Point-of-care Infectious Disease Test based on CMOS Technology

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BSAC

INFECTIOUS DISEASE - MORTALITY

Worldwide mortality due to infectious diseases[9]

Rank	Cause of death	Deaths 2002	Percentage of all deaths	Deaths 1993	1993 Rank
N/A	All infectious diseases	14.7 million	25.9%	16.4 million	32.2%
1	Lower respiratory infections[10]	3.9 million	6.9%	4.1 million	1
2	HIV/AIDS	2.8 million	4.9%	0.7 million	7
3	Diarrheal diseases[11]	1.8 million	3.2%	3.0 million	2
4	Tuberculosis (TB)	1.6 million	2.7%	2.7 million	3
5	Malaria	1.3 million	2.2%	2.0 million	4
6	Measles	0.6 million	1.1%	1.1 million	5
7	Pertussis	0.29 million	0.5%	0.36 million	7
8	Tetanus	0.21 million	0.4%	0.15 million	12
9	Meningitis	0.17 million	0.3%	0.25 million	8
10	Syphilis	0.16 million	0.3%	0.19 million	11
11	Hepatitis B	0.10 million	0.2%	0.93 million	6
12-17	Tropical diseases (6)[12]	0.13 million	0.2%	0.53 million	9, 10, 16-18

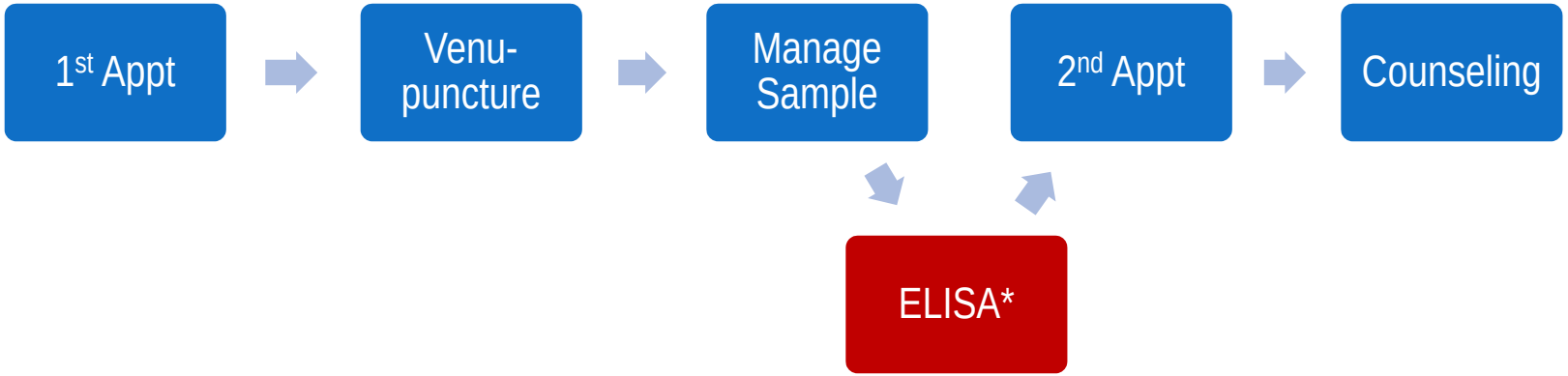
Source: WHO/wikipedia

HIV Problem

- Worldwide 33 million people are infected
- 1 in 4 people who have HIV in the US are unaware and are responsible for up to 75% of new infections
- The CDC recommends routine testing of **everyone** between the ages of 13 and 64

Diagnosing HIV

Current Procedure :



Procedure using Rapid Tests:

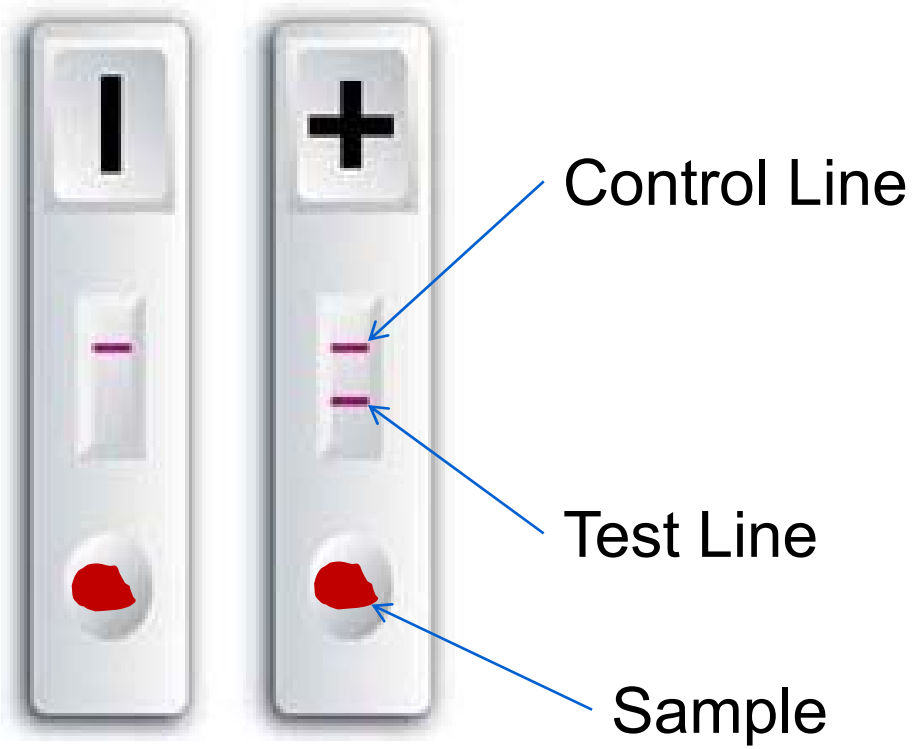
Infectious Disease Testing: Current Solution

Beckman Coulter UniCel DxC 880i
400 immunoassay tests per hour

DEVELOPING WORLD

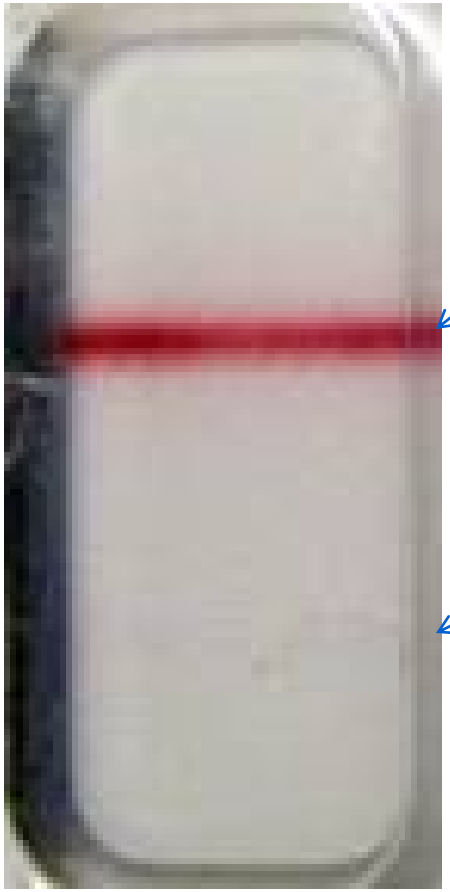
Strip Tests

- Simple, low cost, rapid
- Low sensitivity

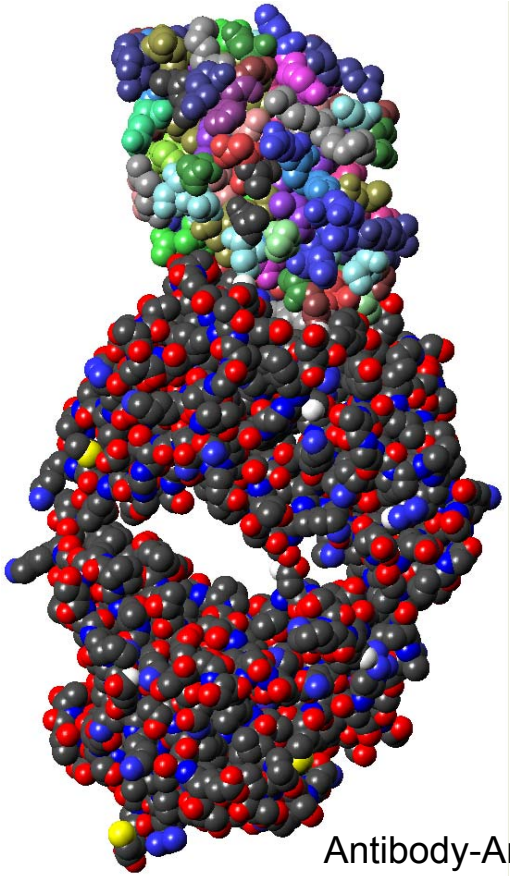


Strip Test Readout

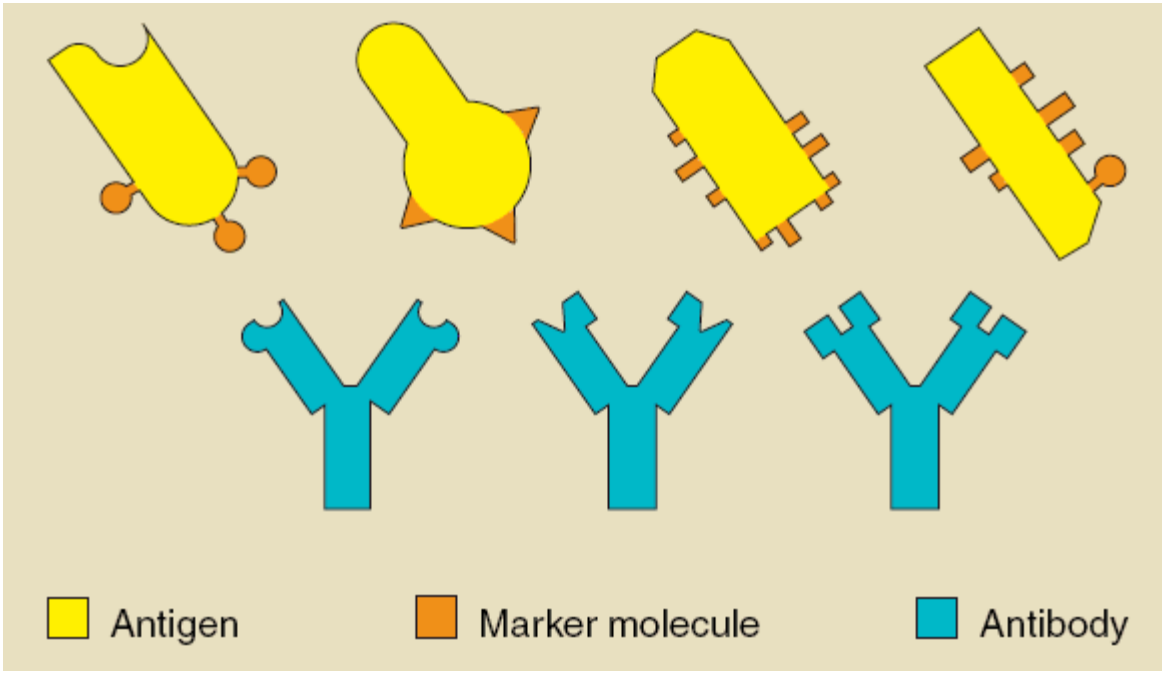
- An example of a weakly positive results that is difficult to read



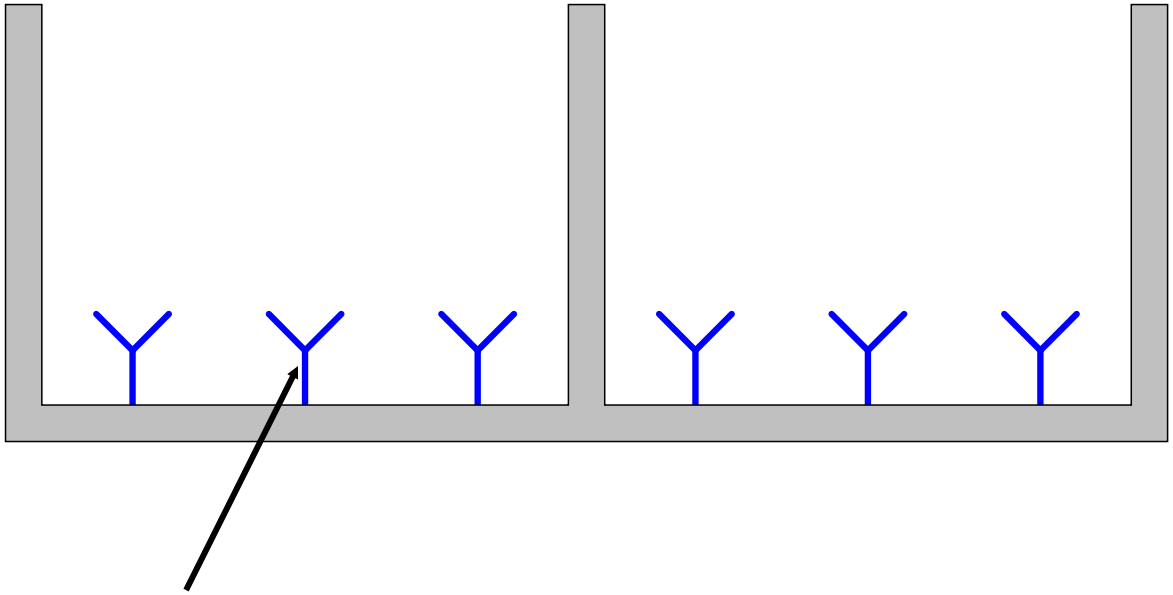
Basis for Infectious Disease Tests: Antigen – Antibody Interactions



Antibody-Antigen Complex

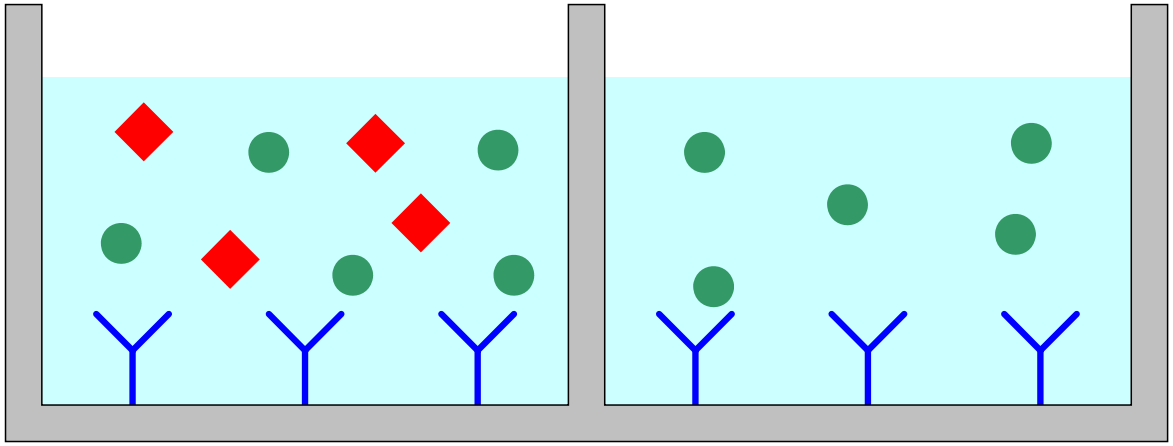


Antibody-Antigen Tests
ELISA (Enzyme-Linked Immunosorbent Assay)

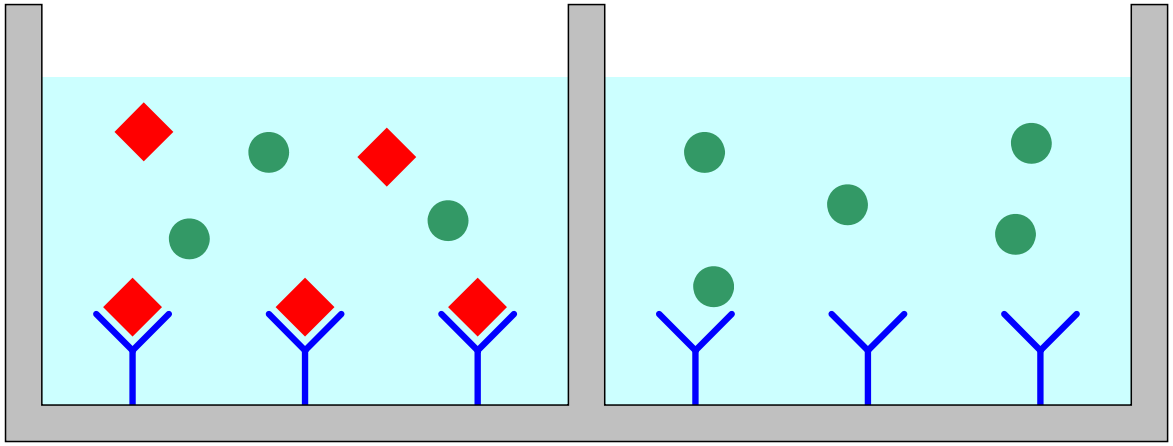


Antibody specific to target analyte (e.g. HIV virus)

