# Detecting and Manipulating Magnetic Nanoparticles: Design of a Magnetic Flow Cytometer

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- General description of Cell Counter (Cytometer)
- Lab-on-a-chip environment / microfluidics
- Manipulation and detection of magnetic objects in microfluidic channels – proof of principles
- Fabrication design – wide channels, small sensor

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www.nve.com/~markt/biomagnetics

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# Motivation for Current R&D Efforts

**Military / Homeland Defense** wants bioassays that are:

- Rugged
- Lightweight / handheld
- Cheap
- Rapid
- Highly sensitive and specific, multi-functional, fool-proof
- Readers, sensors, and fluidics must be mass-manufacturable.

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# Flow Cytometer working definition

- Counts cells in a continuously flowing system
- Usually needs to discriminate between various cell types (e.g. all healthy cells vs. cancerous cells)

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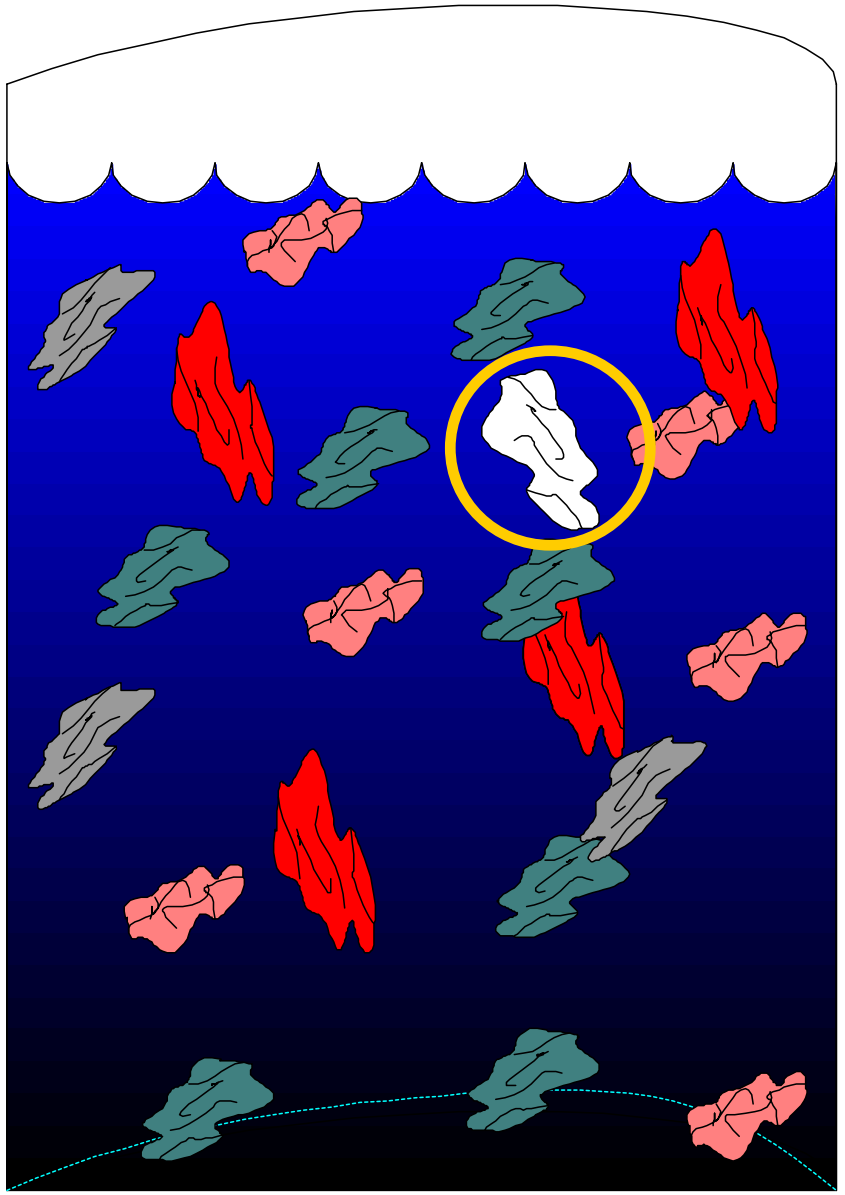
# Prototypical Example: cancer cell isolation

- Want to grab only cancerous cells, count them, and store them for further analysis
- Could be only 1 : $10^9$
- May not be distinguishable by size or color



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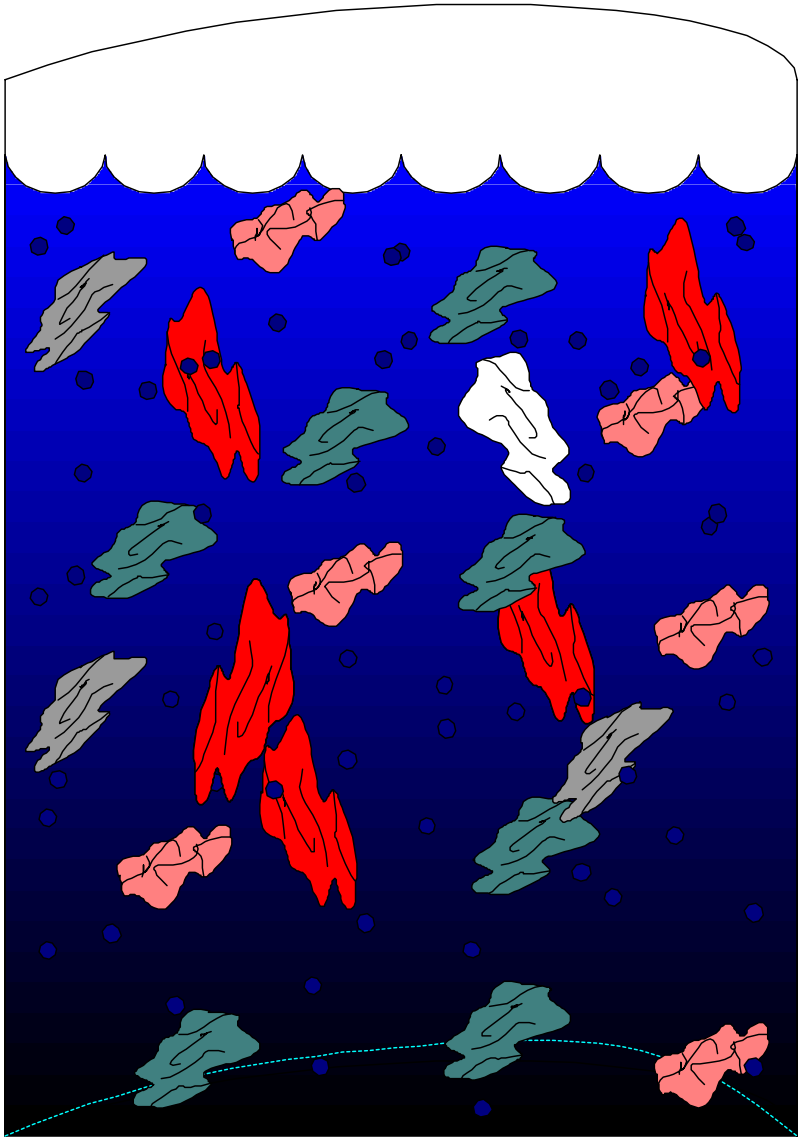
# Magnetic capture is a common approach

- Add special magnetic particles to container



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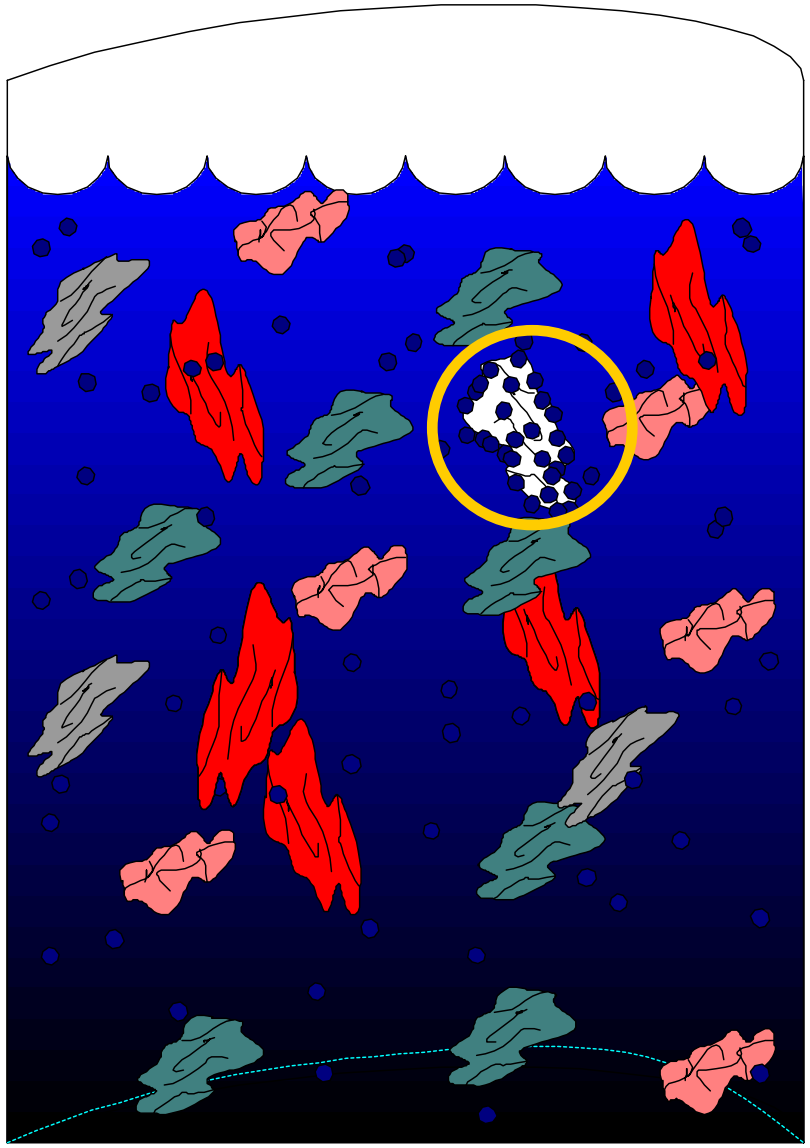
# Magnetic capture is a common approach

