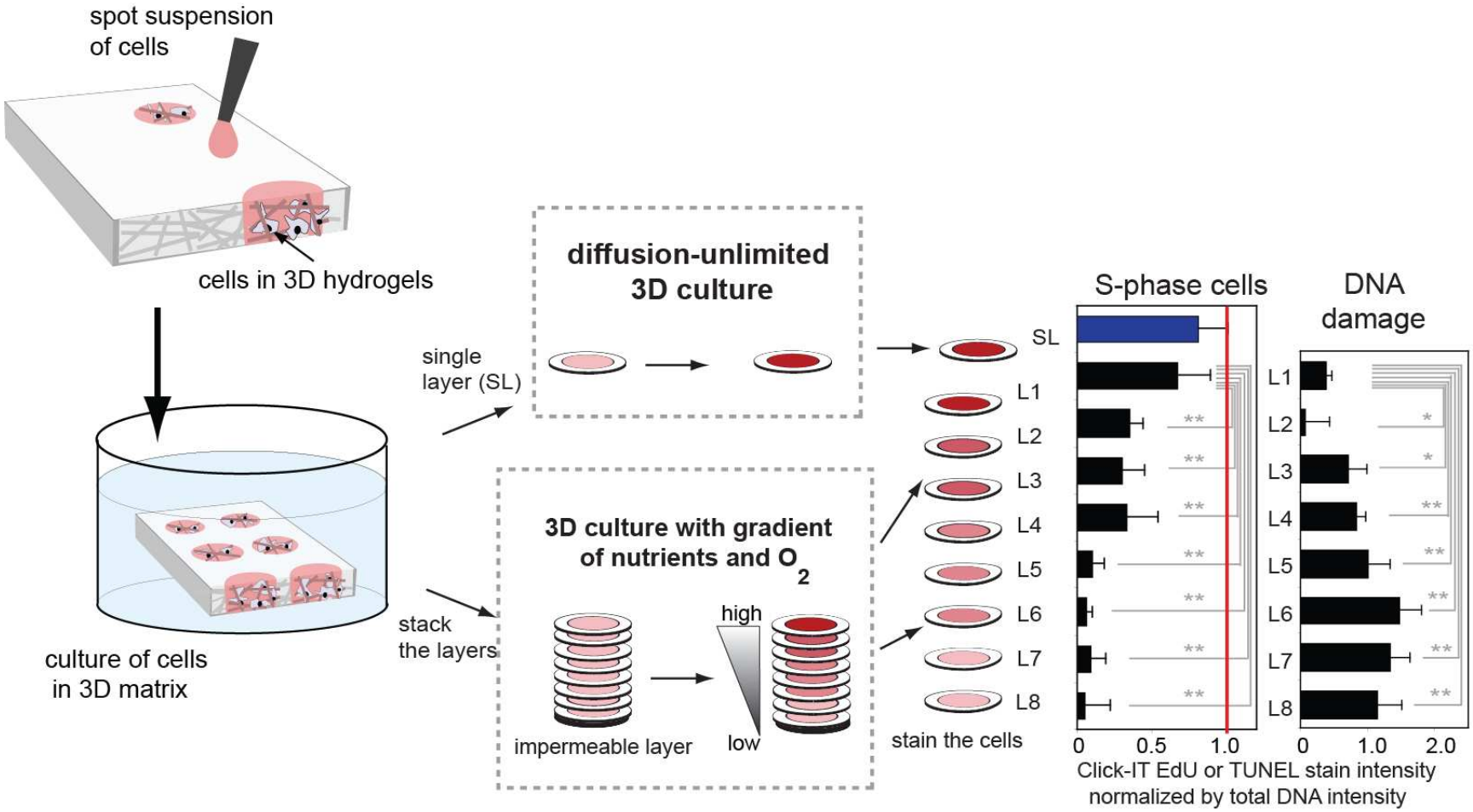
Cells-in-Gels-in-Paper







The main idea



PNAS, web this week,
http://wyss.harvard.edu/viewpressrelease/26/the-book-of-life-can-now-literally-be-written-on-paper-