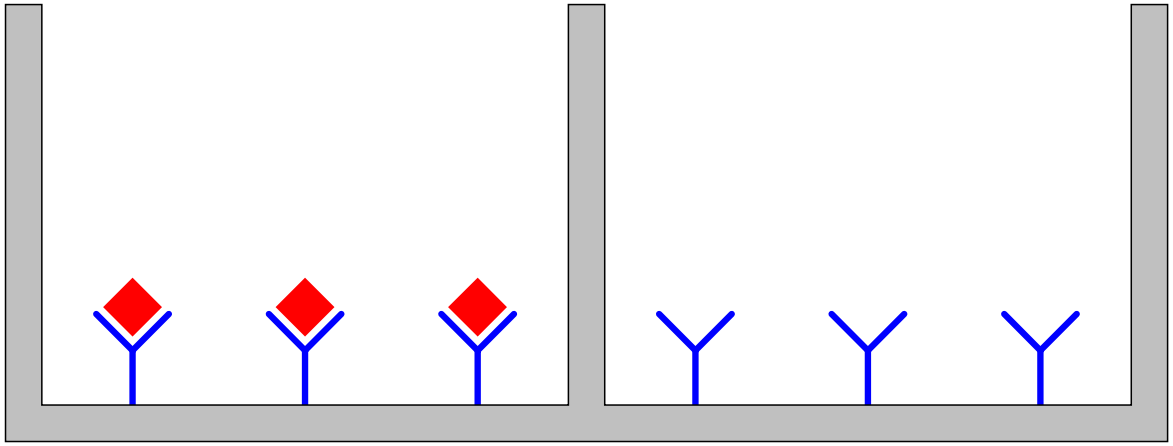
ADD ANALYTE
(E.G. BLOOD SERUM)



INCUBATE



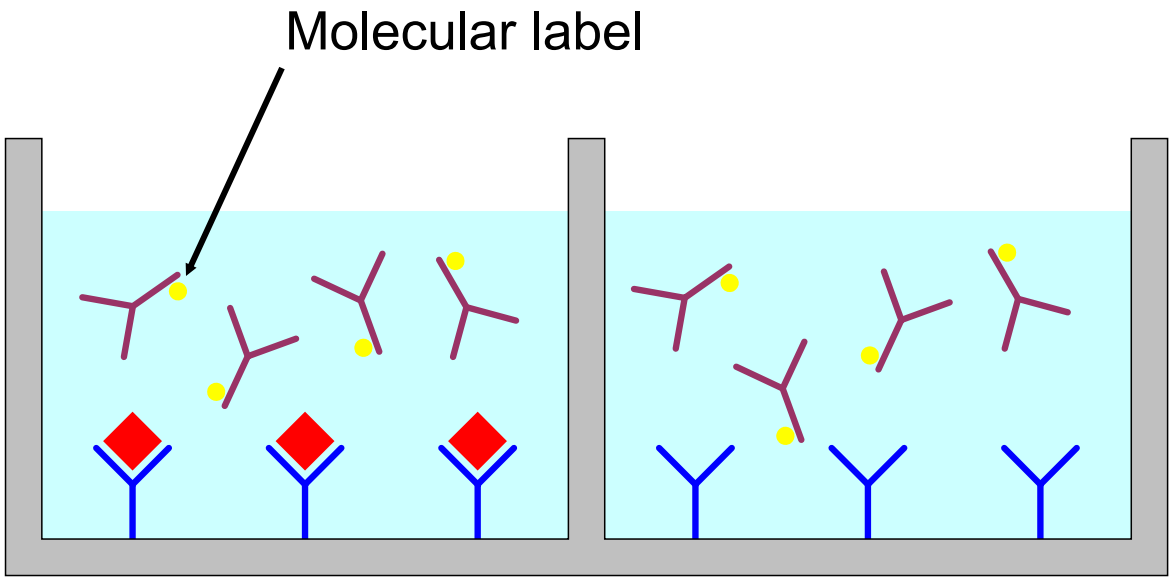
WASH



Captured target

No target

ADD SECONDARY ANTIBODY



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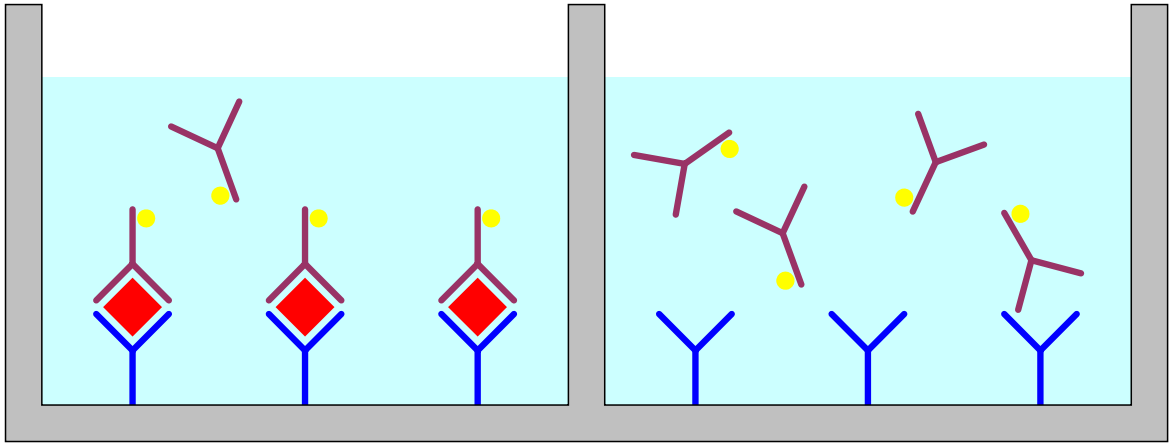
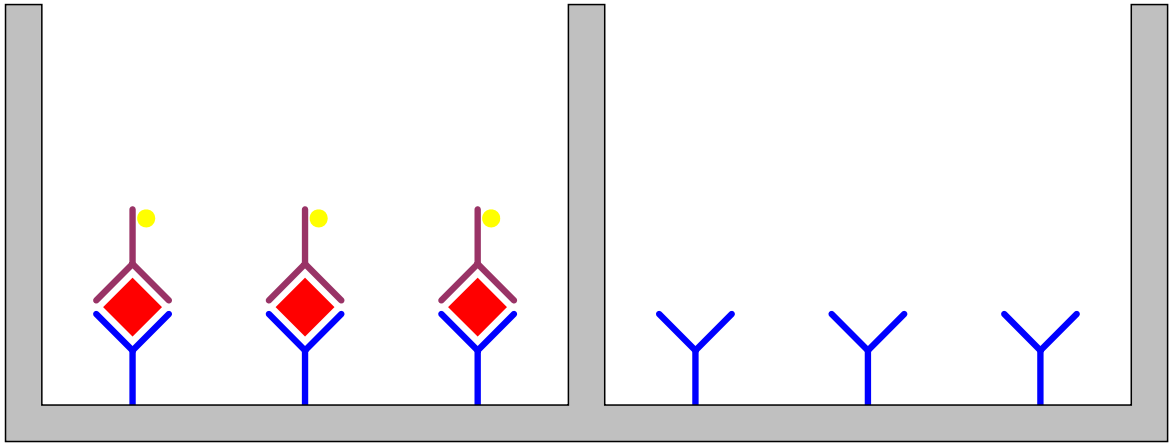


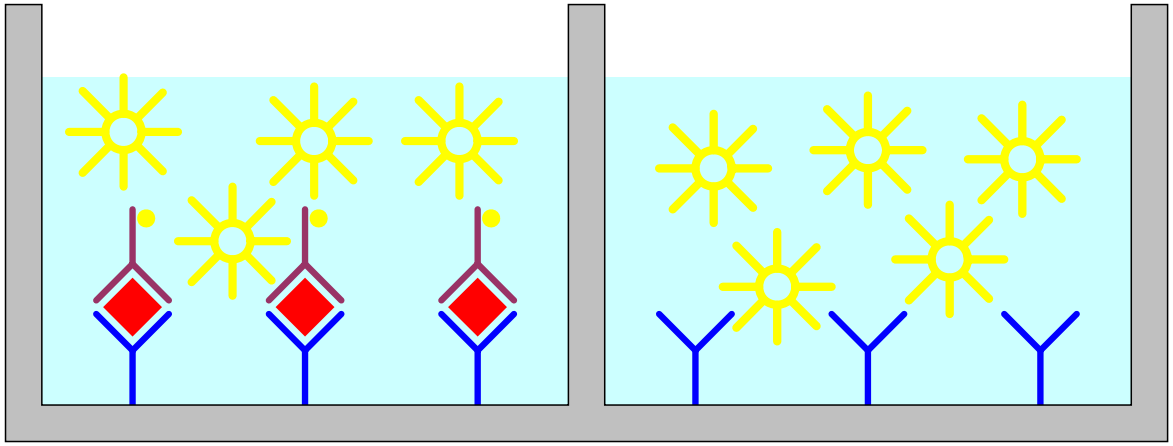
WASH



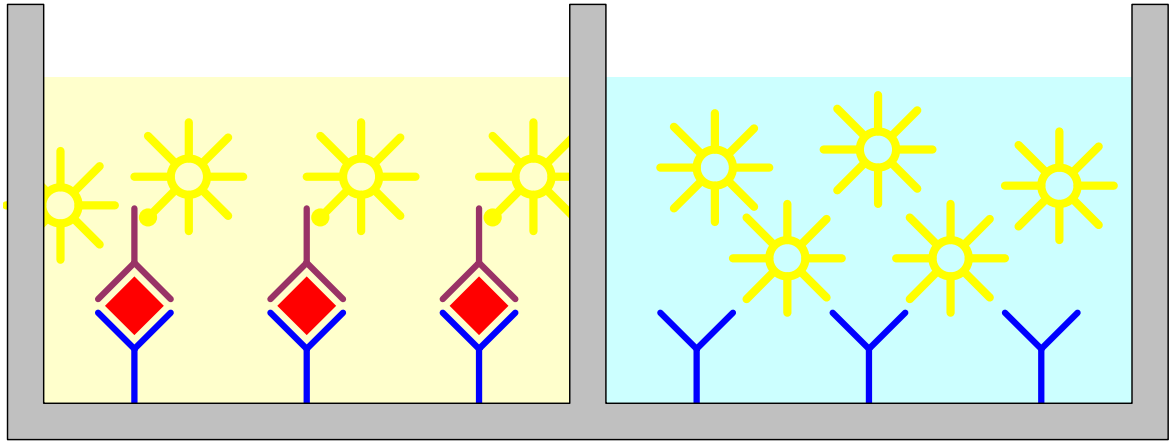
Label bound to analyte

No labels present

ADD SUBSTRATE



Quantify Color Change

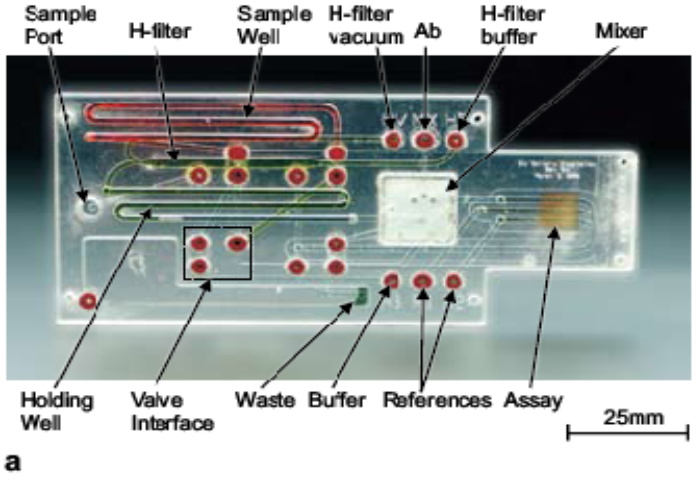


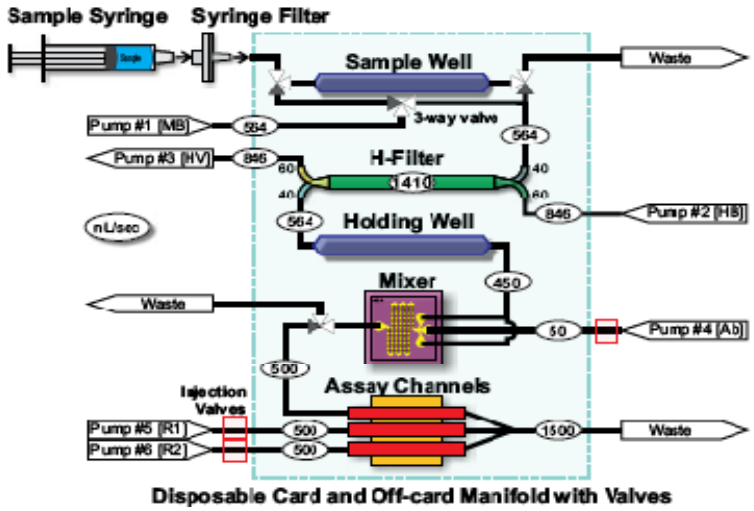
Substrate activated by label
→ Color change

No color change

MICROFLUIDICS/LAB-ON-CHIP

- Reproduce laboratory protocols on a disposable cartridge
- Integration of valves, pumps, filters and mixers
- Requires external support to evaluate assay results

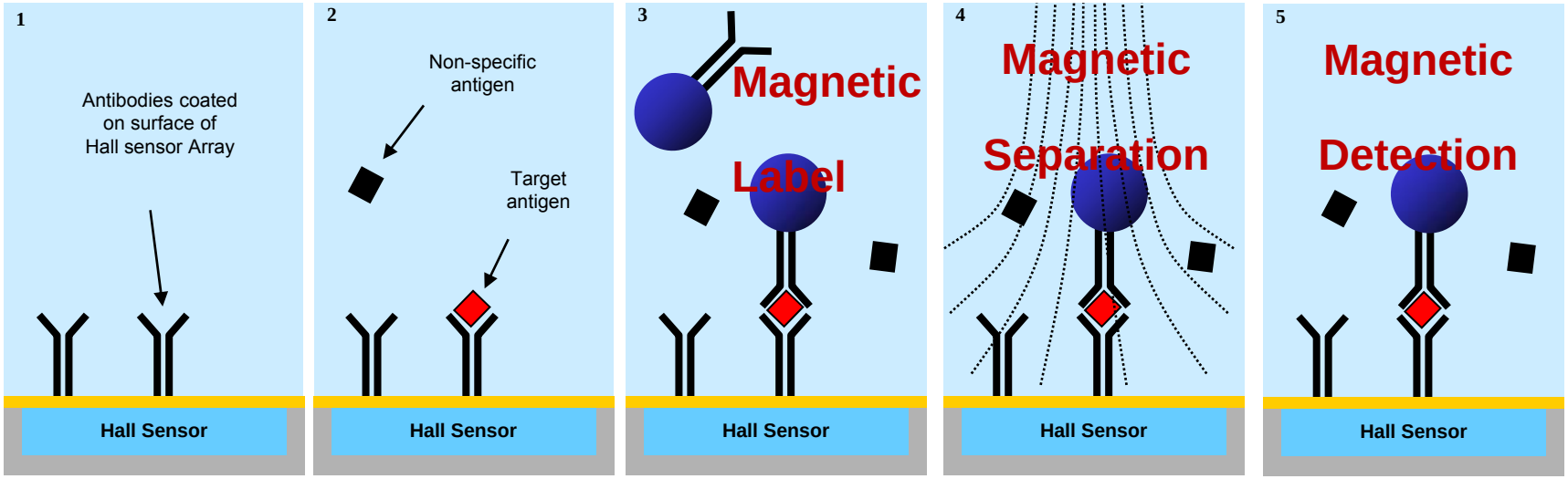




Disposable Card and Off-card Manifold with Valves

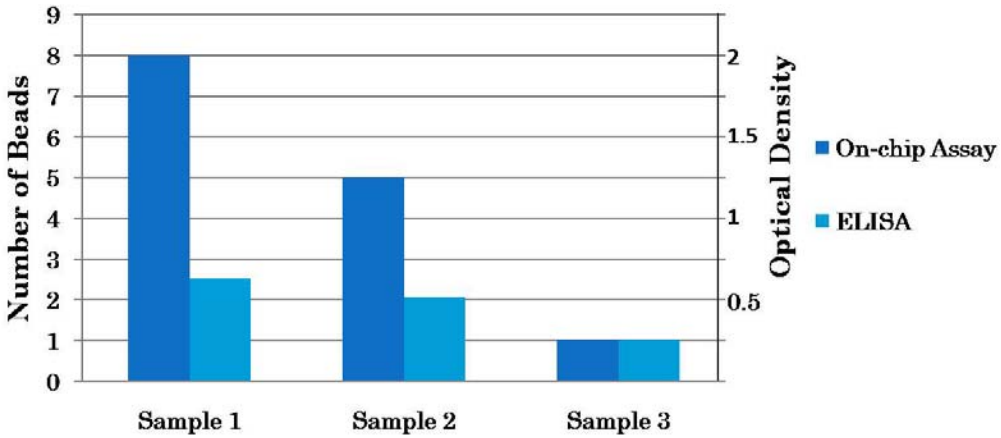
MAGNETIC "ELISA"

1. Retain antibody-antigen chemistry
2. Optical → magnetic label
3. Hydrodynamic → electromagnetic separation
4. Electronic detection