- Add special magnetic particles to container
- Allow specific binding of labels to cell



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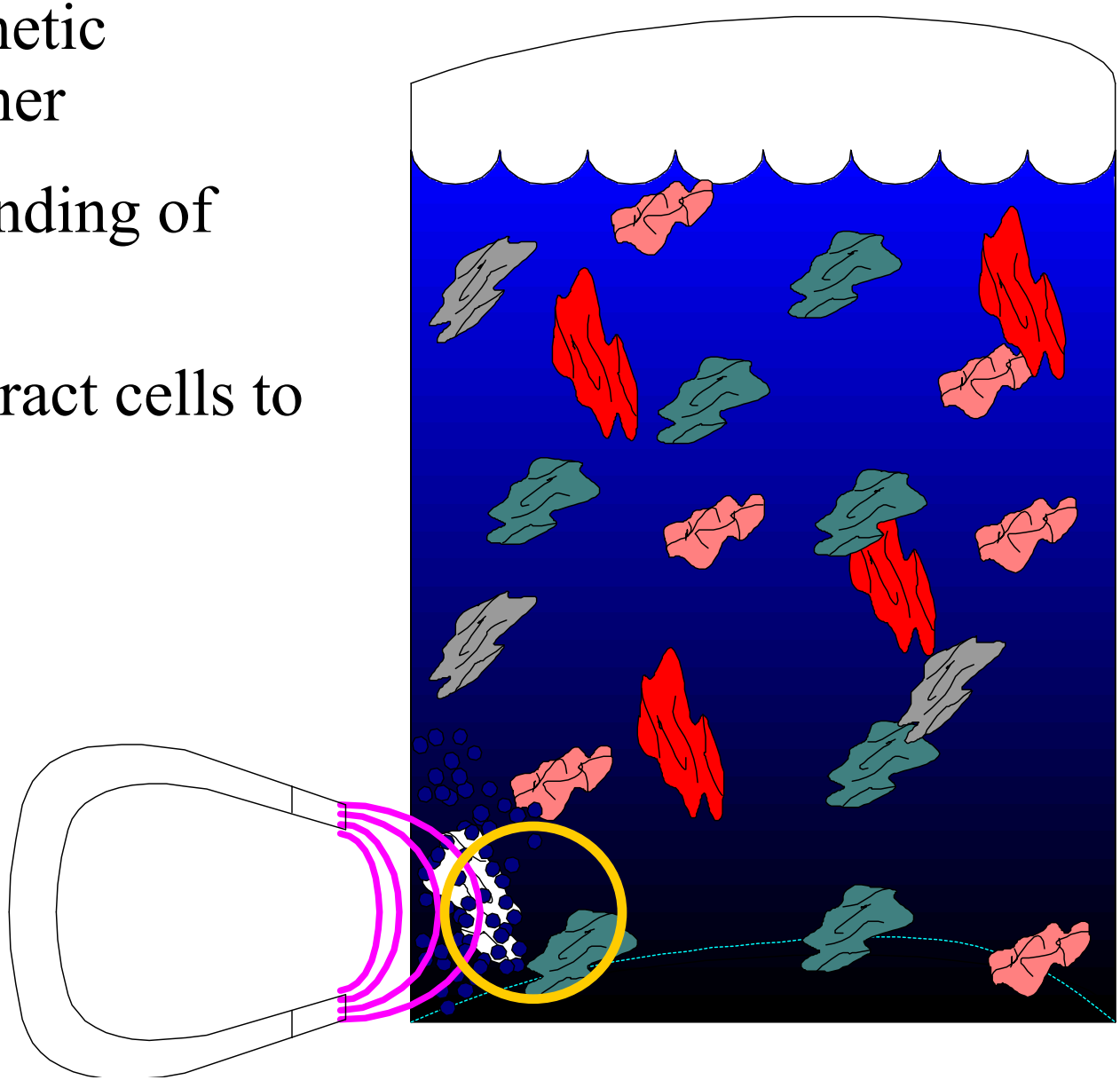
# Magnetic capture is a common approach

- Add special magnetic particles to container
- Allow specific binding of labels to cell
- Use magnet to attract cells to corner



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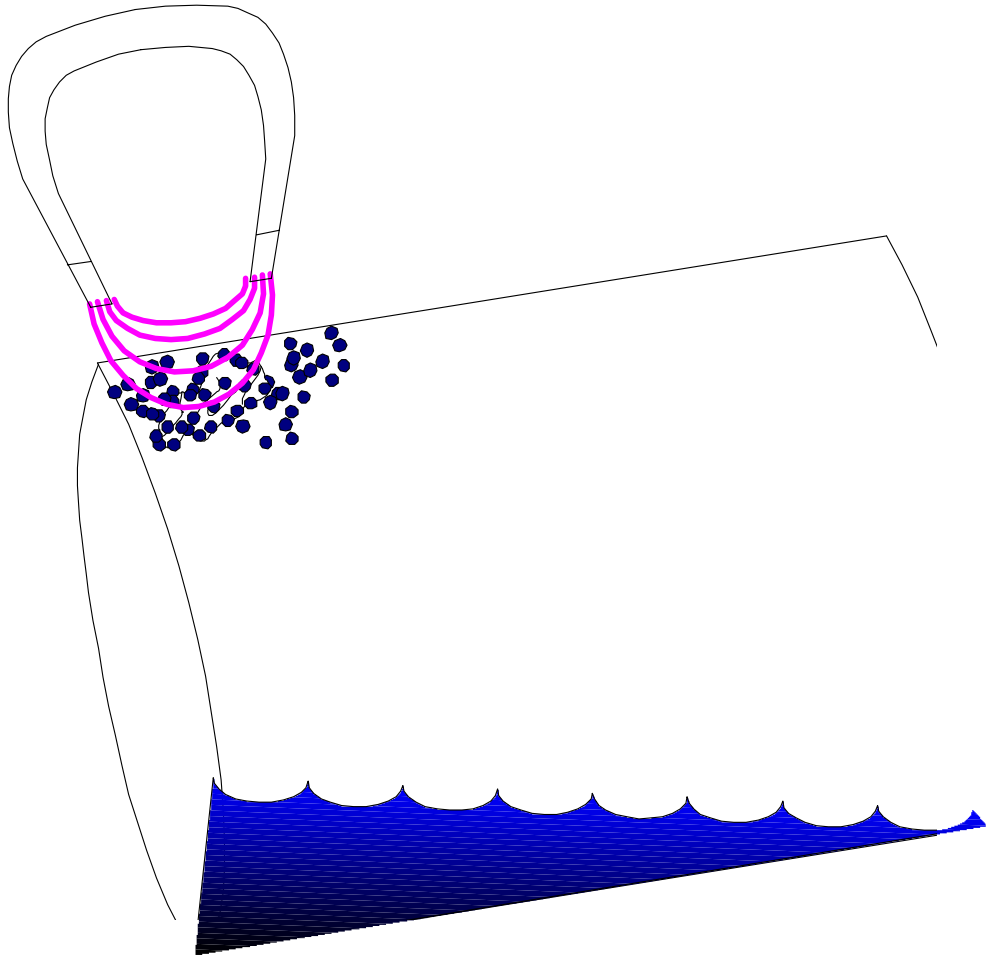
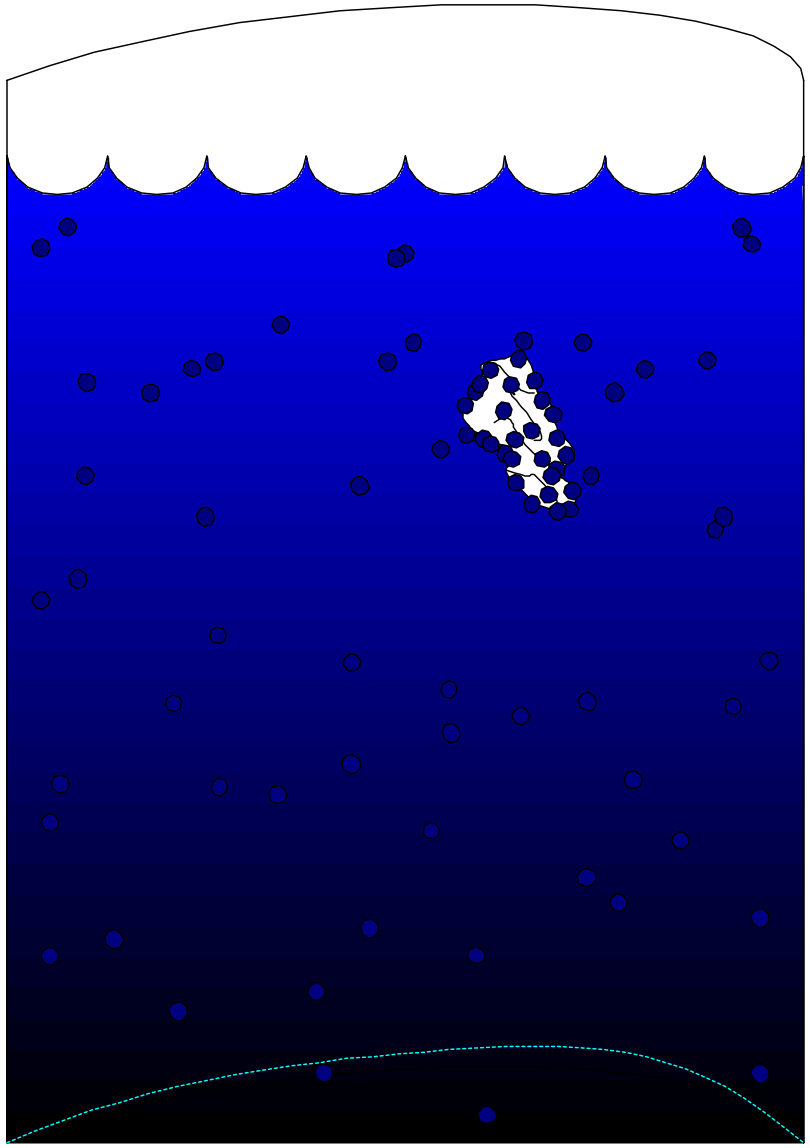
# Magnetic capture is a common approach