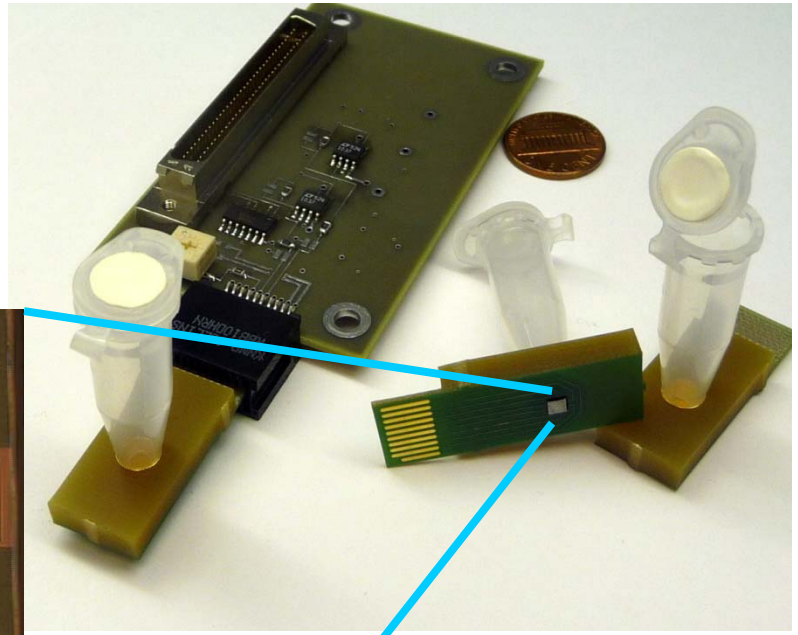


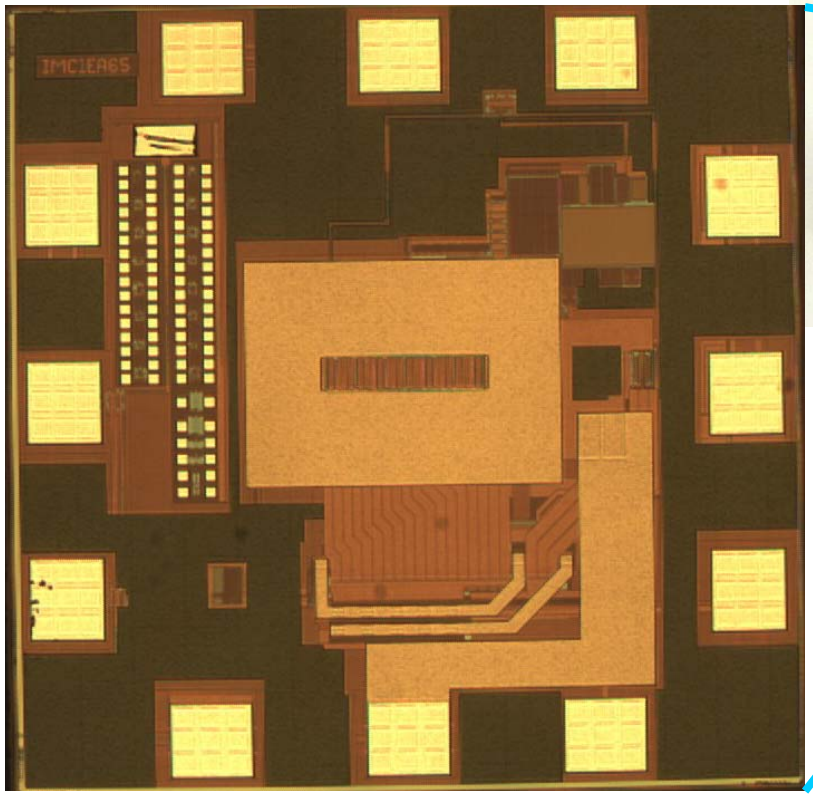
IMMUNOSENSOR

- Blood from finger stick is placed on filter
- Cartridge is agitated and slotted into reader
- 10-20 minutes later, digital, quantitative results are displayed
- Offers ELISA sensitivity

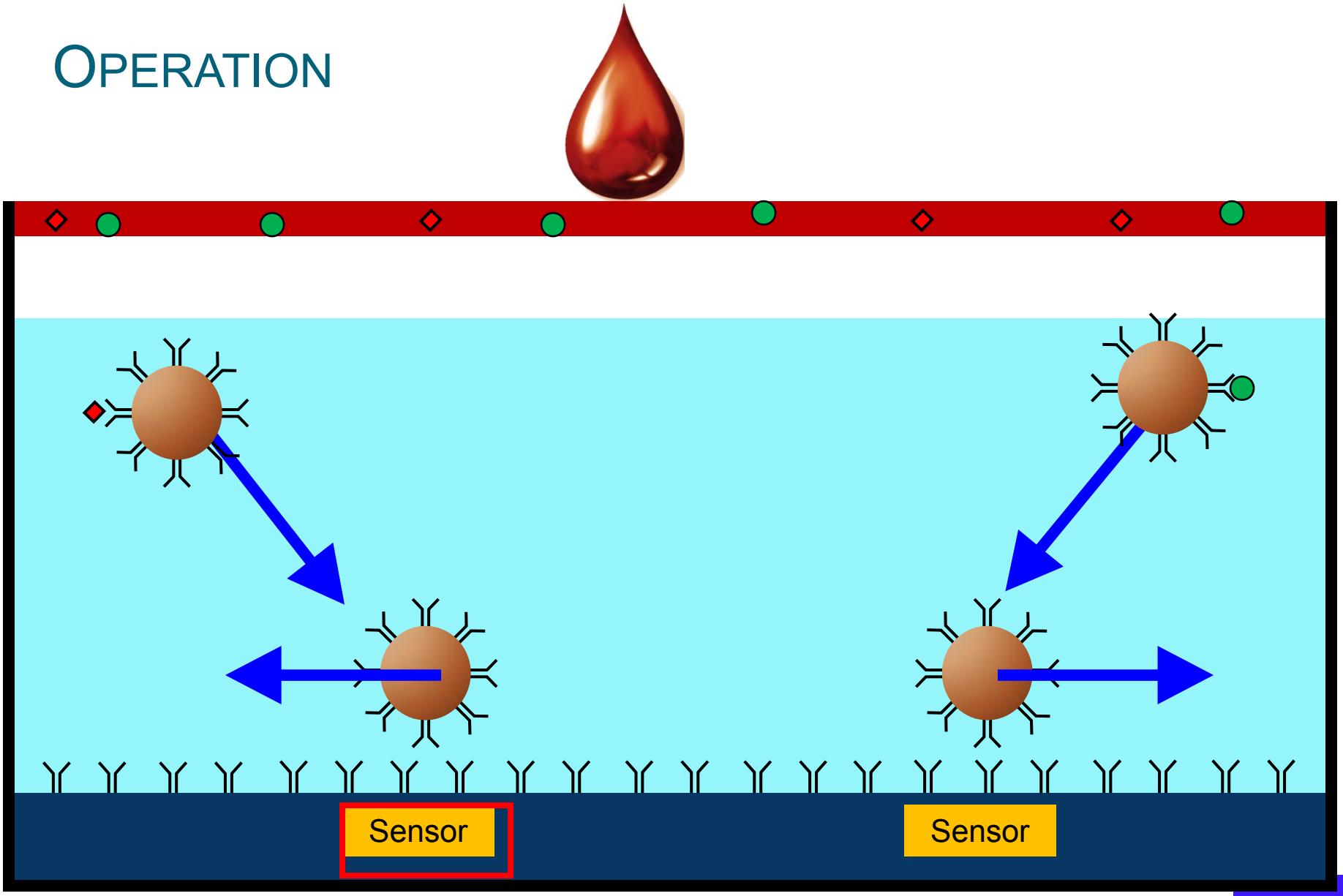


TECHNOLOGY

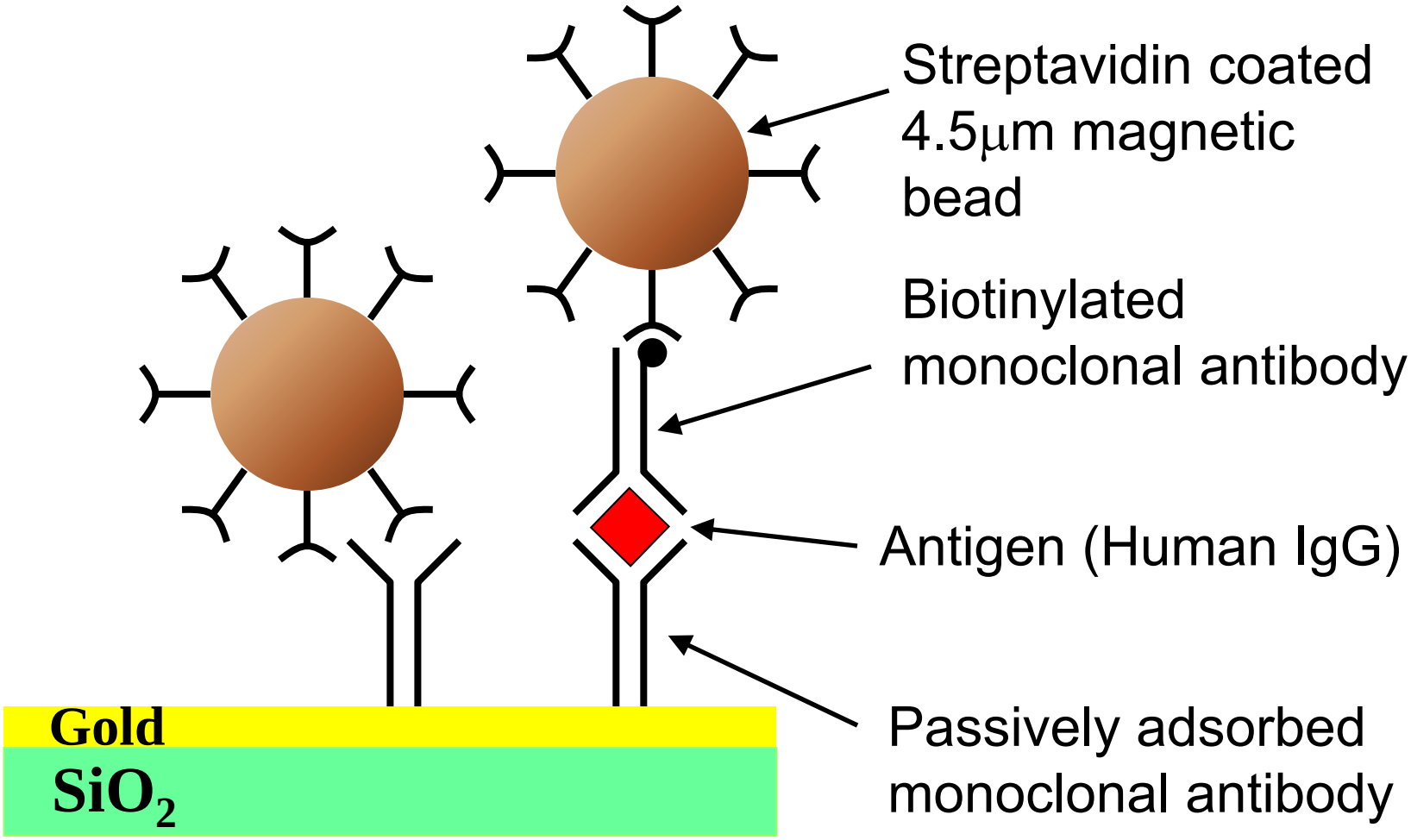




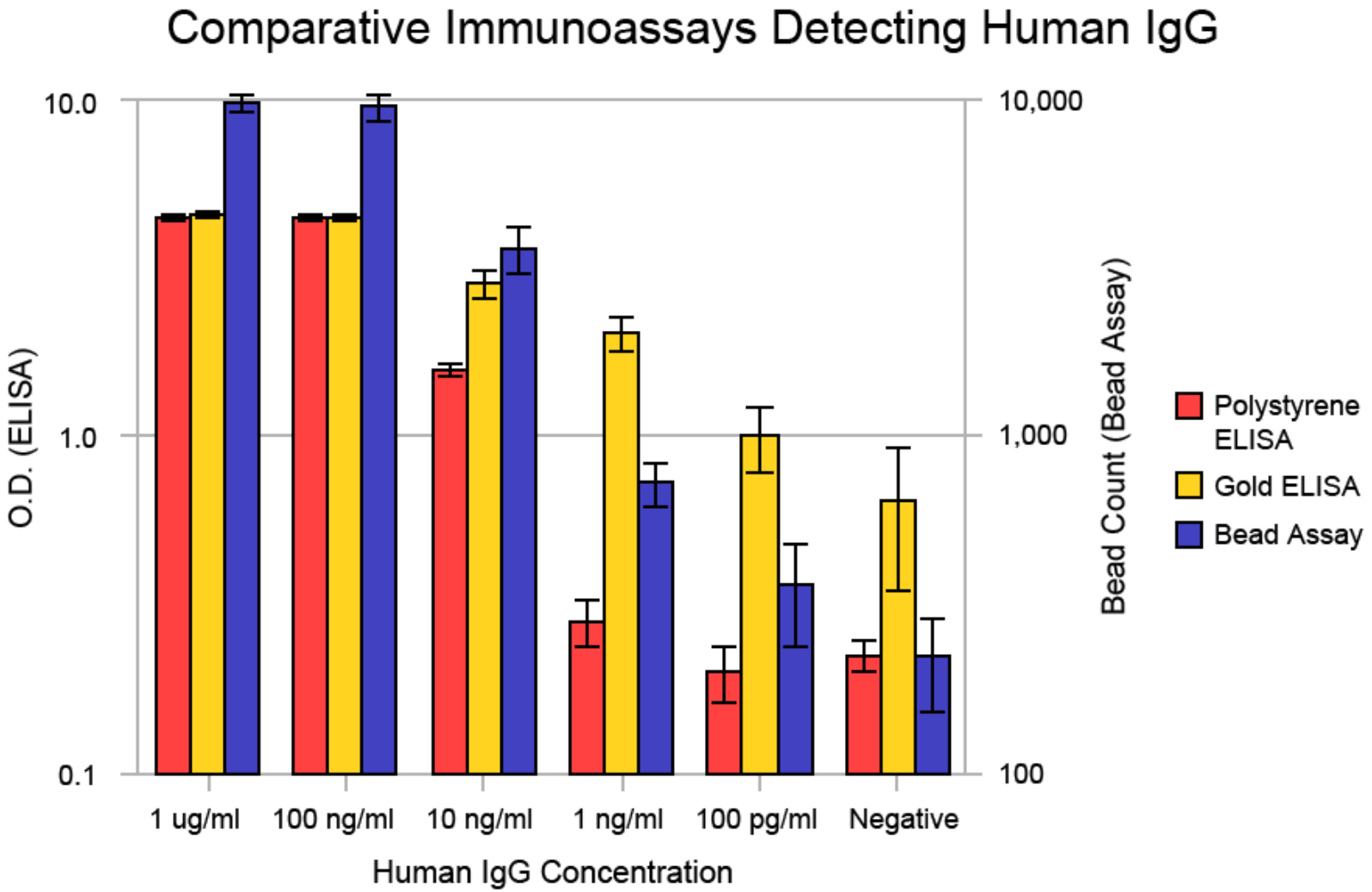
OPERATION



MAGNETIC BEADS AS IMMUNO-LABELS

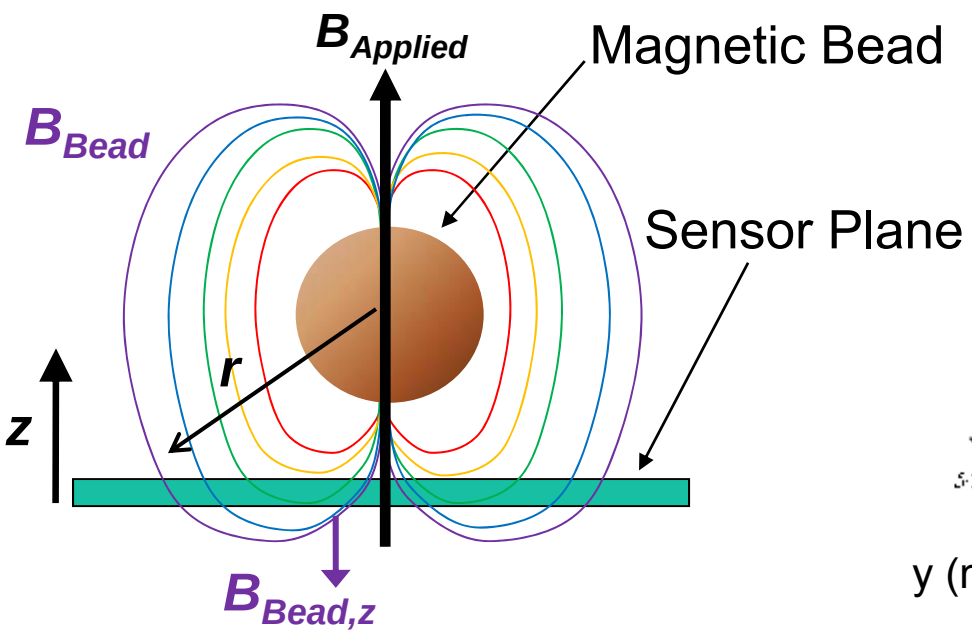


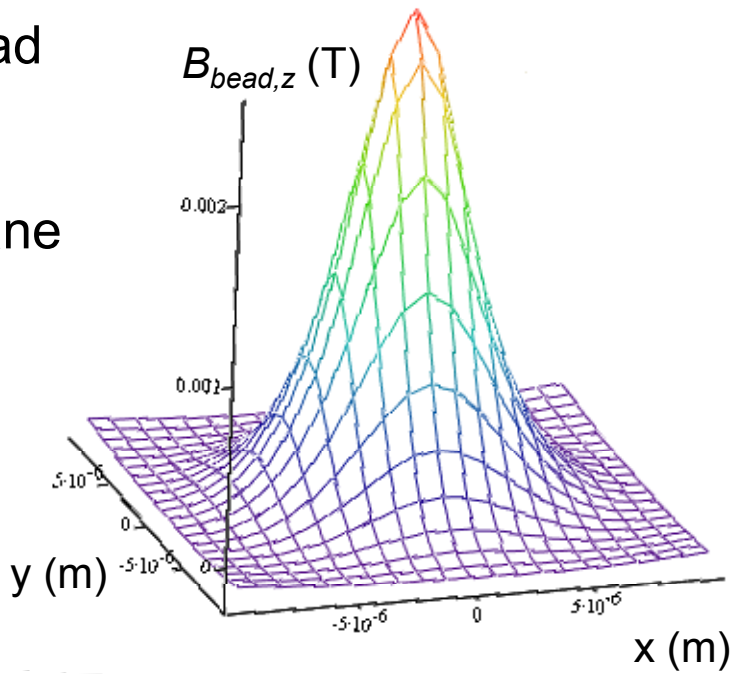
MAGNETIC BEADS AS IMMUNO-LABELS



Florescu et al., "On-chip magnetic washing of super-paramagnetic beads for integrated assay applications", Journal of Applied Physics, In Press (2009)

INTEGRATED MAGNETIC BEAD DETECTION

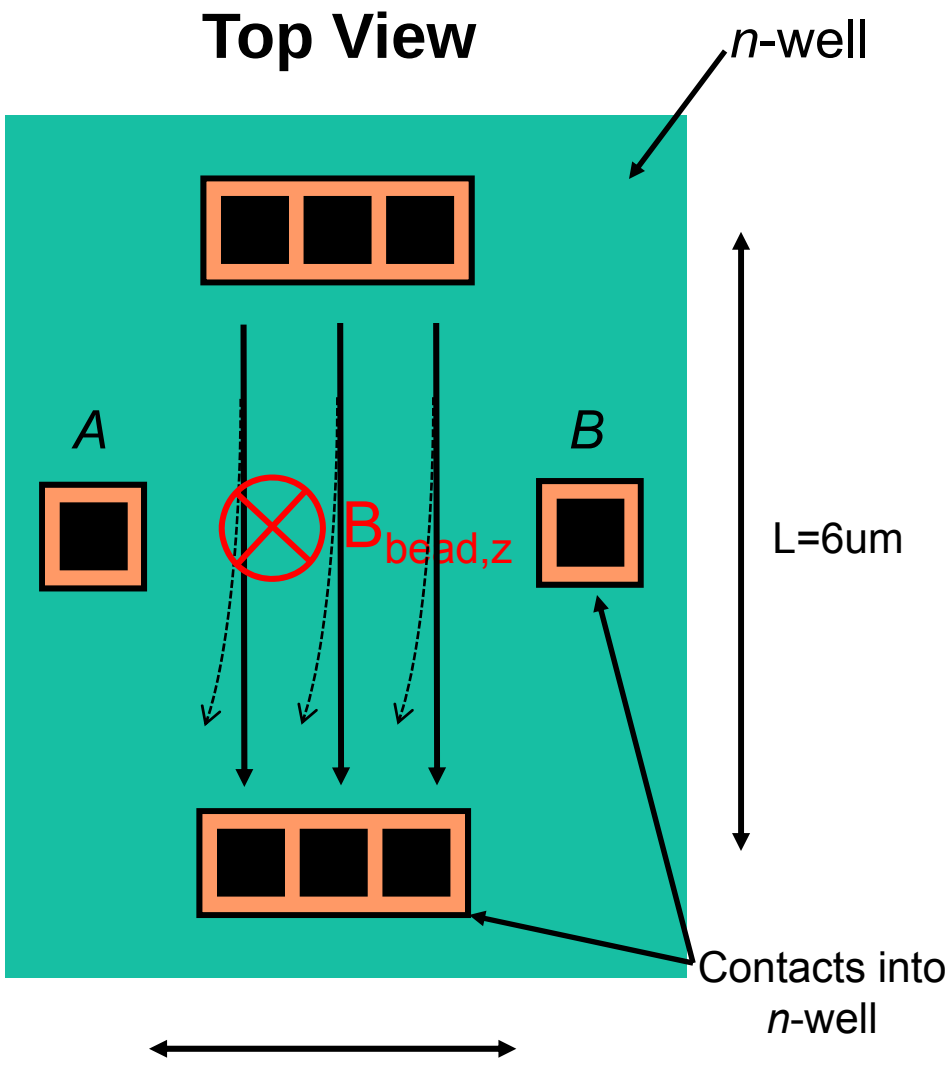




$$\mathbf{m}_{\mathbf{bead}} = \chi_b V_b B_{applied} \mathbf{z} / z$$

$$\mathbf{B}_{\mathbf{bead}} = \frac{\mu_o}{4\pi} \cdot \frac{3(\mathbf{r} \cdot \mathbf{m}_{\mathbf{bead}})\mathbf{r} - (\mathbf{r} \cdot \mathbf{r})\mathbf{m}_{\mathbf{bead}}}{r^5}$$