- Add special magnetic particles to container
- Allow specific binding of labels to cell
- Use magnet to attract cells to corner
- Dump out waste



# Magnetic capture is a common approach

- Add special magnetic particles to container
- Allow specific binding of labels to cell
- Use magnet to attract cells to corner
- Dump out waste
- Add water
- Repeat as needed



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# Laboratory-on-a-Chip

- Shrink clinical or diagnostic laboratory setup onto a Si-type chip
- MEMS and microfluidics
- Not yet a commercial reality

# Detection of magnetic objects in flow

- Giant Magnetoresistive (GMR) detector
- Microfluidic flow channel passes directly over GMR detector
- Present channel is too small

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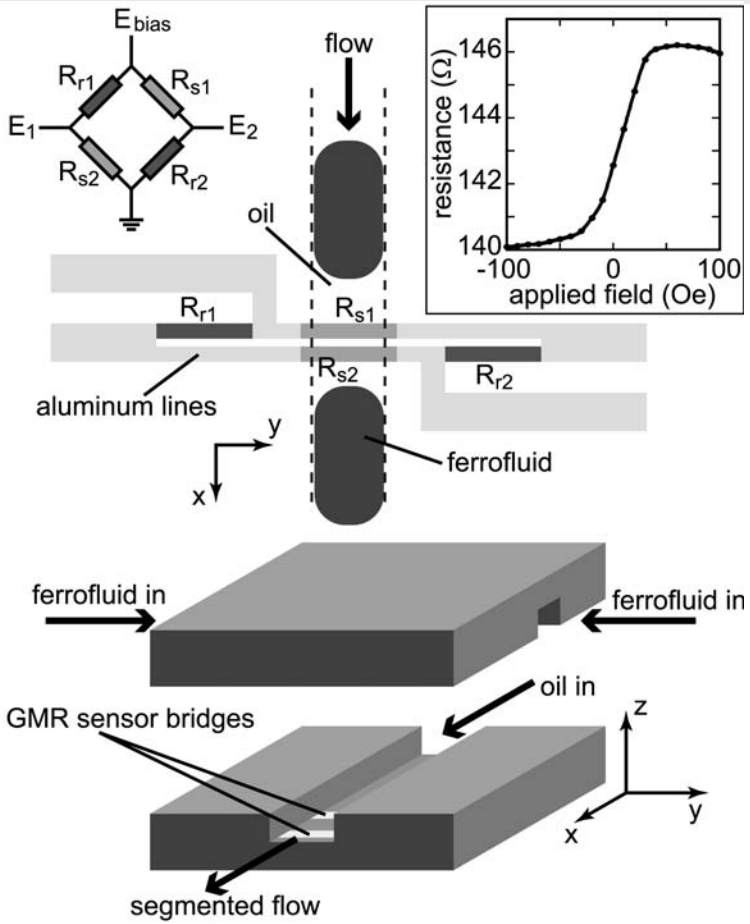
# GMR Sensing of Magnetic Picodroplets




- Picoliter-sized droplets of ferrofluid formed at a fluidic junction

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Plug dimensions:
13 μm wide 18 μm deep 85 μm long

FerroTec 307 10nm ferrite particles
~1% by volume

- GMR sensitivity 0.07%/Oe
- Wheatstone bridge configuration


Pekas et al., Appl. Phys. Lett., 85, (2004)

T. Thorsen, R. W. Roberts, F. H. Arnold, and S. R. Quake, Phys. Rev. Lett., 86, 4163 (2001)

H. Song, J. D. Tice, and R. F. Ismagilov, Angew. Chem. Int. Ed. 42 (7), 768 (2003)


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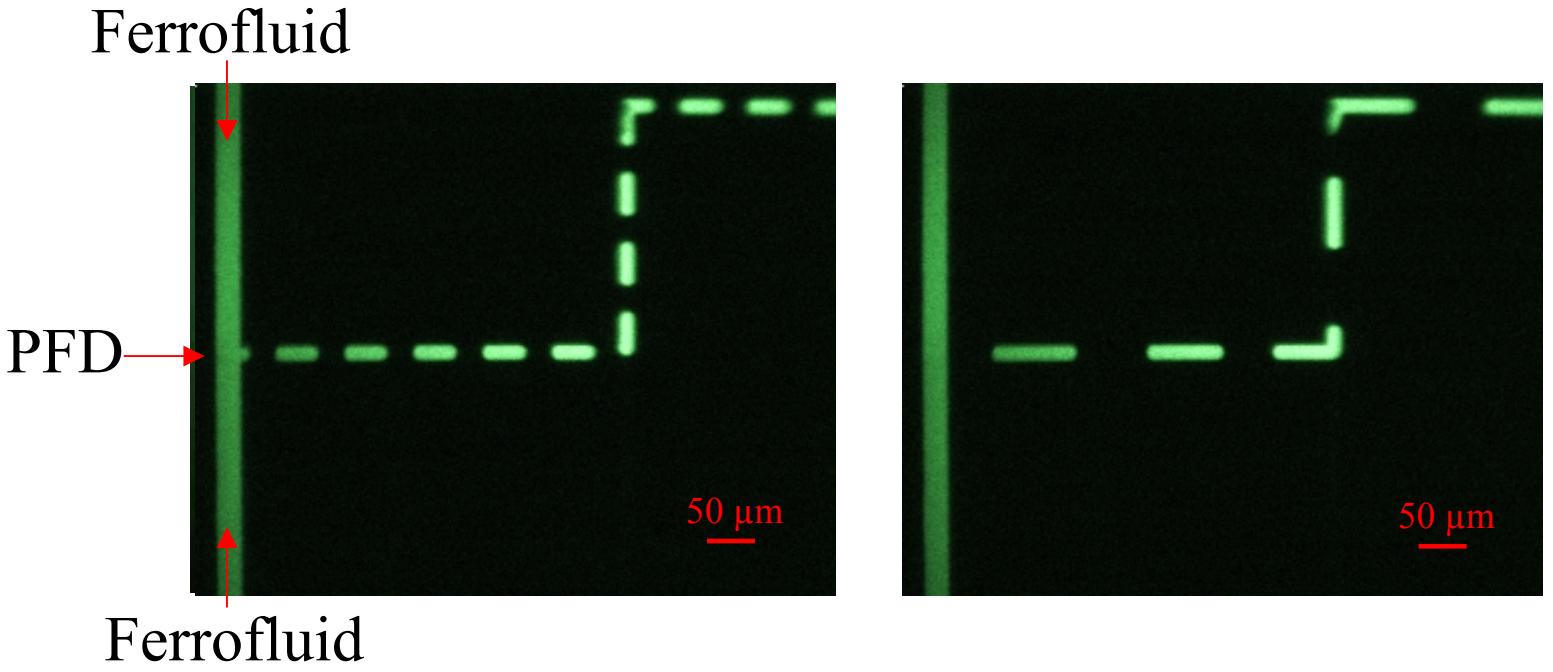
# Ferrofluid Plug Formation




- Flow rate 1.0 µL/min
- Plugs formed at approx. 500 Hz

- Flow rate 0.2 µL/min
- Plugs formed at approx. 50 Hz

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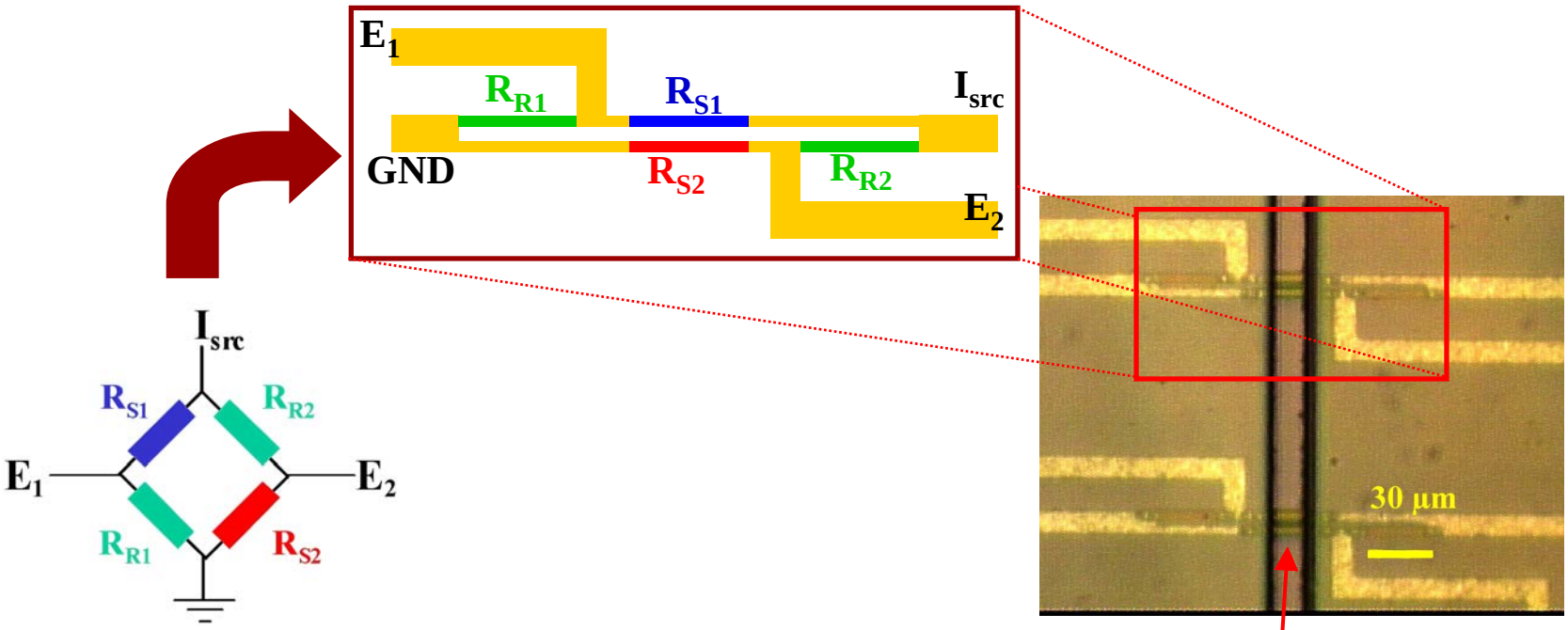
# GMR Sensor Architecture

•Two reference and two sensing GMRs configured as a Wheatstone bridge




•Channel passes over sensing GMRs

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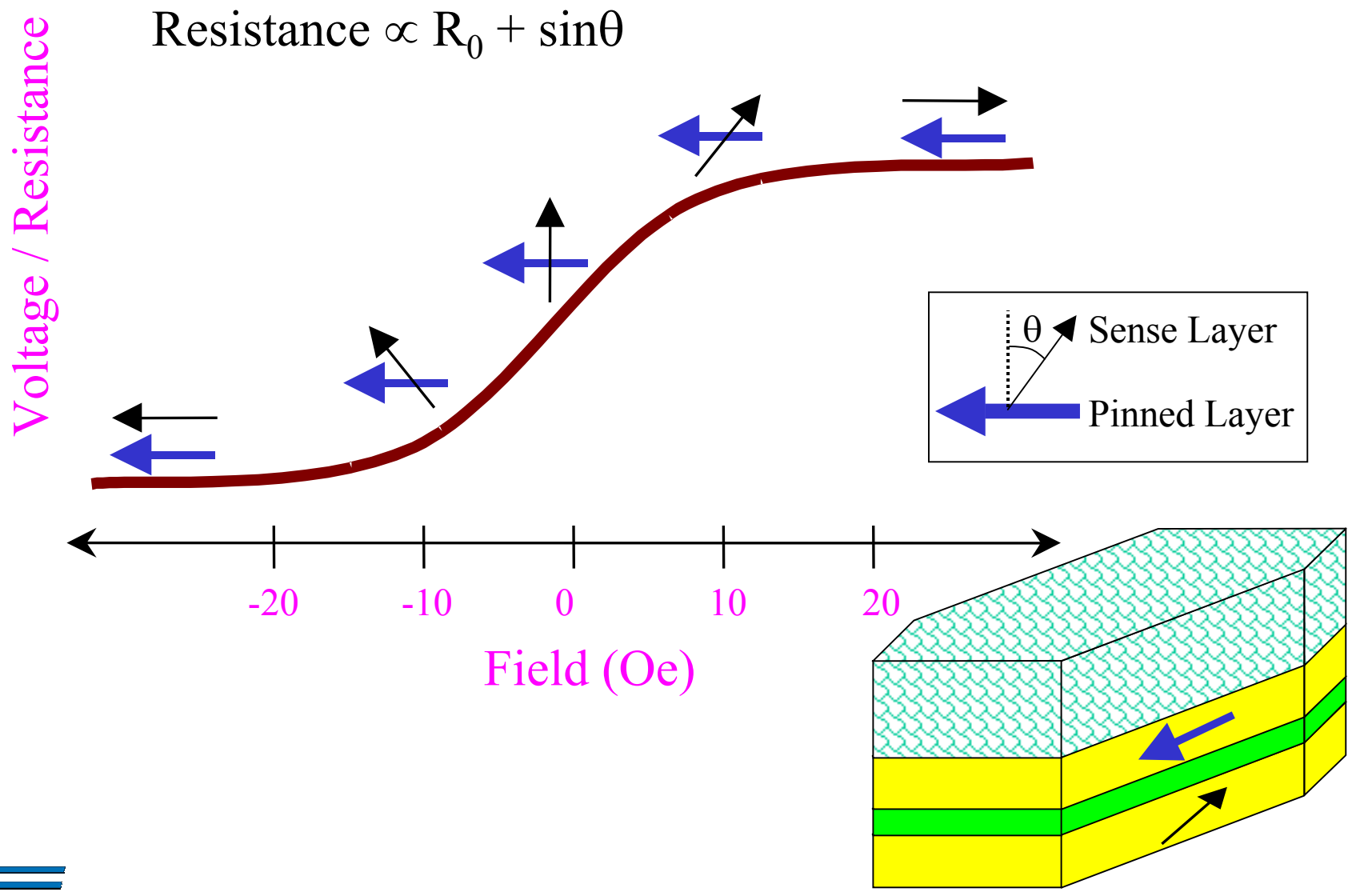
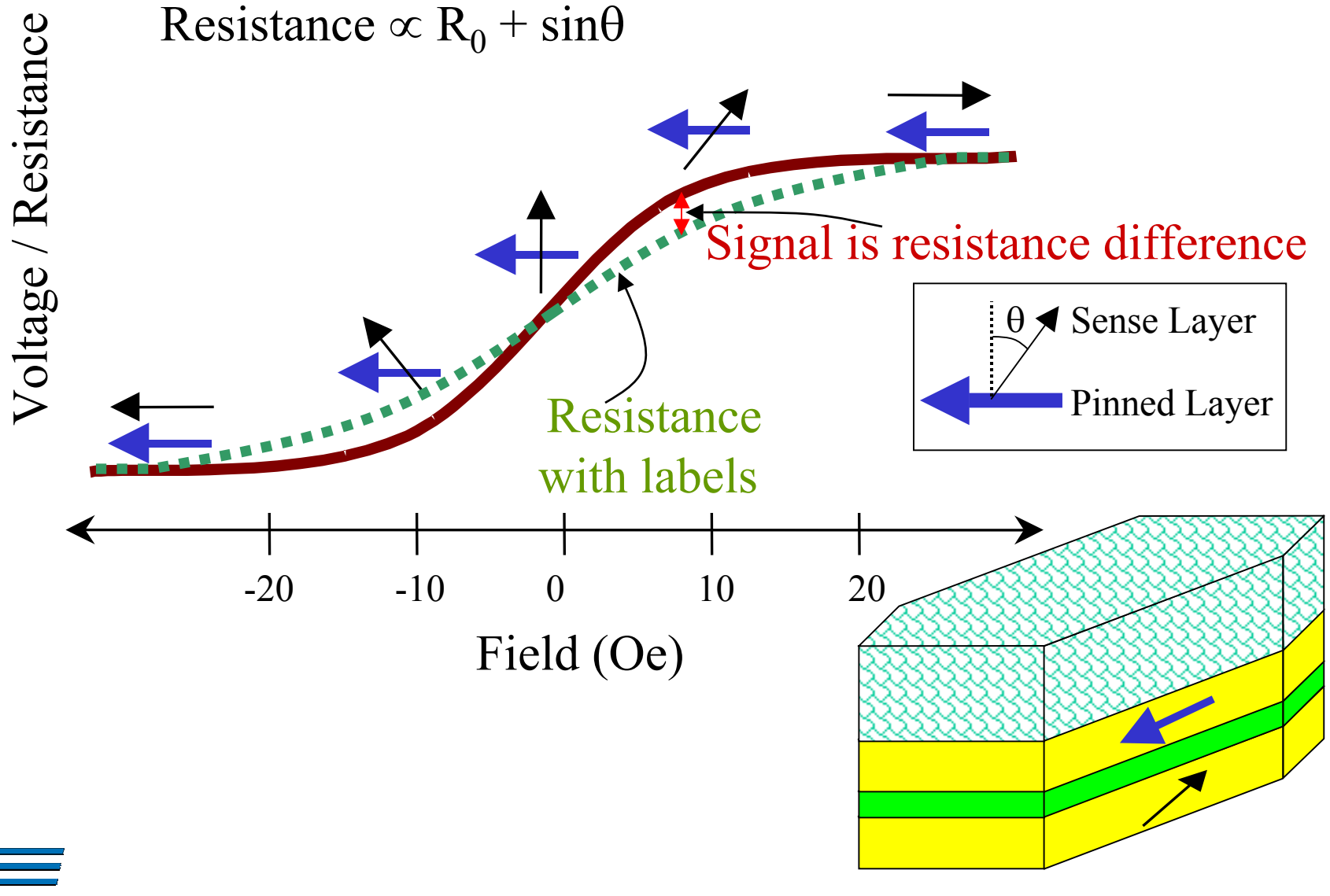
# Idealized Spin Valve Transfer Curve



# Resistance when labels are present

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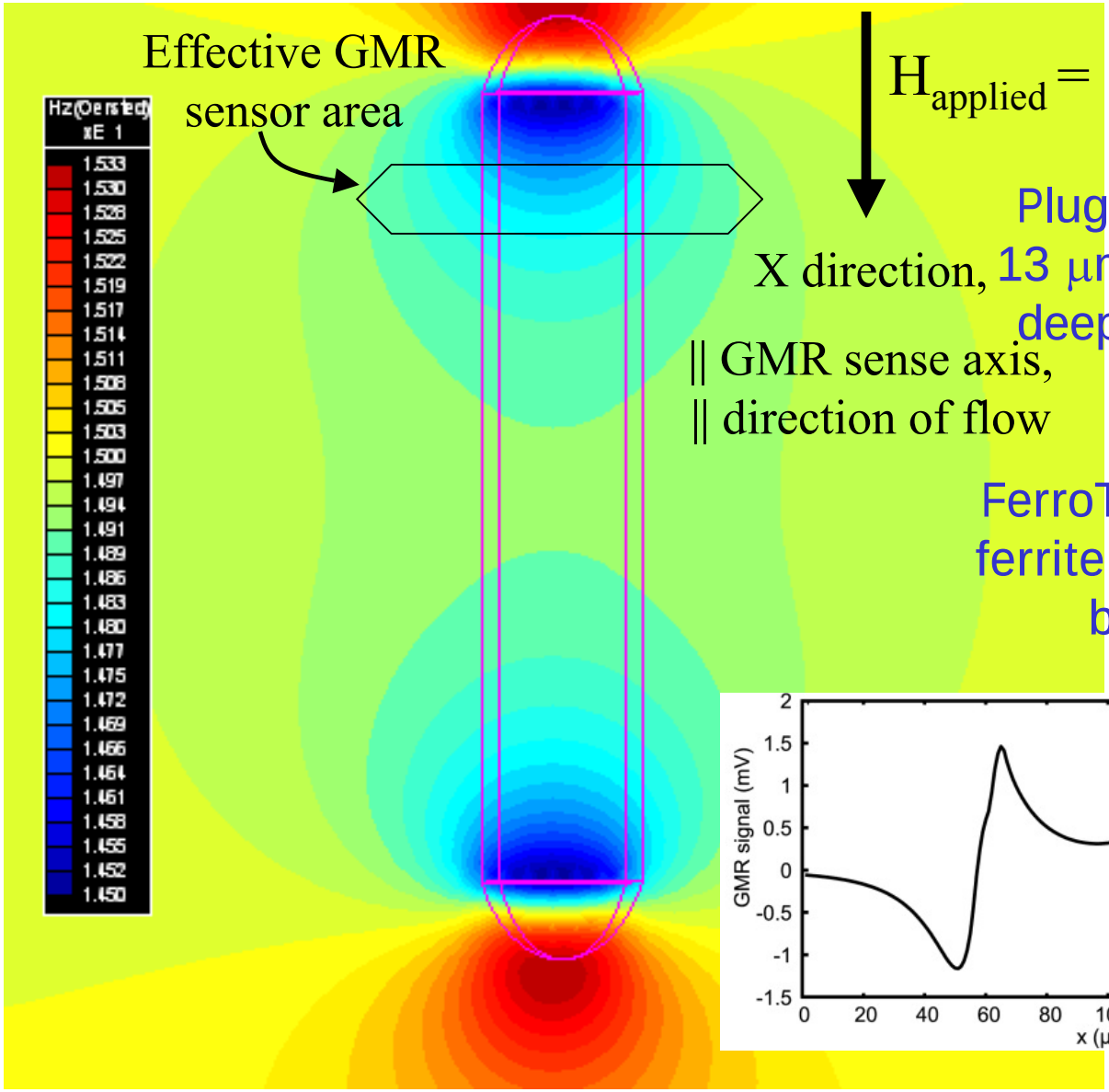
# $H_x$ in Sensor Plane, Flowing Ferrofluid Plug