Integrated Magnetic Bead Detection

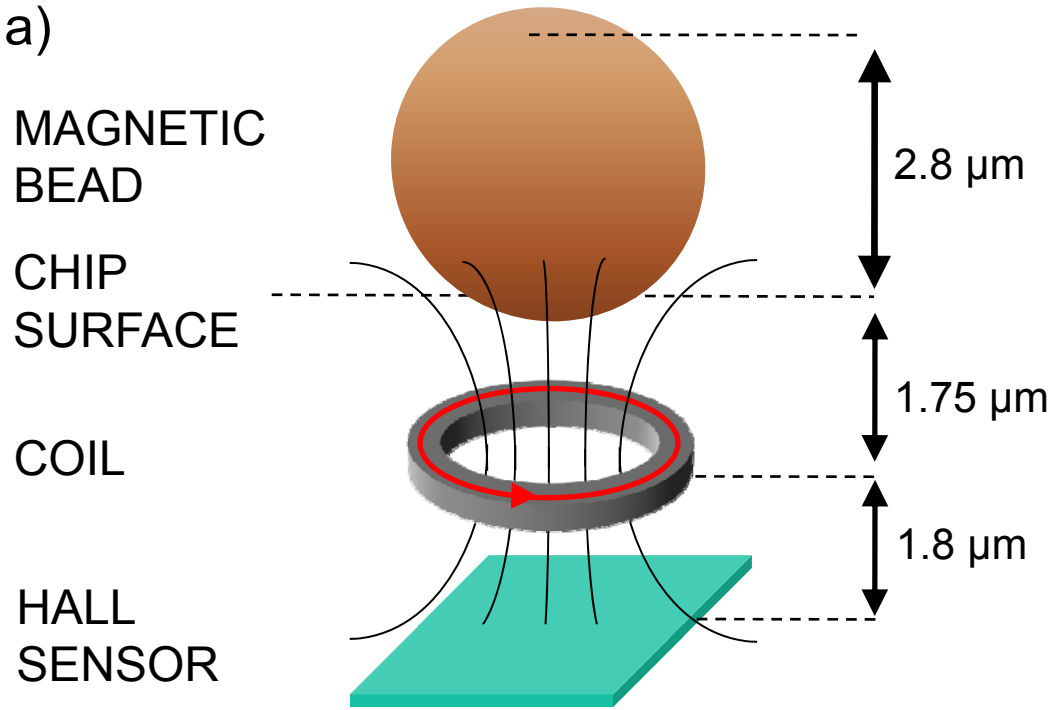


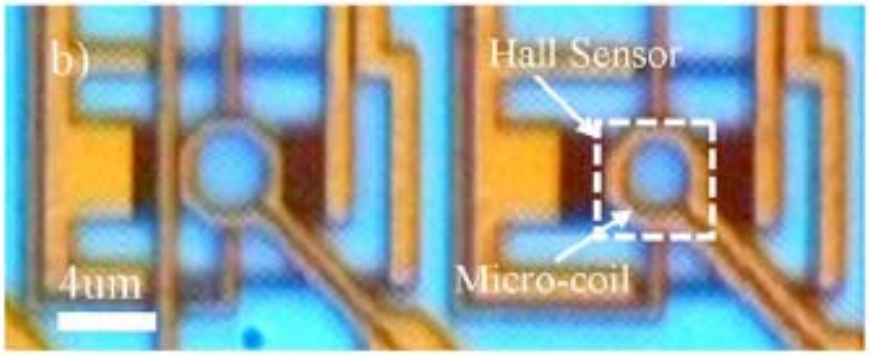
$$F_e = qv \times B_{bead,z}$$

$$V_H = \int_A^B \frac{F_e}{q} dl$$

$$V_H = G_H \mu_{Hall} \frac{W}{L} B_{bead,z}$$

Integrated Magnetic Bead Detection





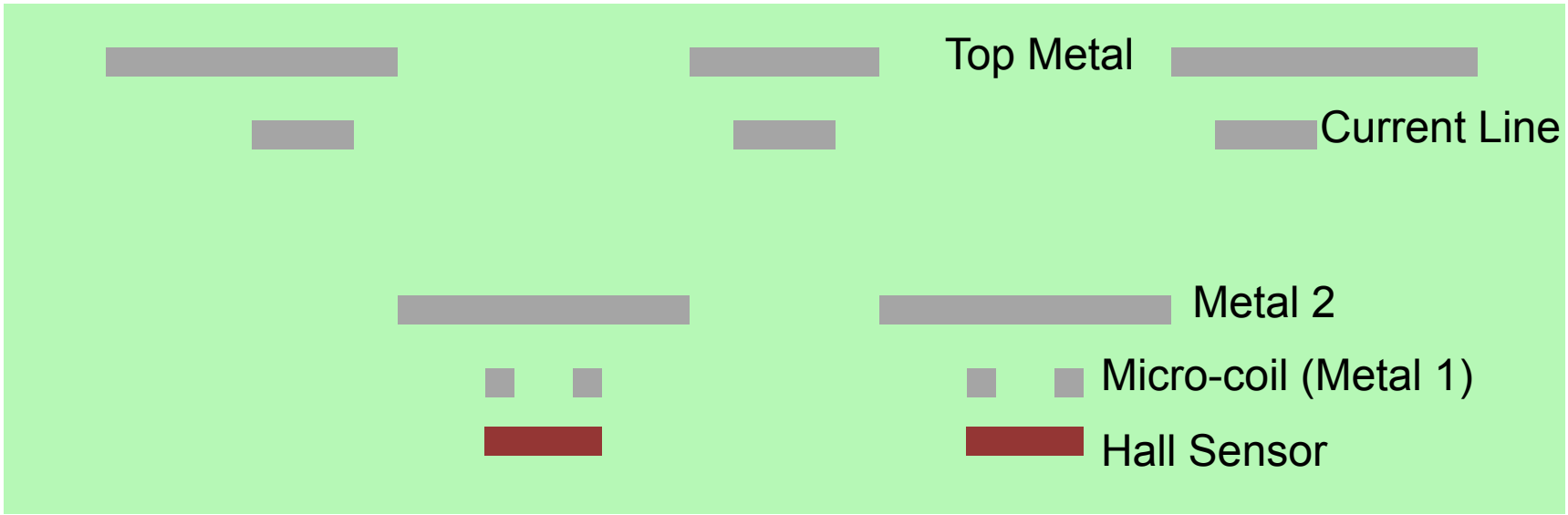
I_{coil} = 10mA

$B_{applied}$= 800uT

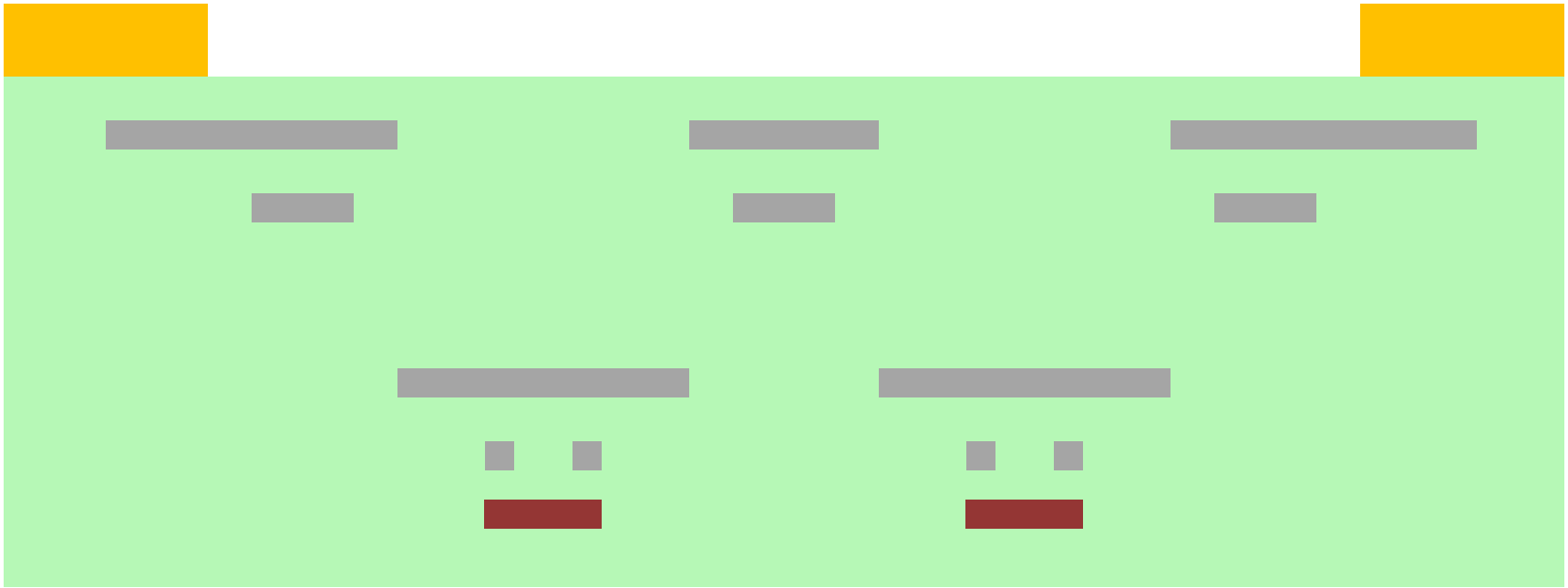
$B_{bead,z}$= 10uT

S_{Hall}= 1.7%/T

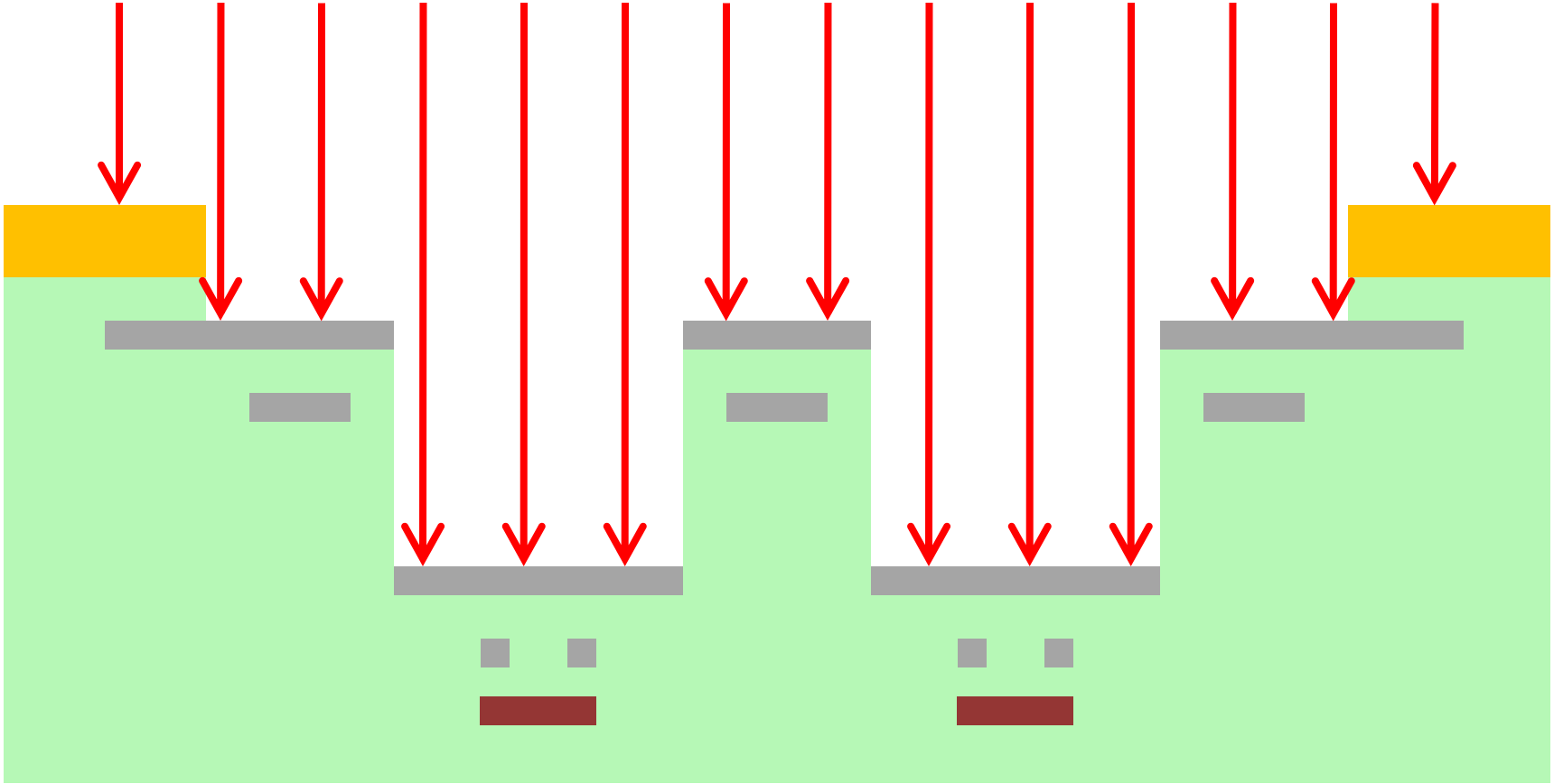
Post CMOS Processing: Expose Sensors



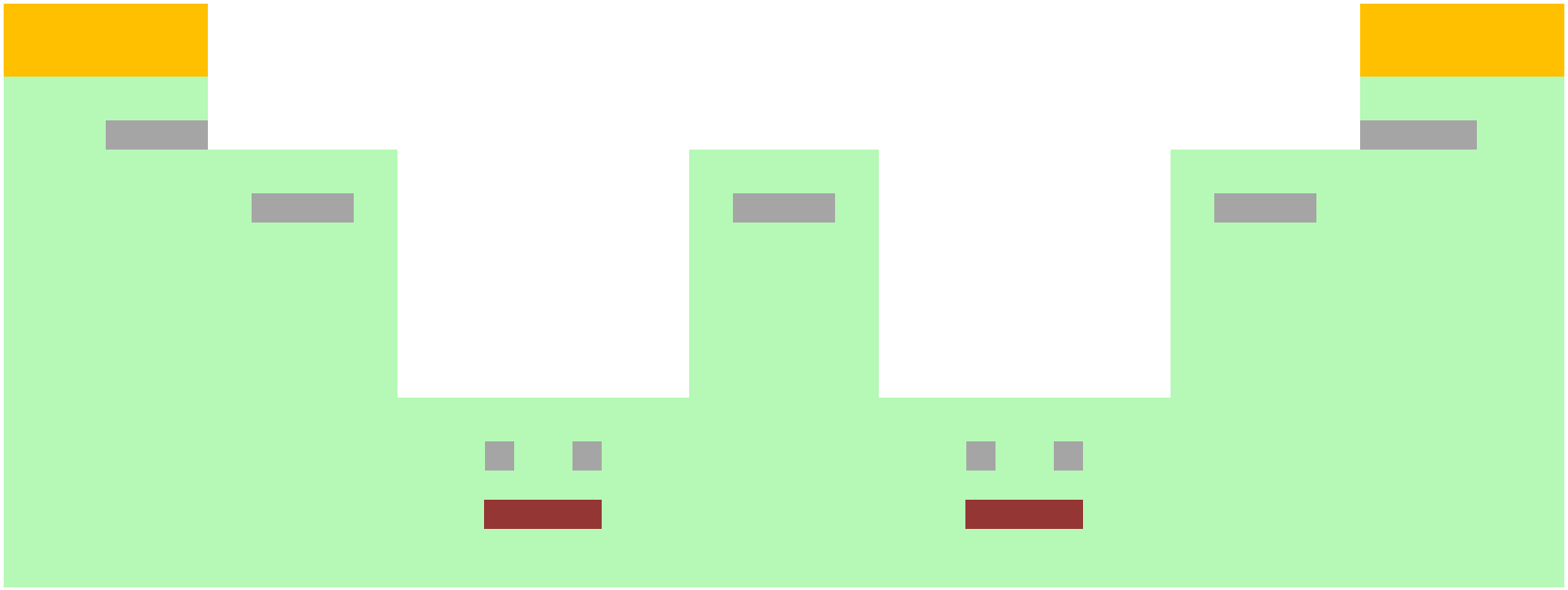
POST CMOS PROCESSING: PROTECT PADS



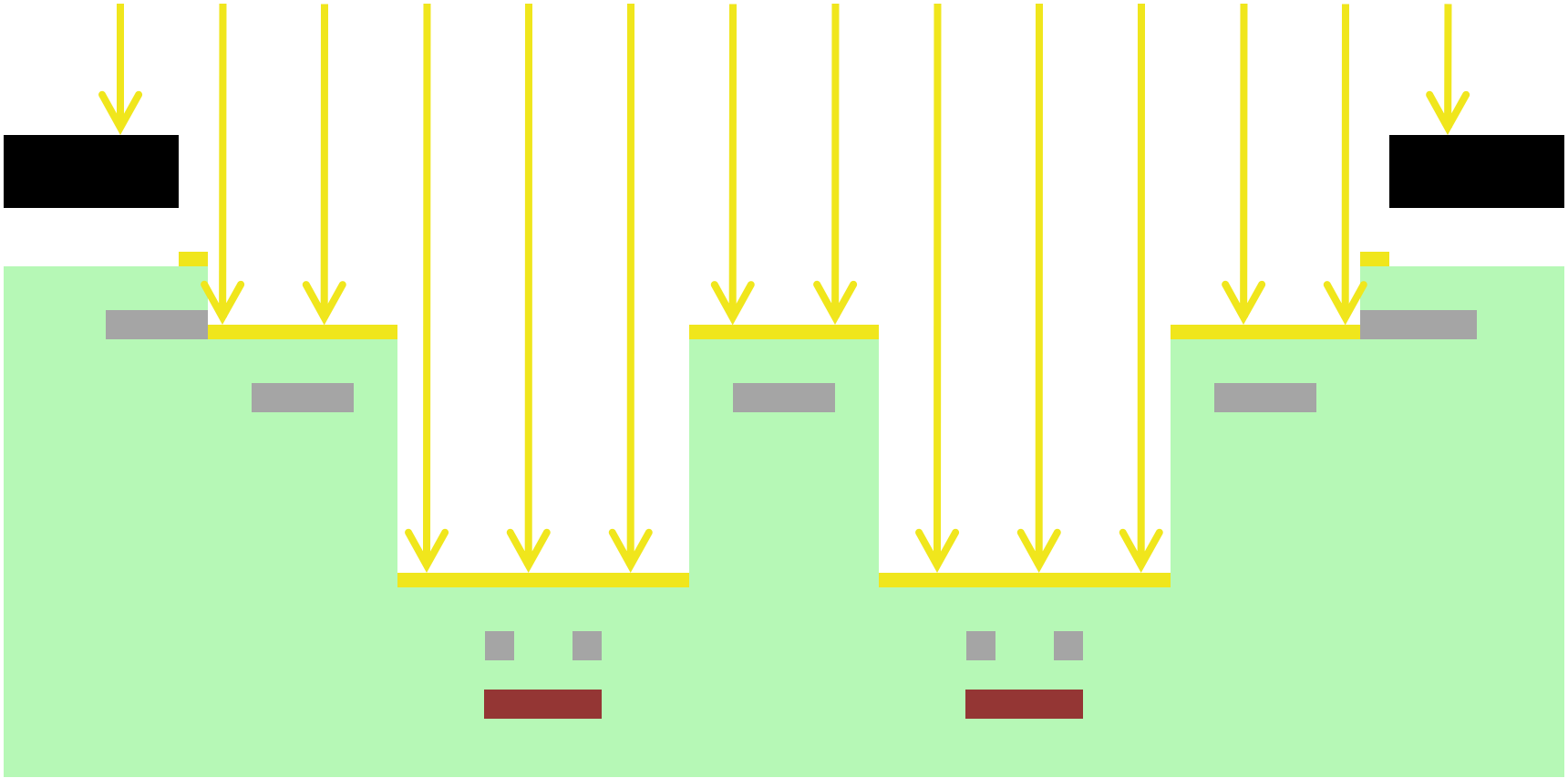
POST CMOS PROCESSING: ETCH



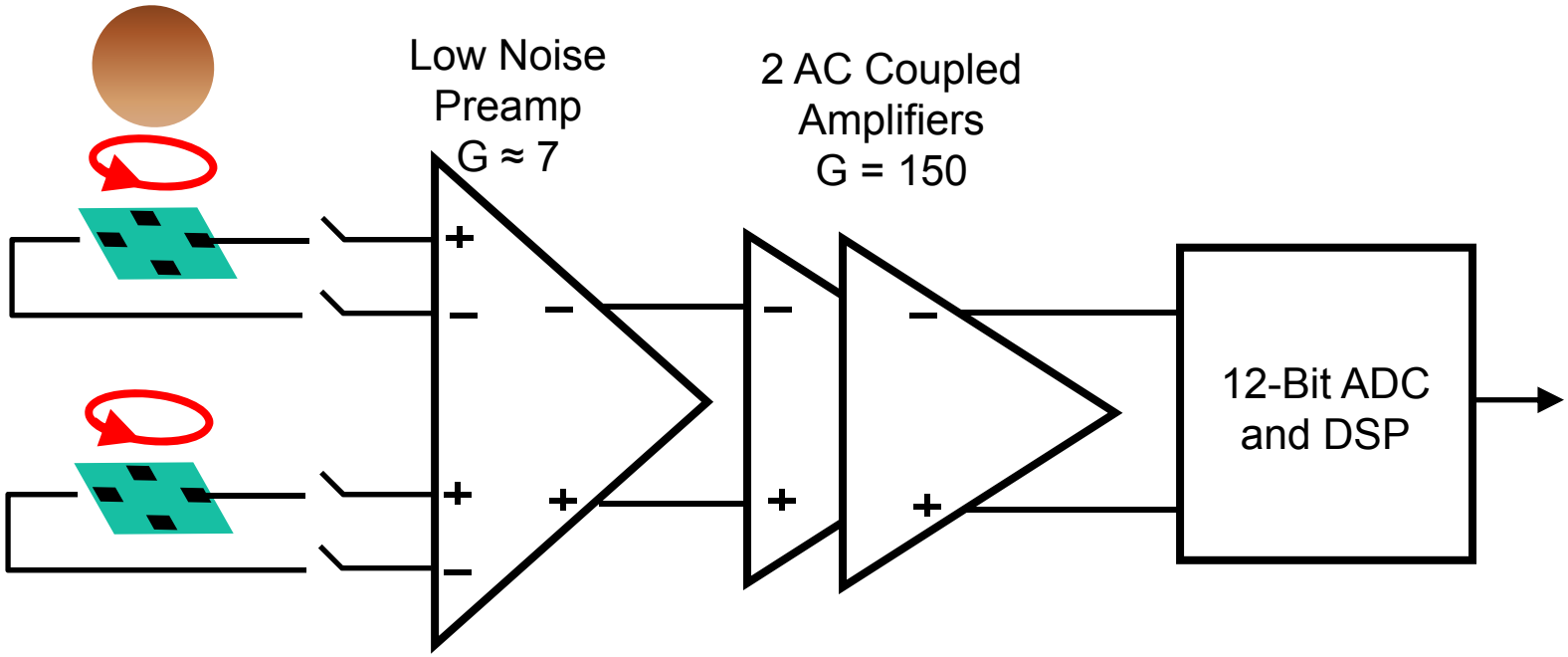
POST CMOS PROCESSING: REMOVE METAL



POST CMOS PROCESSING: GOLD COATING



Integrated Magnetic Bead Detection

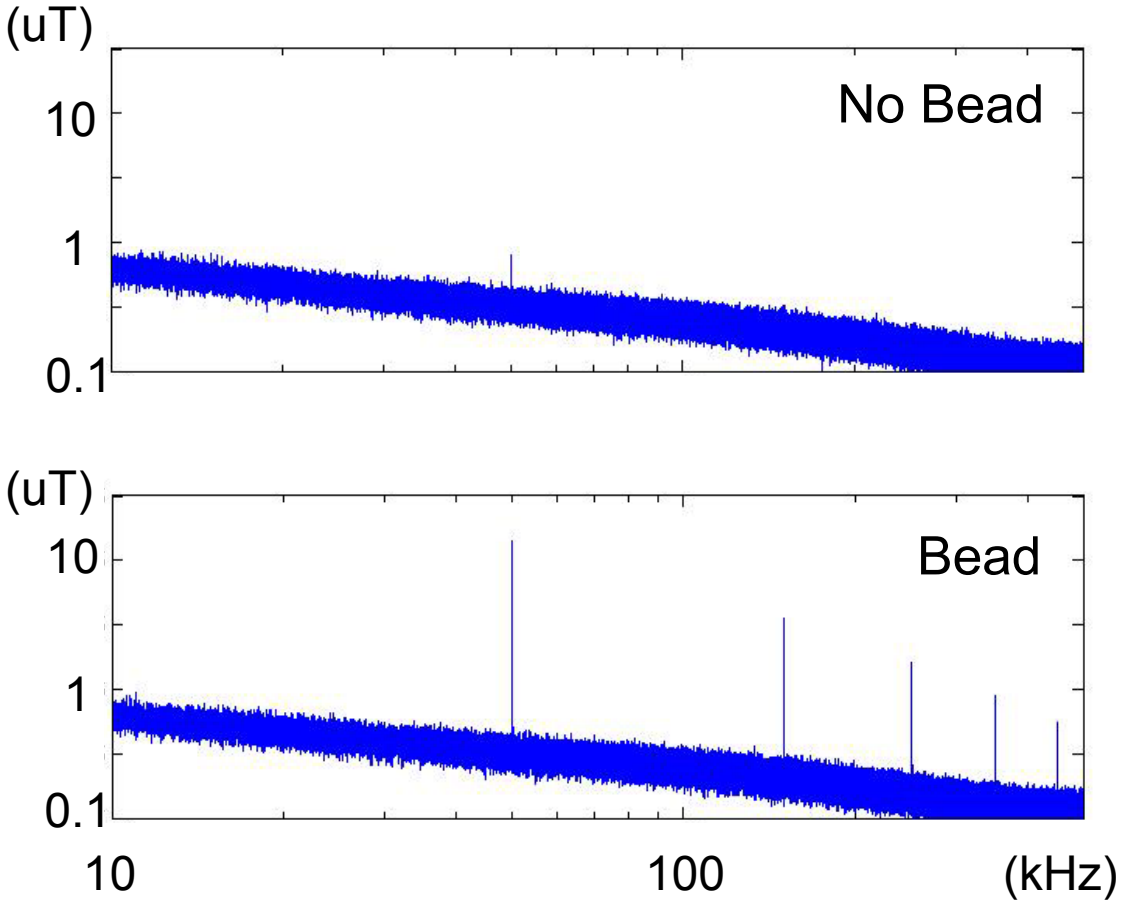


B_n= 300nT/√Hz

Matching < 5%, before auto-zeroing

Matching < 0.05%, after auto-zeroing

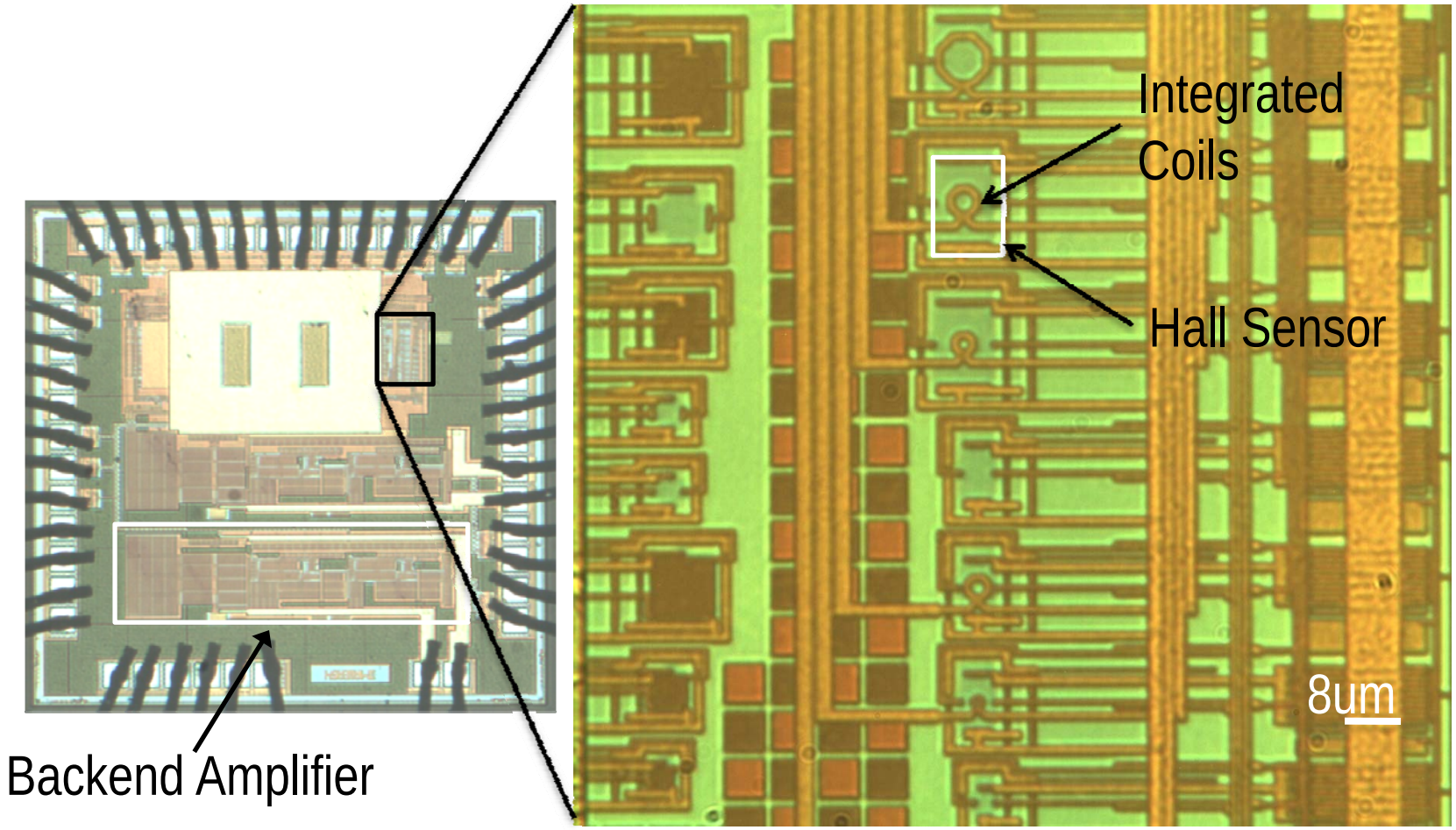
Integrated Magnetic Bead Detection



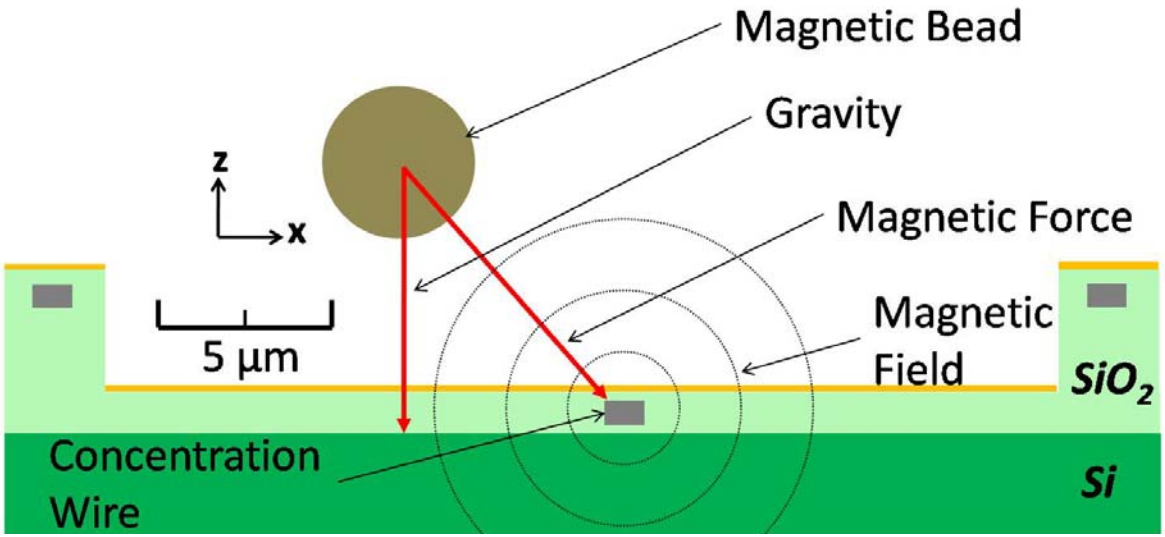
A single 2.8um magnetic bead was detected with 35dB of SNR for a 1Hz noise bandwidth