Simulation using "Amperes" magnetic modeling software




$H_{applied}$ = 15 Oersted

X direction, || GMR sense axis, || direction of flow

Plug dimensions: 13 μm wide 18 μm deep 85 μm long

FerroTec 307 10nm ferrite particles ~1% by volume

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# Direct Flow Velocity Monitoring

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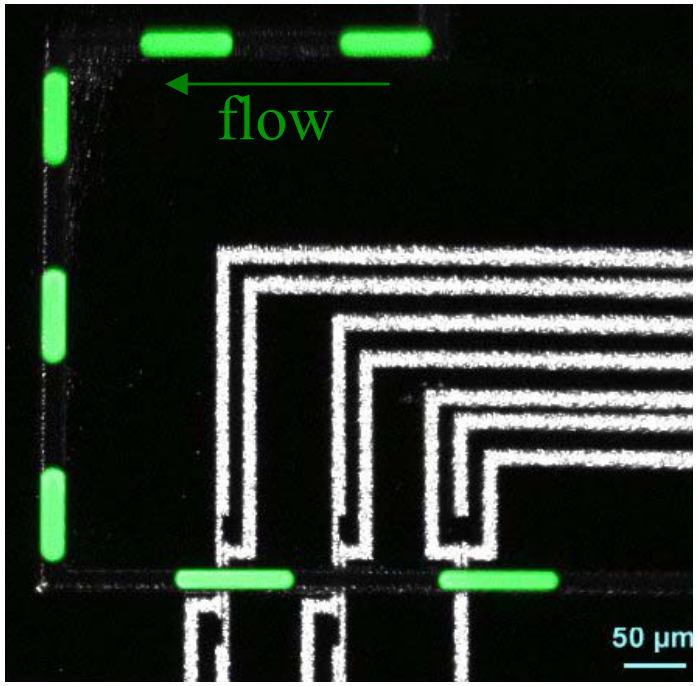


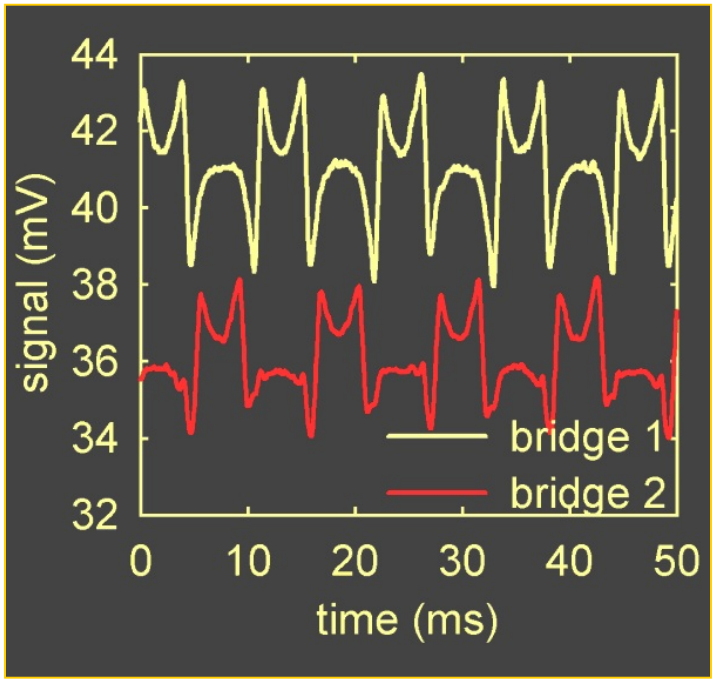


Excitation field 15 Oe; Flow rate 250 nL/min; 1.2% magnetite v/v

Velocity determined by cross-correlating the signals from two bridges

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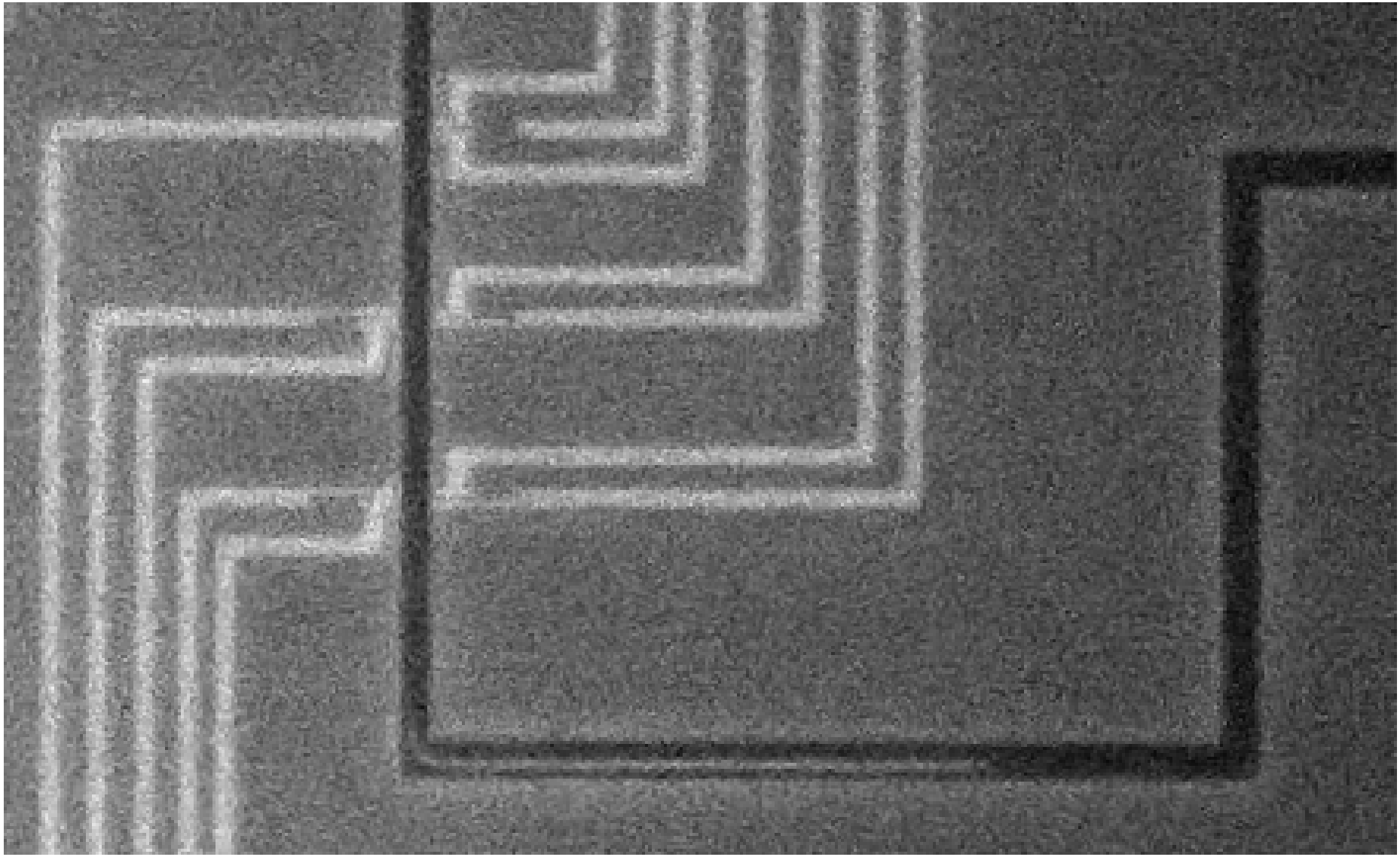
# Detection of single ~5 micron beads in flow



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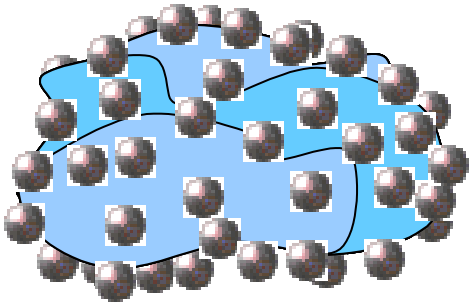
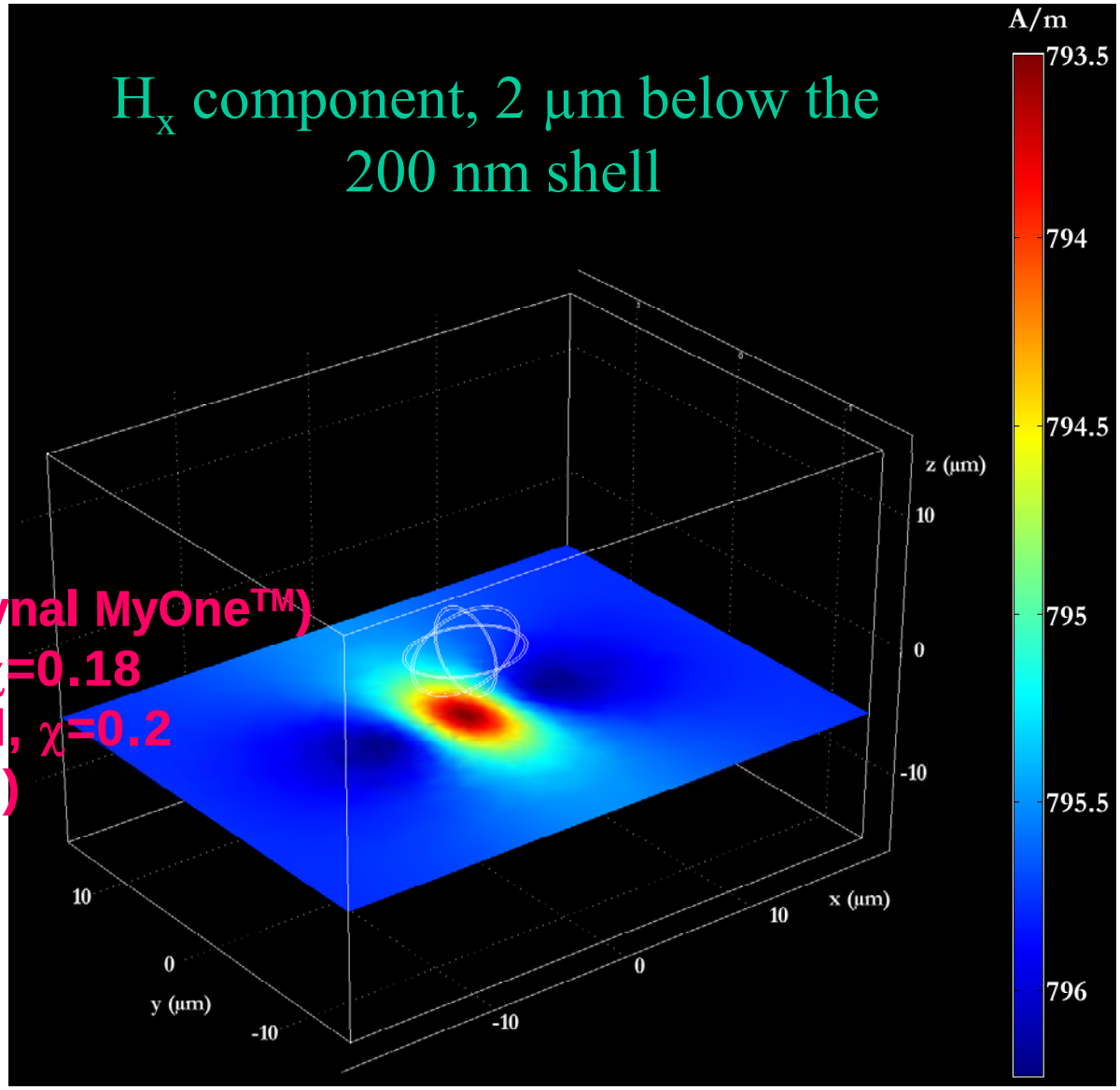
# Model data from cell covered by "shell" of magnetic labels

**Hypothetical cell covered with magnetic labels**



**FEMLAB package**
**Protozoan cell 8x6x6 µm**
**48 1-µm spheres, $\chi$=0.3 (Dynal MyOne™)**
**Homogeneous 1-µm shell, $\chi$=0.18**
**Homogeneous 200-nm shell, $\chi$=0.2**
**(Micromod nanomag-D, $\chi$=2)**

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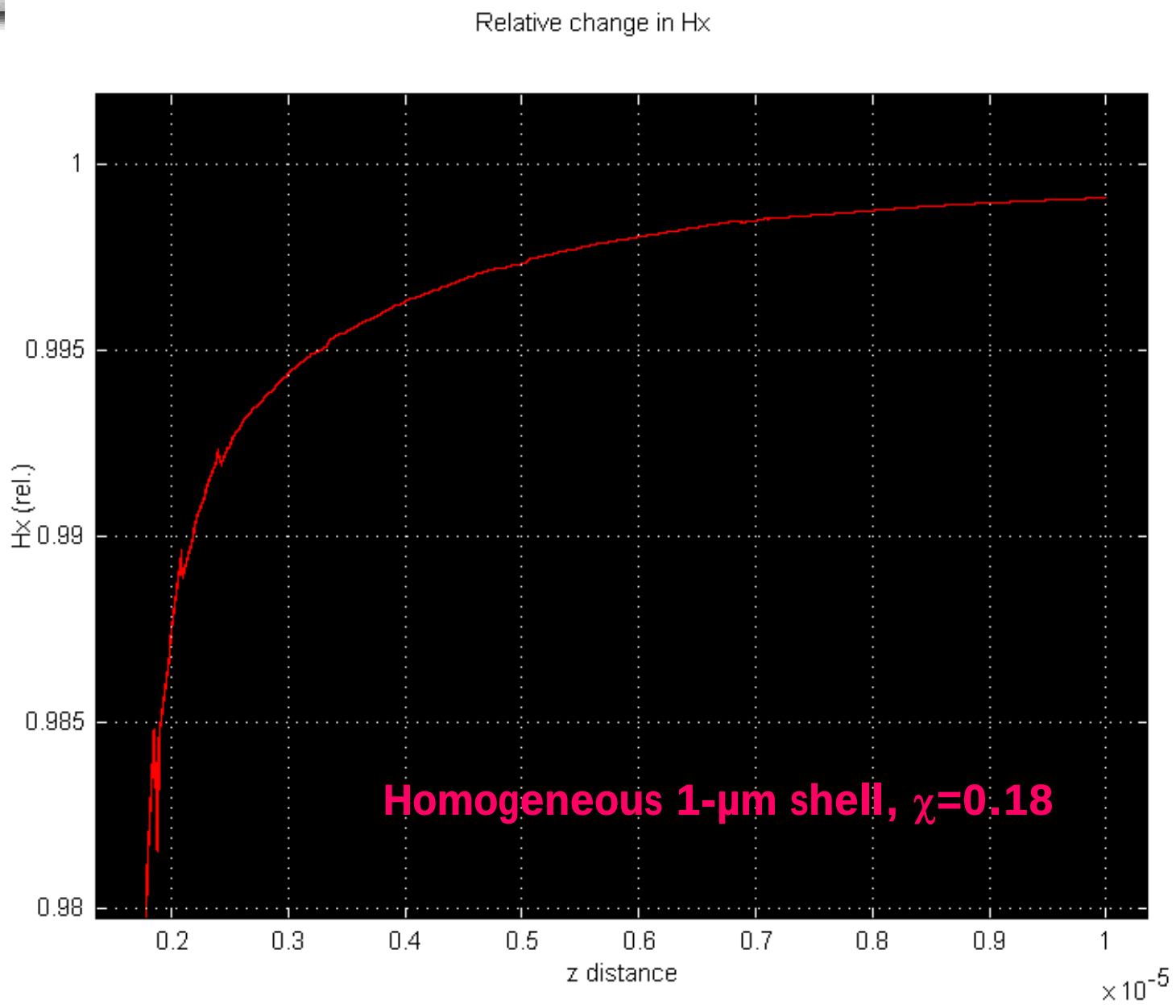
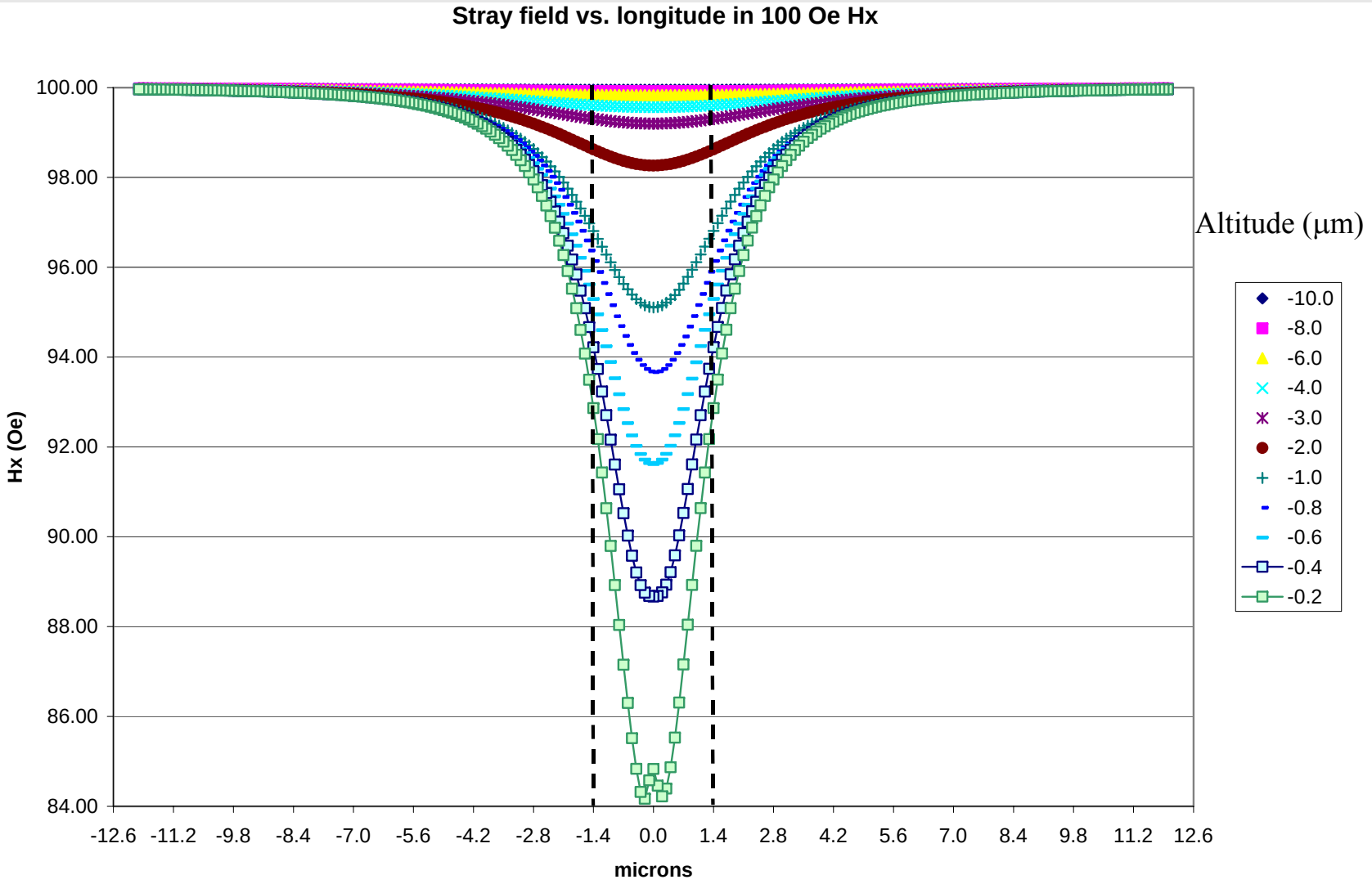
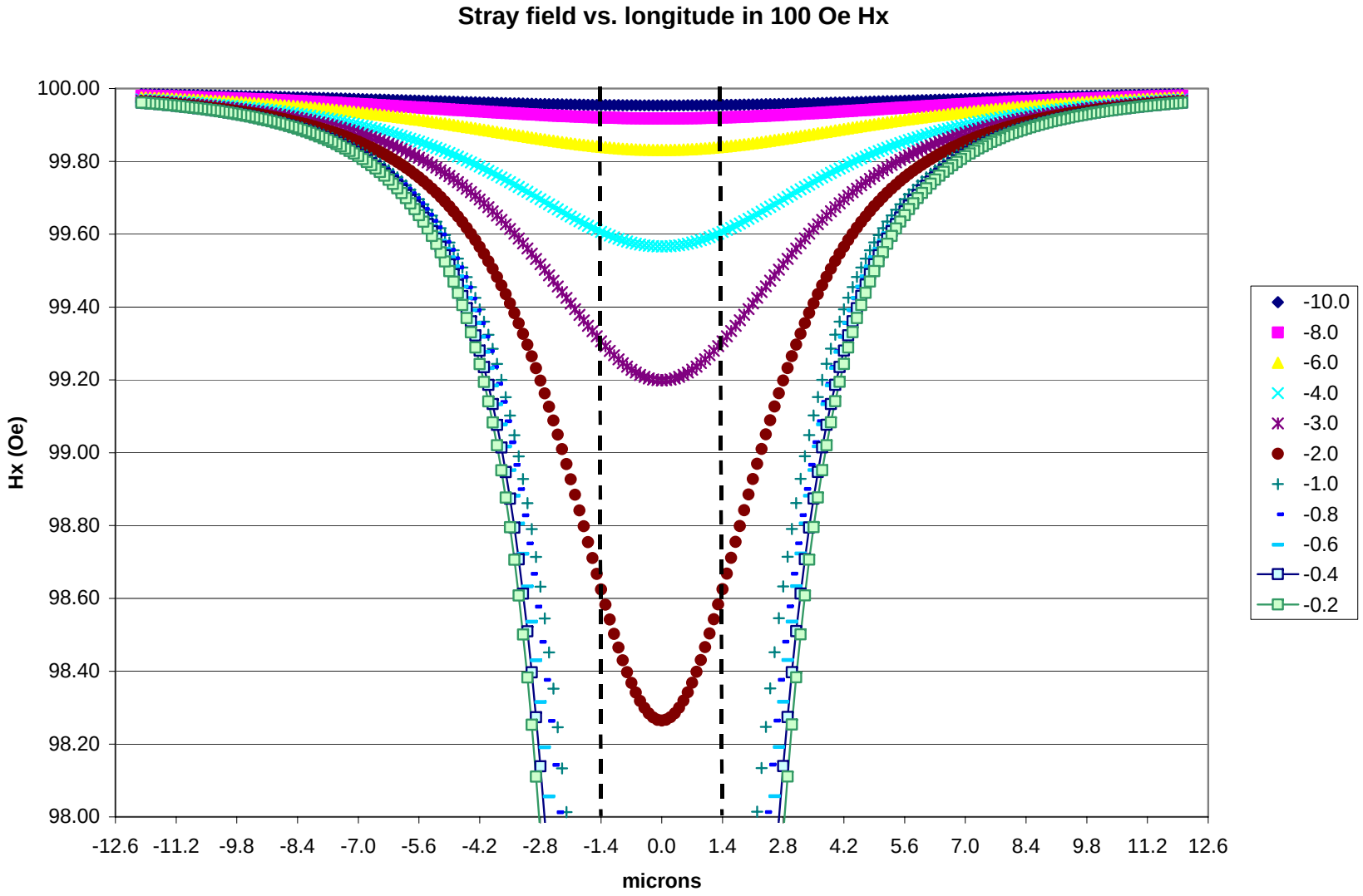
# Model: fractional field change vs. distance