Florescu et al., “Fully integrated detection of single magnetic beads in complementary metal-oxide-semiconductor”, Journal of Applied Physics, Volume 103, Issue 4, pp. 046101-046101-3 (2008)

Integrated Magnetic Bead Detection



Integrated Magnetic Bead Concentration



$$F_{mag} = \frac{V_{bead}\chi_{bead}}{\mu_o}(\mathbf{B}_{\mathbf{wash}} \cdot \nabla)\mathbf{B}_{\mathbf{wash}}$$

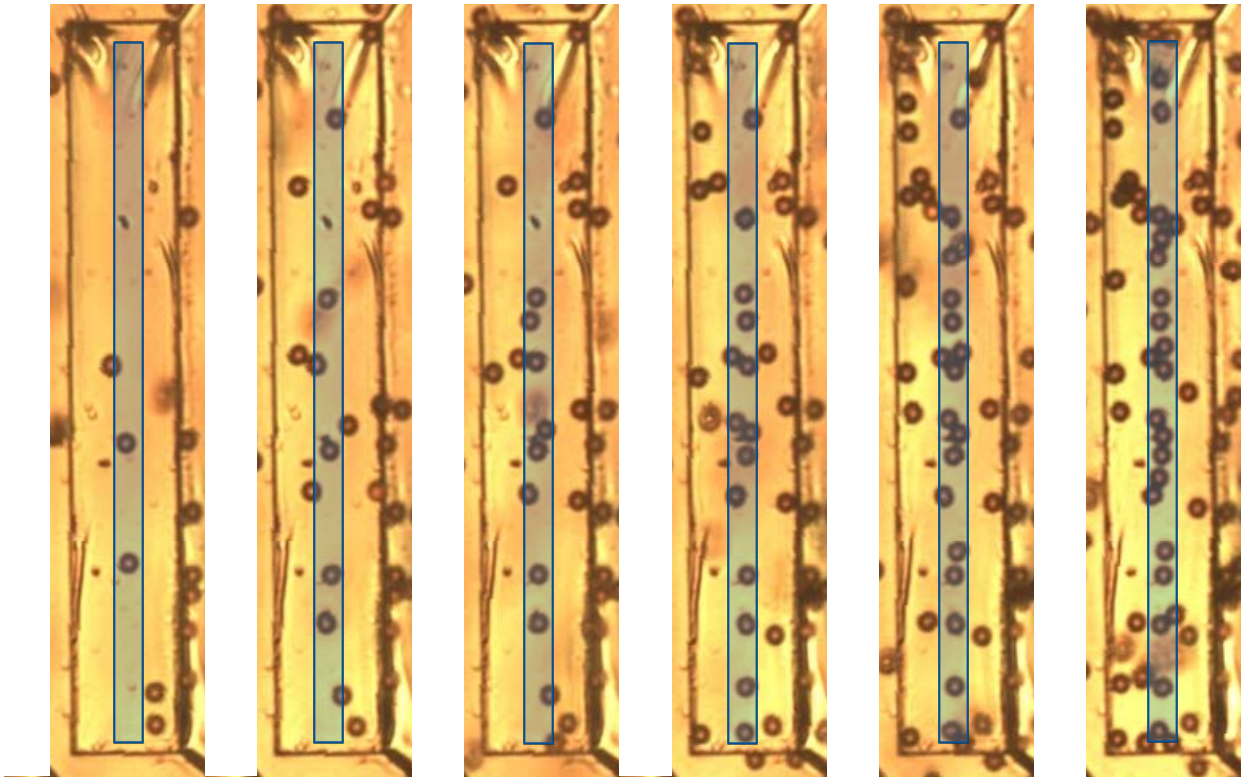
$$F_{mag} = \frac{\mu_o \cdot \chi_{bead} \cdot r_{bead} \cdot I_{wash}^{\ 2}}{3\pi x_{bead}^{\ 3}}$$

Integrated Magnetic Bead Concentration

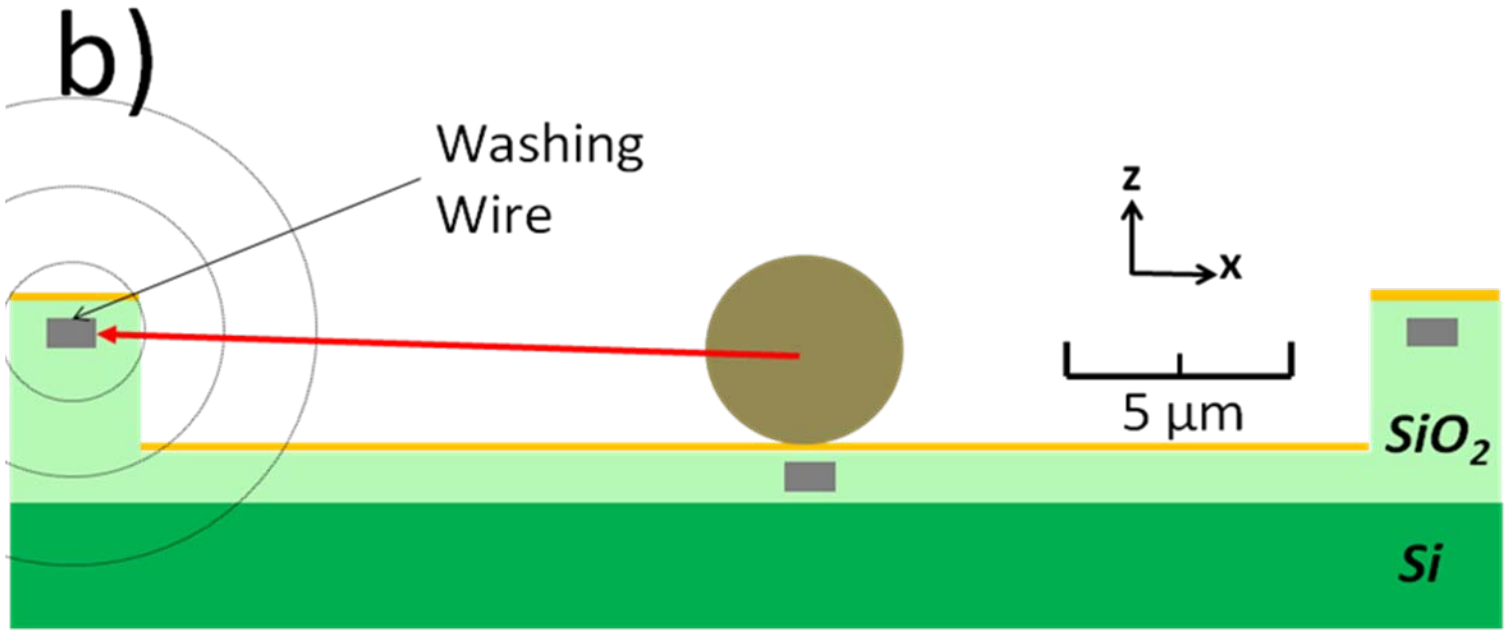
$I_{concentrate}$ = 2mA

F_{mag} = 0.2pN
from 4um away

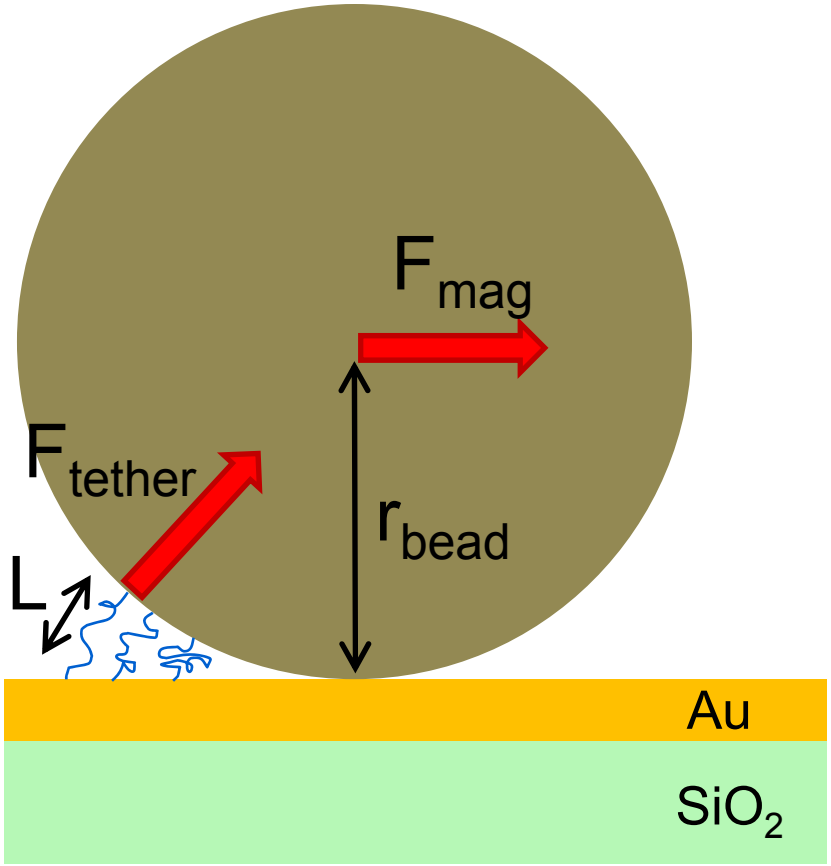
60% of beads land in center of trench



Integrated Magnetic Bead Washing



Integrated Magnetic Bead Washing



$$F_{tether} = F_{mag}\sqrt{\frac{r_{bead}}{2L}}$$

L = 20nm

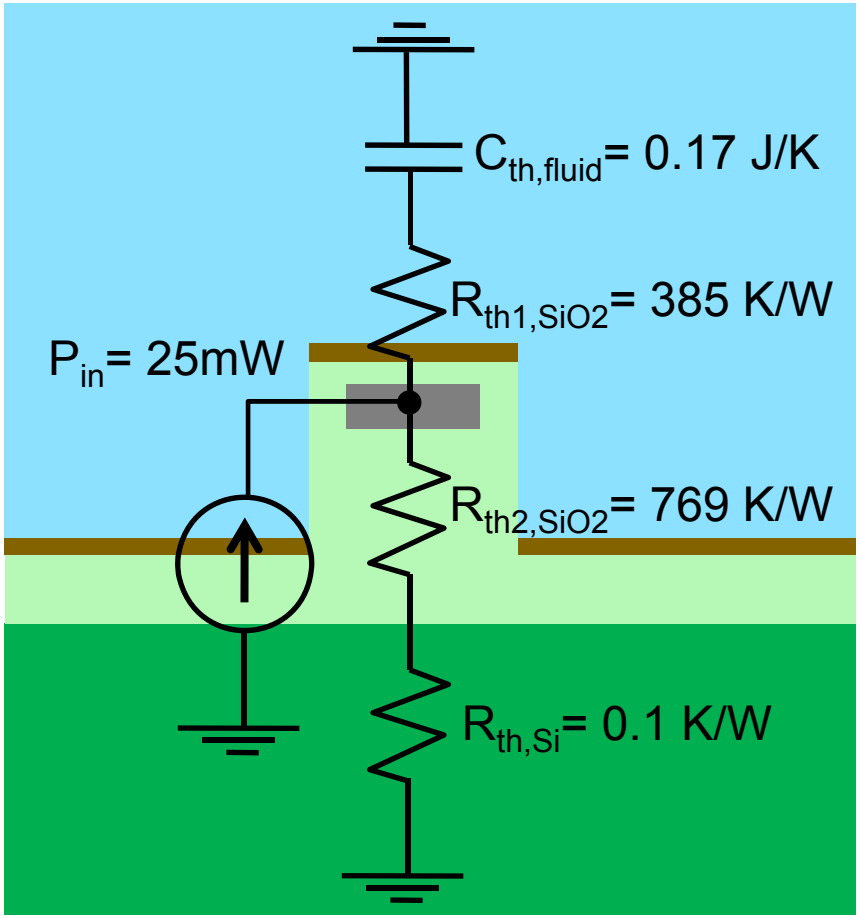
r_{bead} = 2.5μm

Amplification = 8

I_{wash} = 50mA

F_{tether} = 9pN from 18μm away

Integrated Magnetic Bead Washing



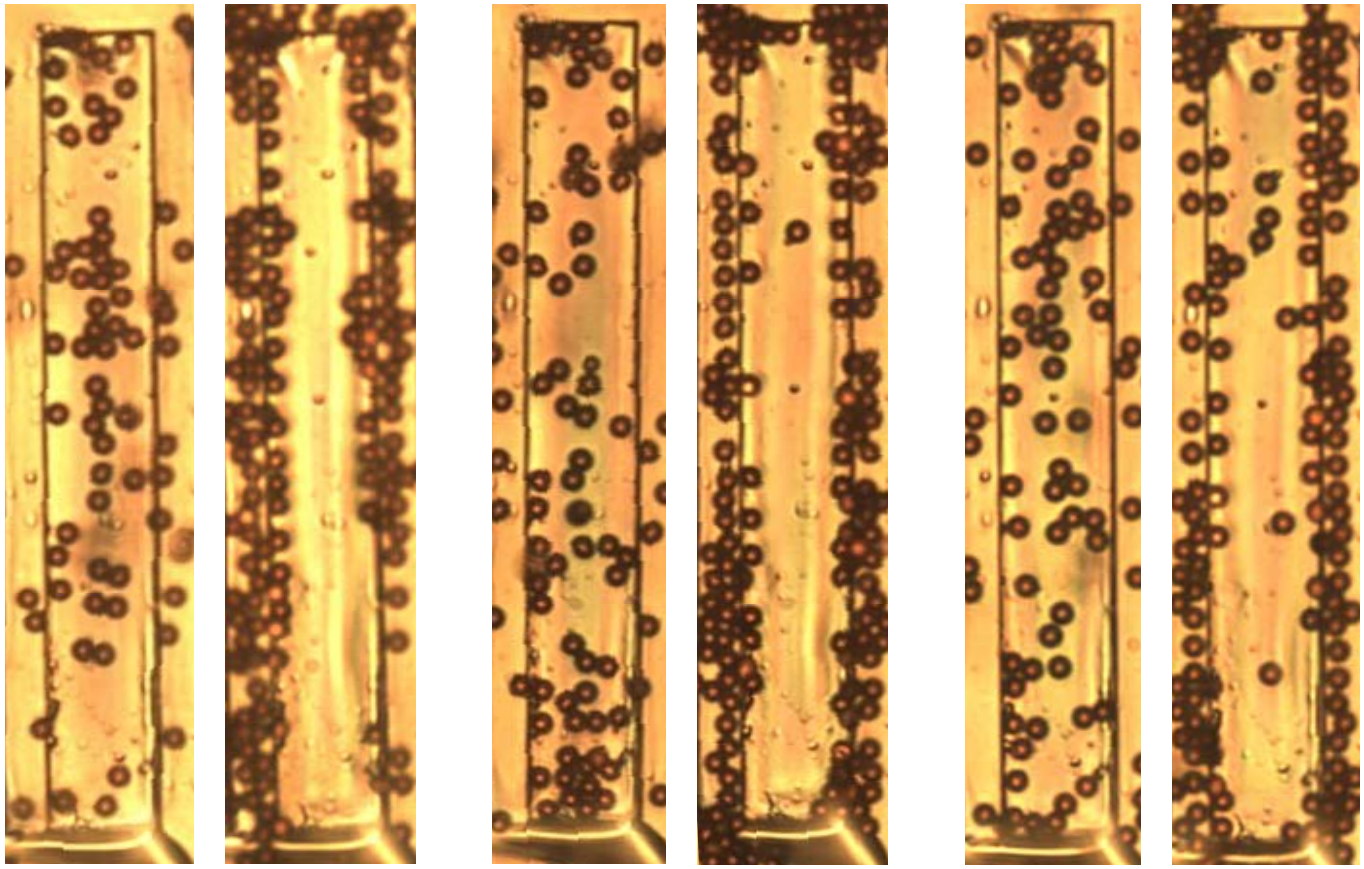
$$\Delta T = T\left(1 - e^{-t/\tau}\right)$$