# Field vs. position (time) for 2.8 micron Dynal Bead



# Field vs. position (time) for 2.8 micron Dynal Bead



# Detection of labels and cells in small channels is magnetically easy

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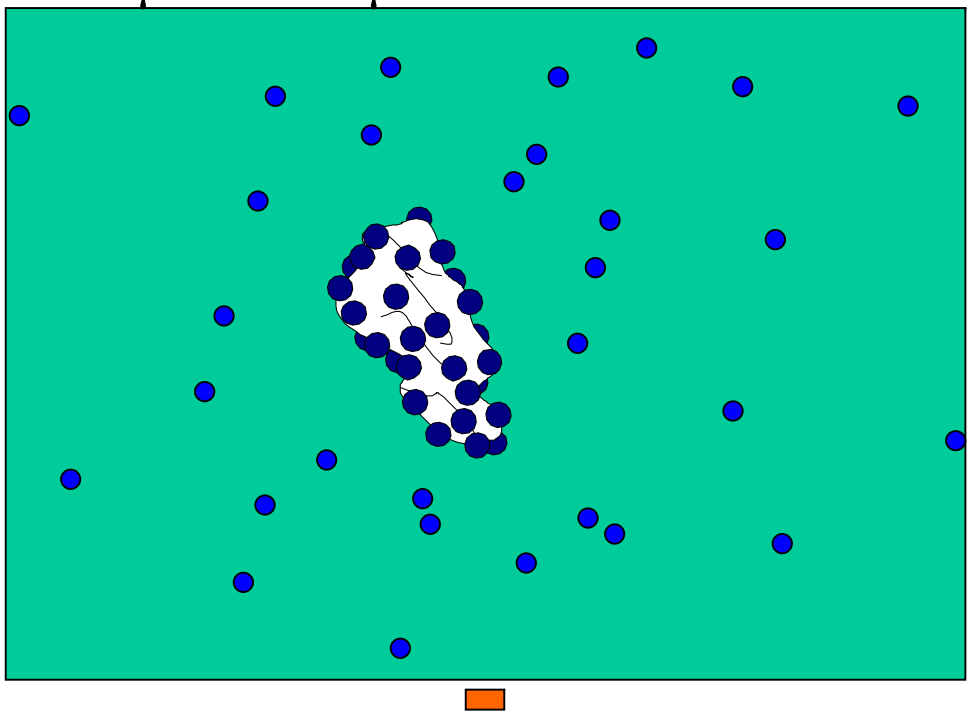
# But, channel is too small, gets plugged up

- Detection is much easier in small channel (12 μm x 15 μm)
- Cells are about 10 microns, fairly easy to plug
- As channel size gets bigger, location of magnetic objects is more varied

# Comparing channel widths

## new design

50 µm x 35 µm channel x-section

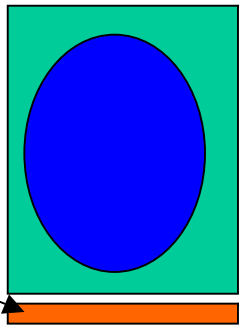


2 µm x 2 µm
detector area

GMR detector

## old design

12 µm x 15 µm
channel x-section



3 µm x 15 µm
detector area

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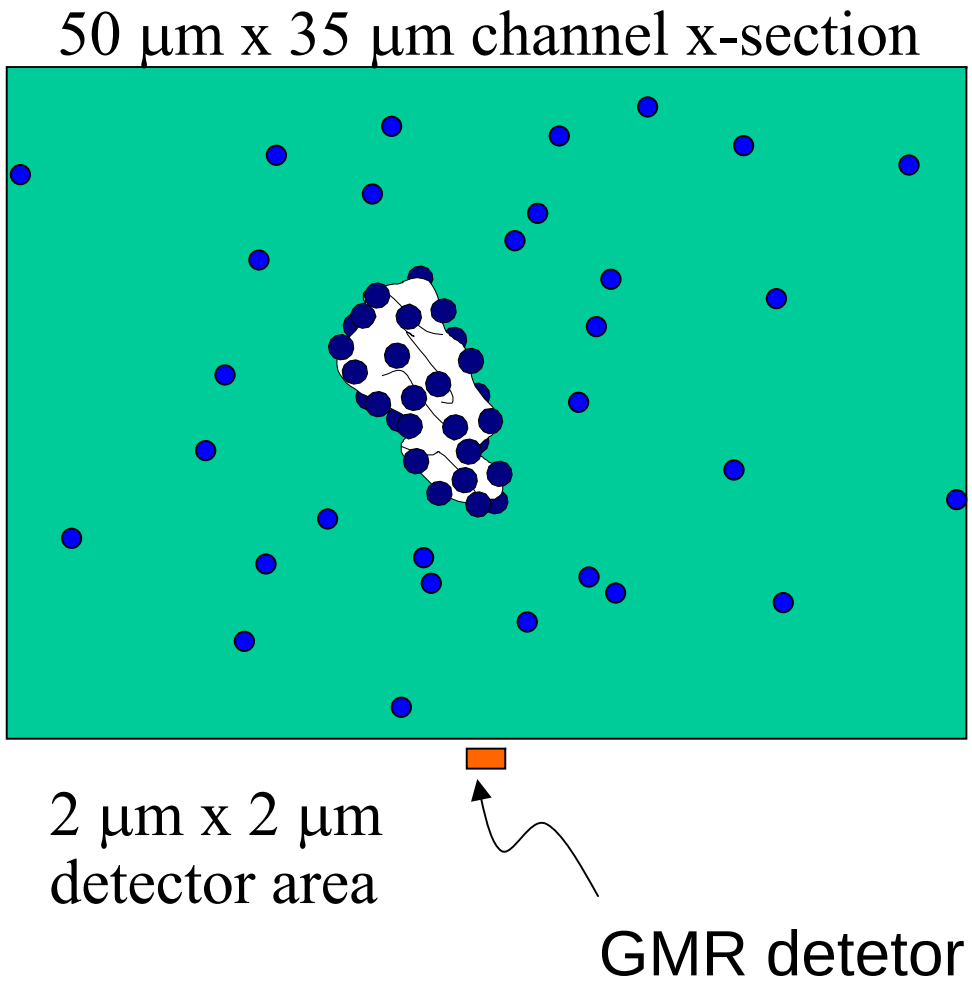
# Challenges

new design




How do you know if a detected magnetic object is a cell or an unbound label?