$$T = P_{in}(R_{th2,SiO2} + R_{th,Si})$$

$$\tau = (R_{th2,SiO2} + R_{th2,SiO2} + R_{th,Si})C_{th,fluid}$$

ΔT = 2.7°C after 30 seconds of washing

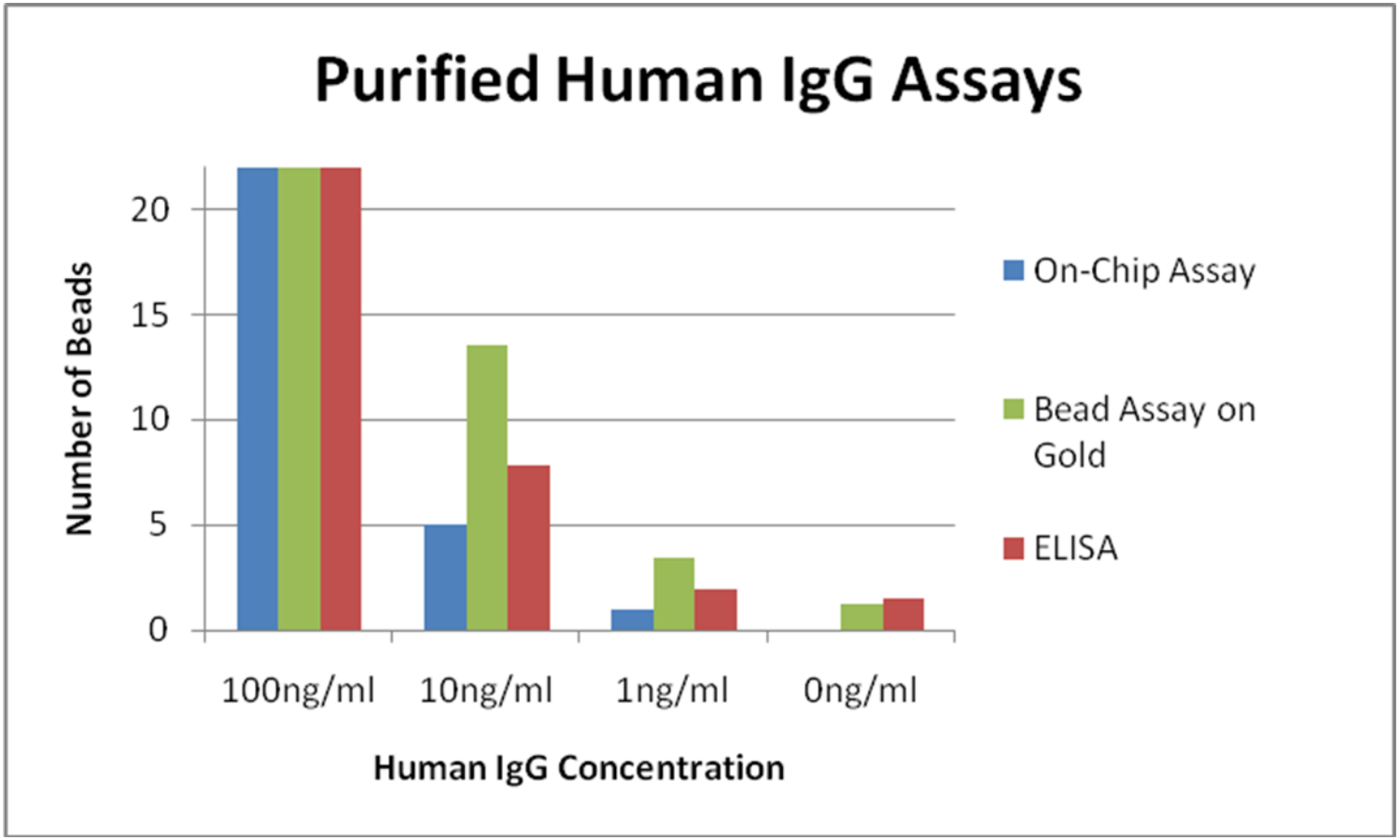
Integrated Magnetic Bead Washing



BW AW BW AW BW AW

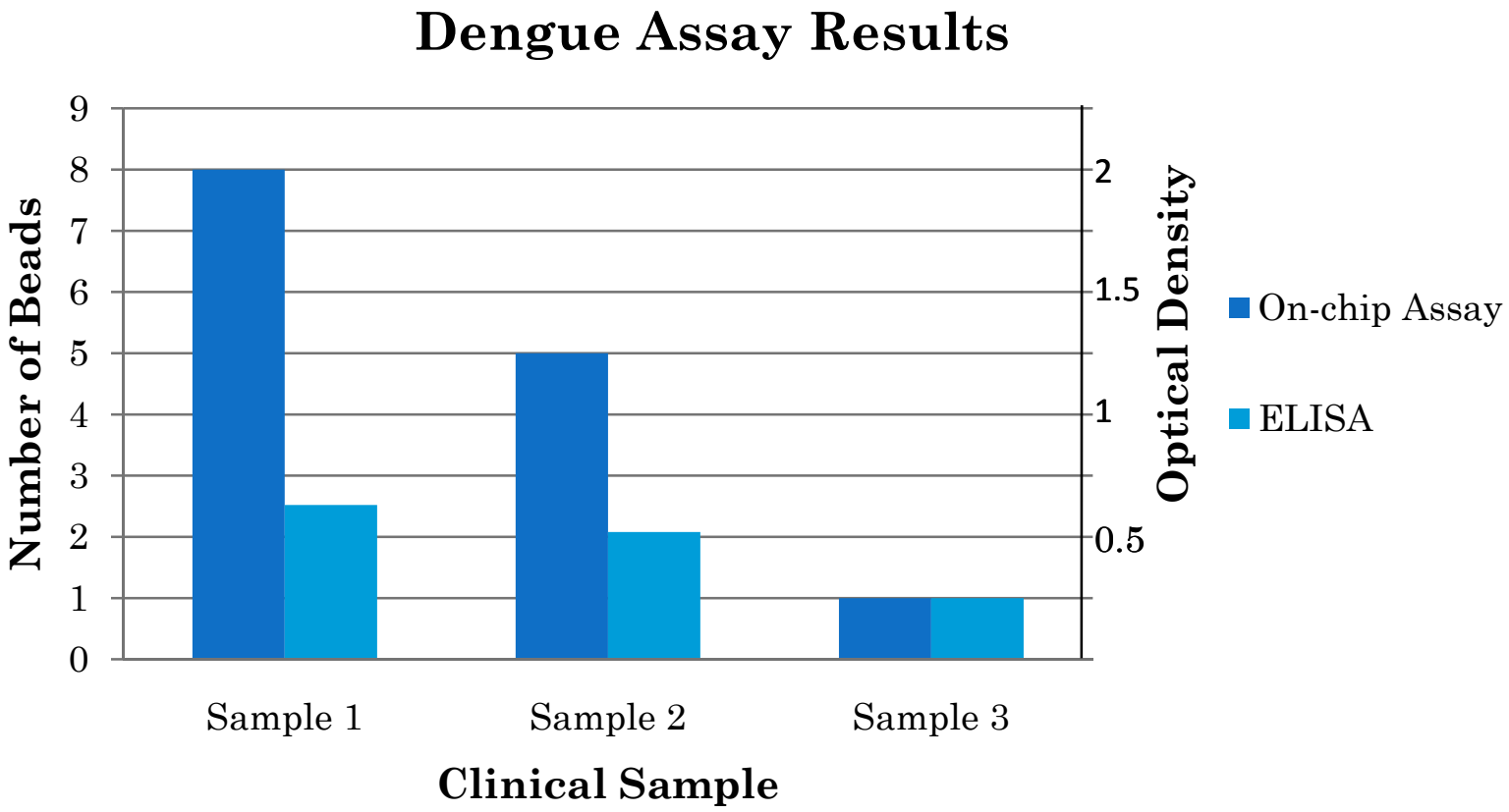
0ng/ml 1ng/ml 10ng/ml

Integrated Magnetic Bead Washing

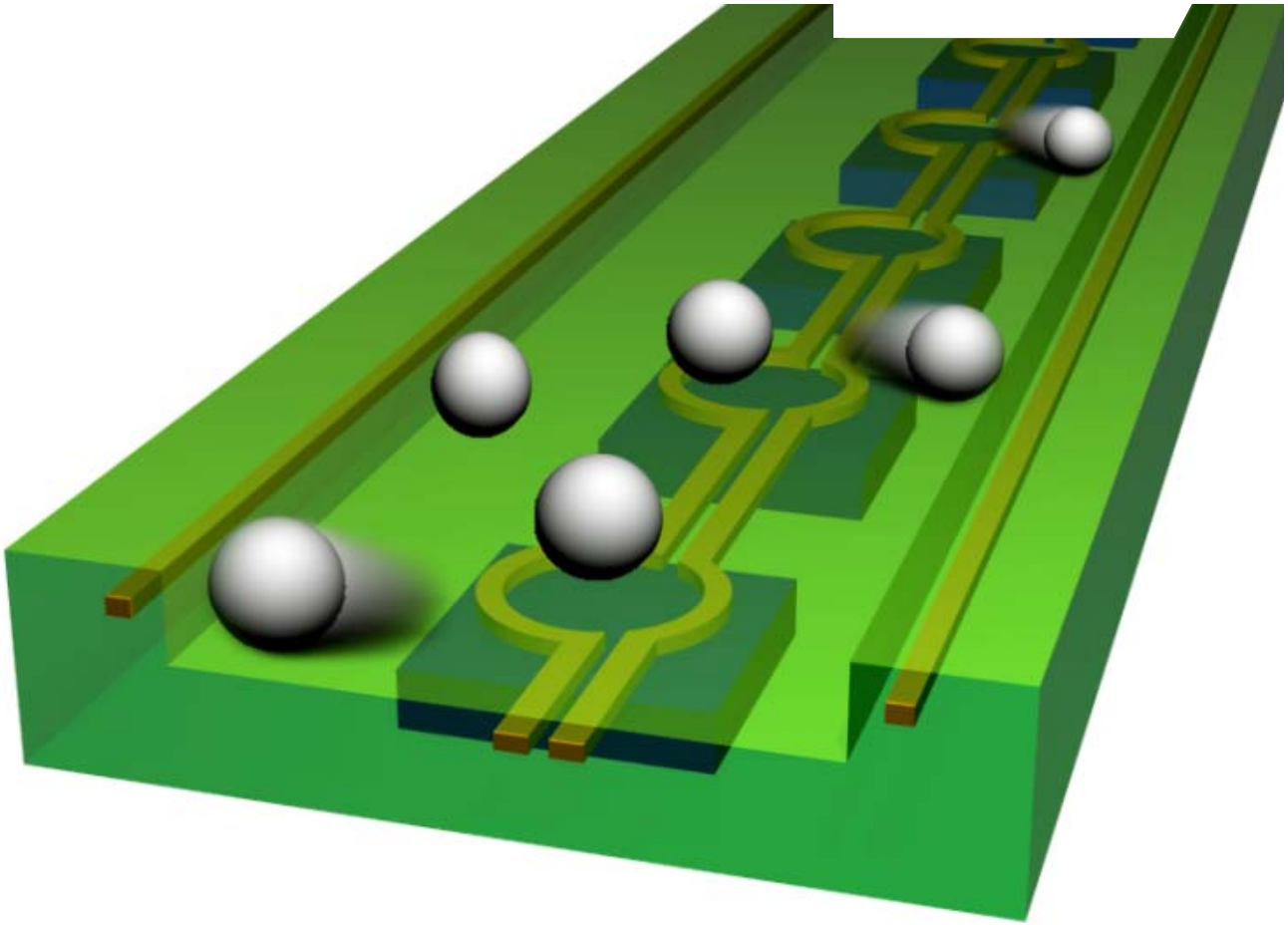


Florescu et al., “On-chip magnetic washing of super-paramagnetic beads for integrated assay applications”, Journal of Applied Physics, In Press (2009)

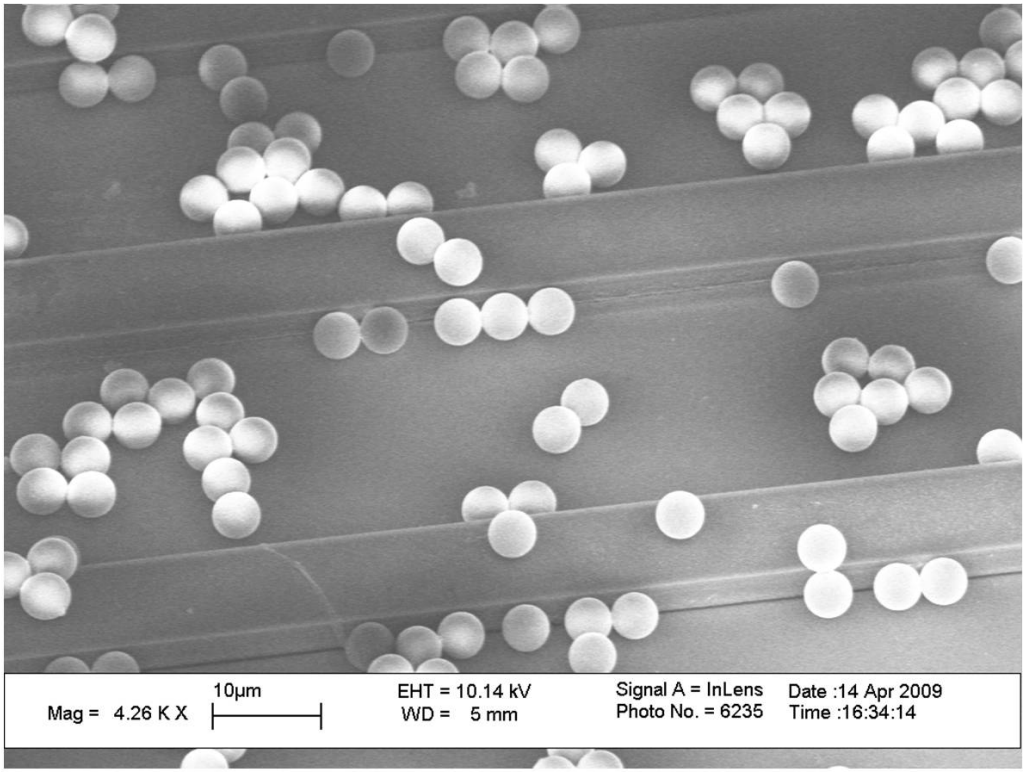
INTEGRATED MAGNETIC BEAD WASHING



Integrated Assay Platform



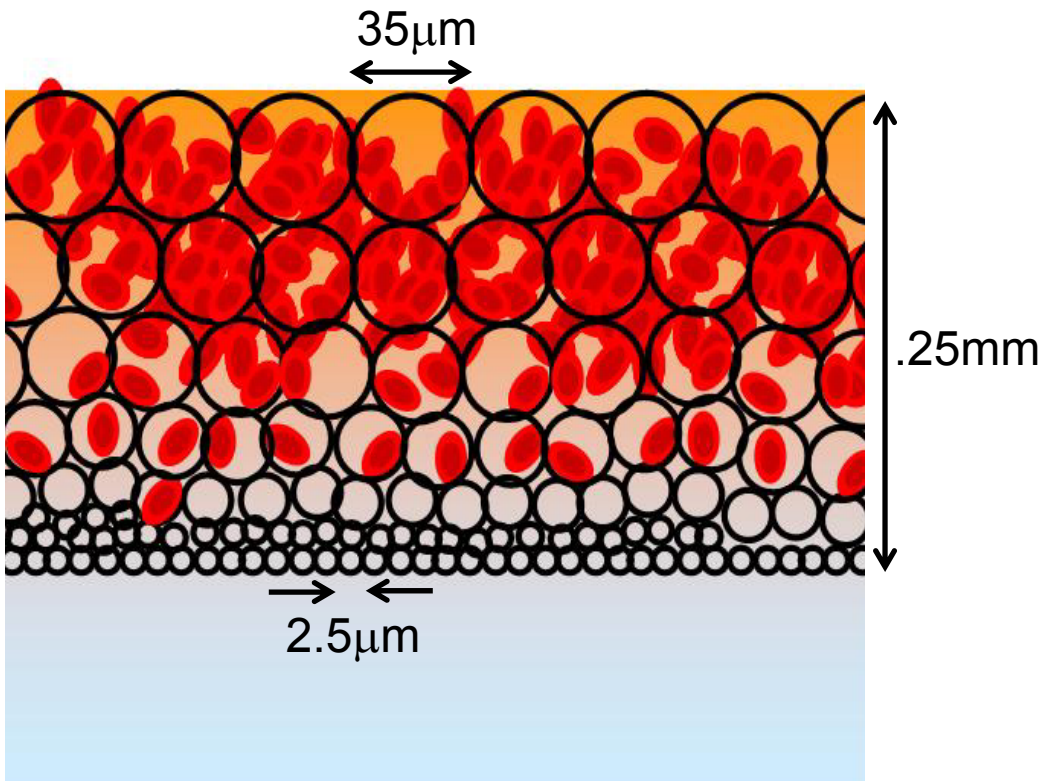
Integrated Assay Platform



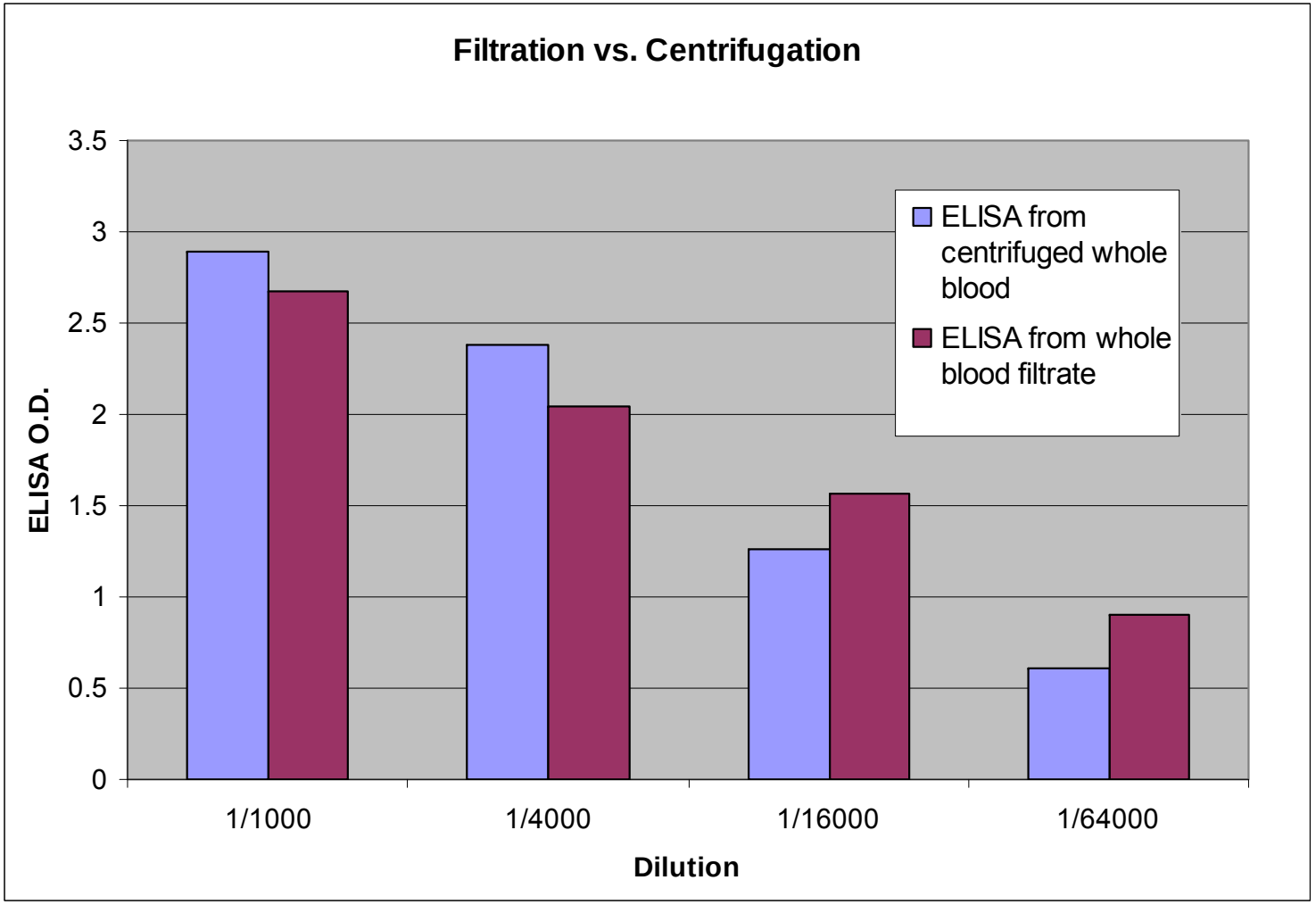
Membrane Filtration

Membrane Filtration

- Hydrophilic polymeric membrane
  - Combination of PVP/PES
  - No hemolysis
  - No non-specific protein binding
- Graduated pore size
  - 35μm – 2.5μm
  - ~250μm thick



FILTRATION VS. CENTRIFUGATION



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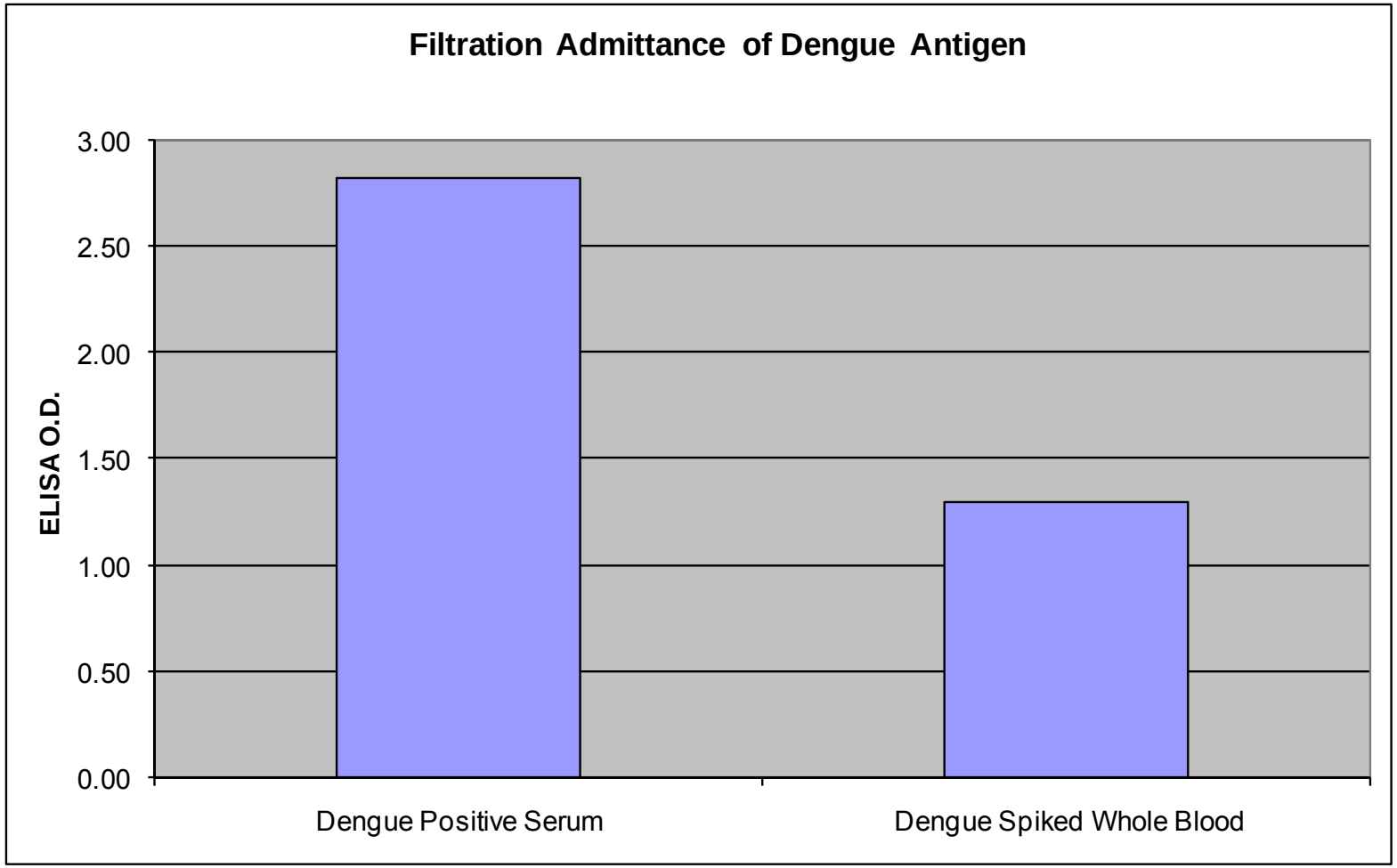
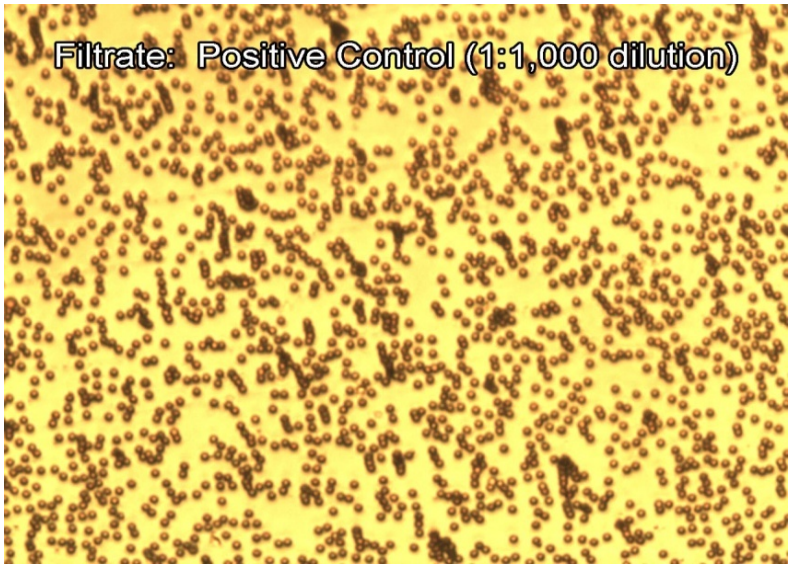
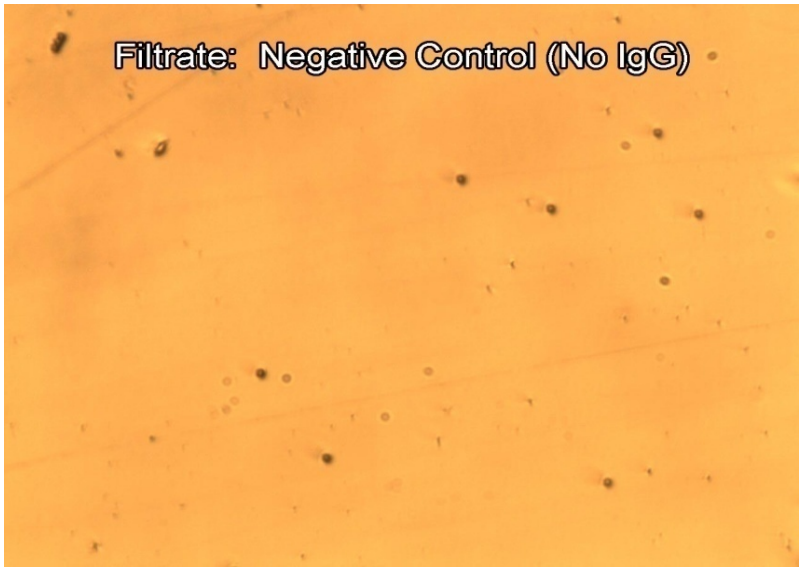
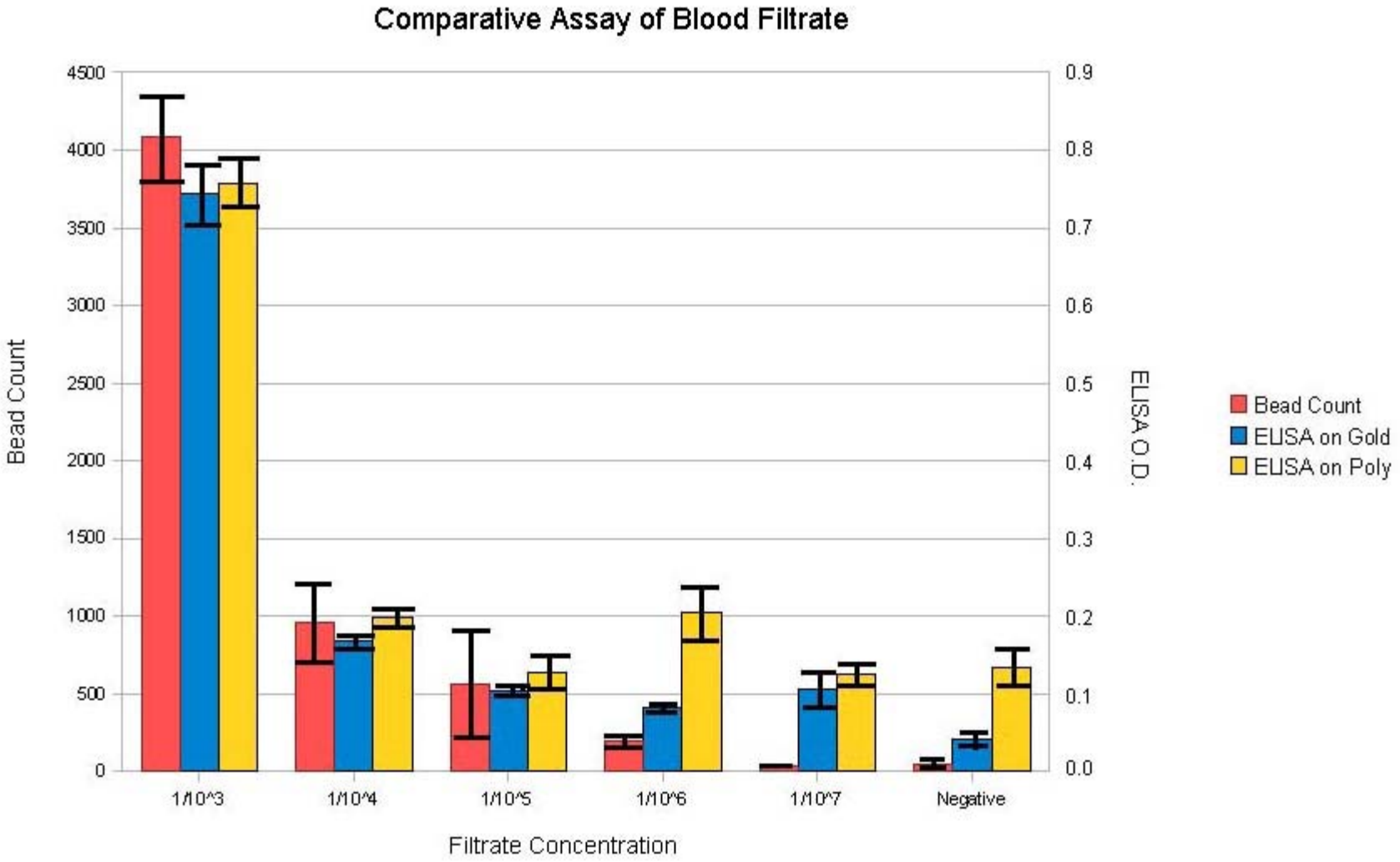


Bead Assays on Whole Blood Filtrate



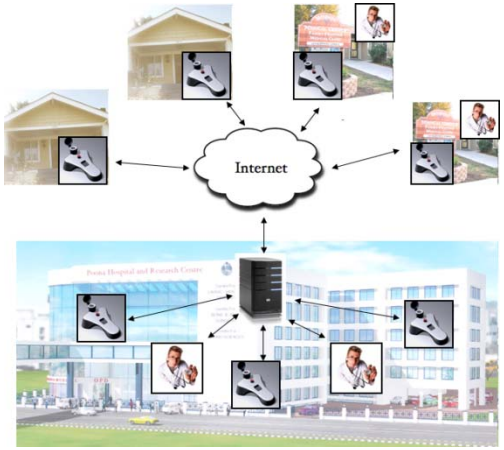


BEAD ASSAYS ON WHOLE BLOOD FILTRATE



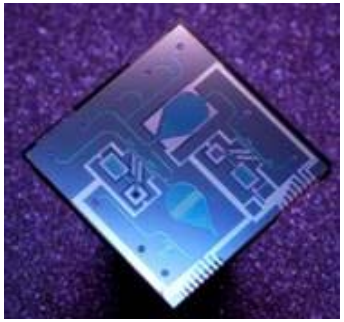
L NCE P

Wireless Integration

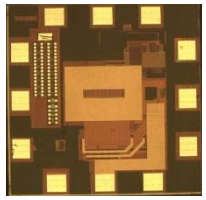


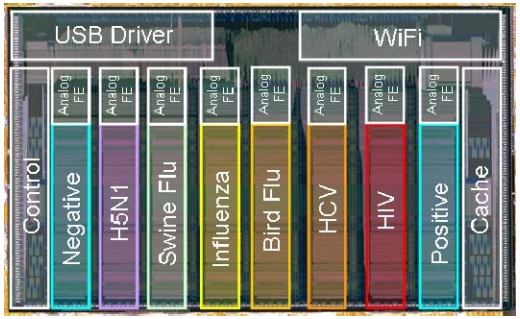
Epidemic Monitoring

POC Diagnostics

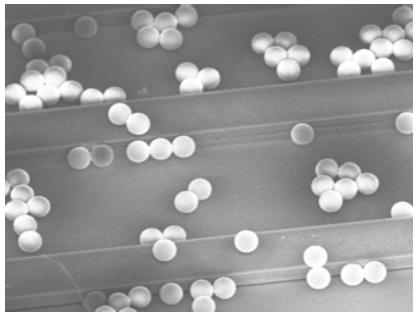


POC PCR

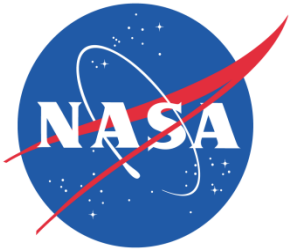




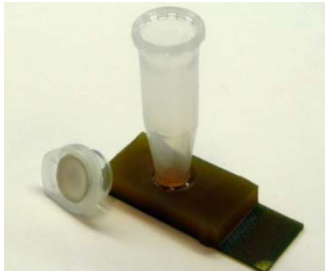
Multiplexed Assays



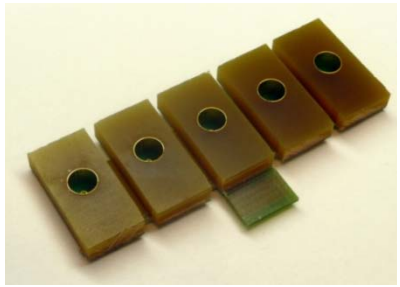
Proteomics/Genomics



Mars Trip Dx



Developing World Dx



Low Cost Assay Kits

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