How do you know if a magnetic signal is from a small-close object, or a large-faraway object?

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# In-Flow Manipulation of Magnetic Particles

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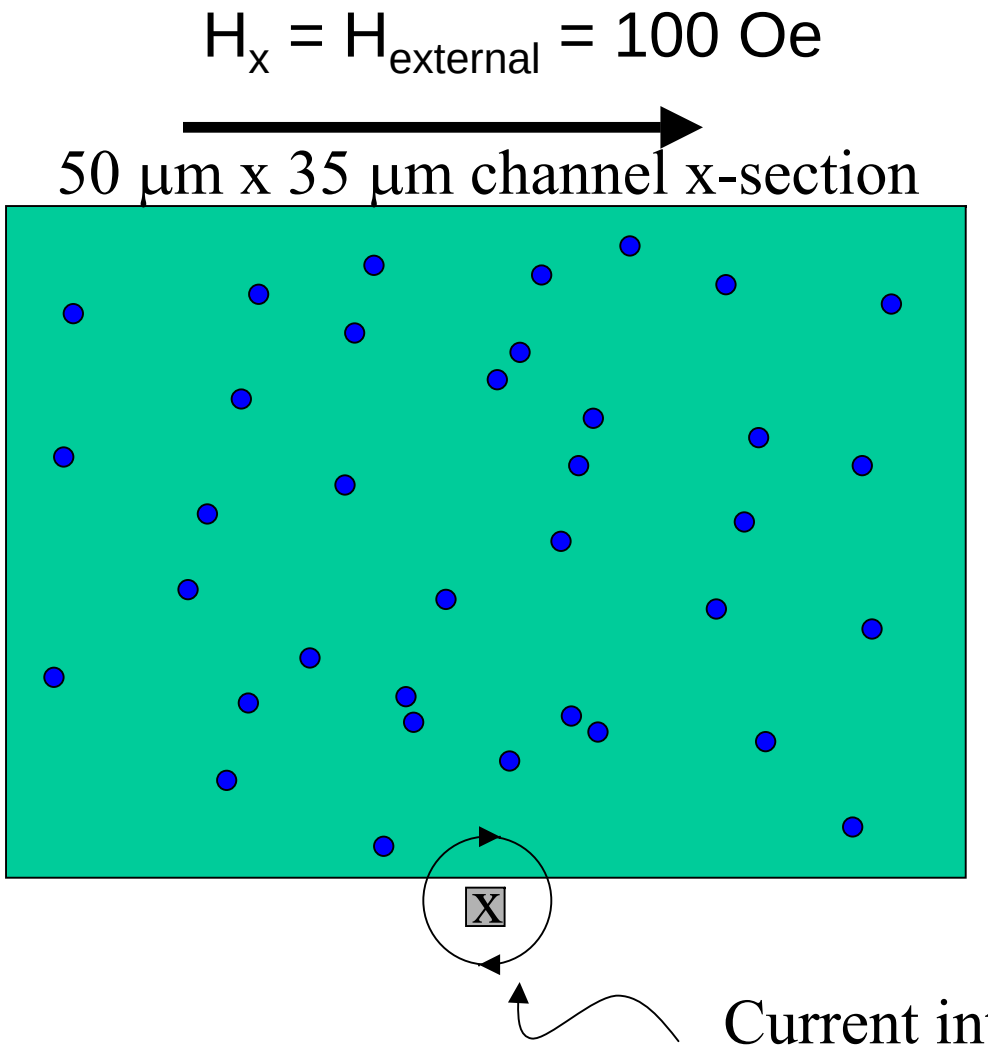
# Simple situation: qualitative force calc.




1 μm diameter
Paramagnetic
Small wire x-section
$H_{external}$ across channel
$H_{external}$ parallel $H_{wire}$

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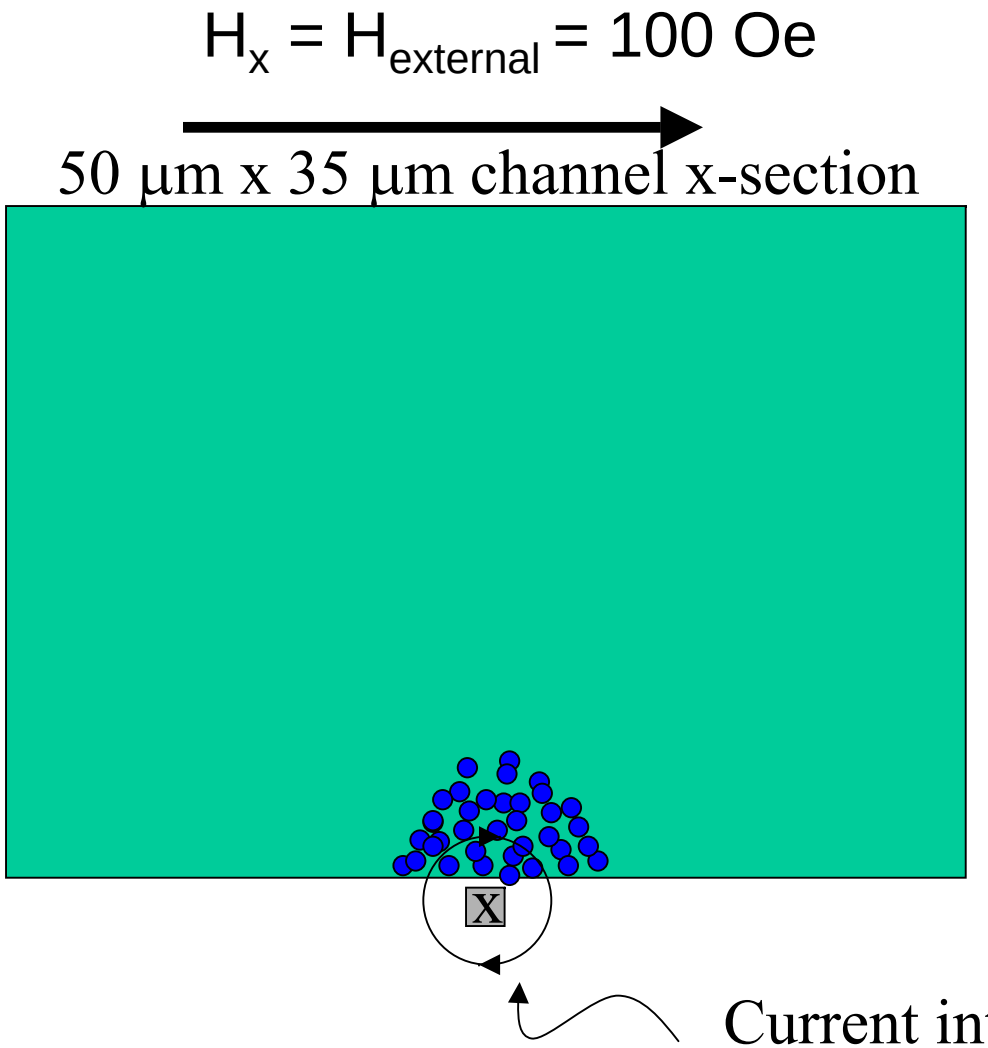
# Simple situation: qualitative force calc.




Particles are **attracted**
(Flip sign of current, particles are repulsed)

1 μm diam. Particles paramagnetic
Small wire x-section
$H_{external}$ across channel
$H_{external}$ parallel $H_{wire}$

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# Quantitative Theoretical Assessment

Equation of motion

$$m\frac{d\mathbf{v}}{dt} = -3\pi\eta a\mathbf{v} + \mathbf{F}_{mag}$$

Integrate to get velocity

$$v(t) = \frac{F_{mag}}{3\pi\eta a}\left(1 - e^{-\frac{3\pi\eta a}{m}t}\right)$$

a: particle diameter = 1 micron

n: viscosity (water)

m: particle mass

$F_{mag}$: Force in channel cross-section due to $H_{wire}$ and $H_{external}$

v: velocity

t: time

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# Quantitative Theoretical Assessment

Equation of motion

$$m\frac{d\mathbf{v}}{dt} = -3\pi\eta a\mathbf{v} + \mathbf{F}_{mag}$$

For a given $F_{mag}$, one can calculate:

"terminal velocity"

"characteristic time"

Integrate to get velocity

$$v(t) = \frac{F_{mag}}{3\pi\eta a}\left(1 - e^{-\frac{3\pi\eta a}{m}t}\right)$$

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# Quantitative Theoretical Assessment

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$$m\frac{d\mathbf{v}}{dt} = -3\pi\eta a\mathbf{v} + \mathbf{F}_{mag}$$

$$v(t) = \frac{F_{mag}}{3\pi\eta a}\left(1 - e^{-\frac{3\pi\eta a}{m}t}\right)$$

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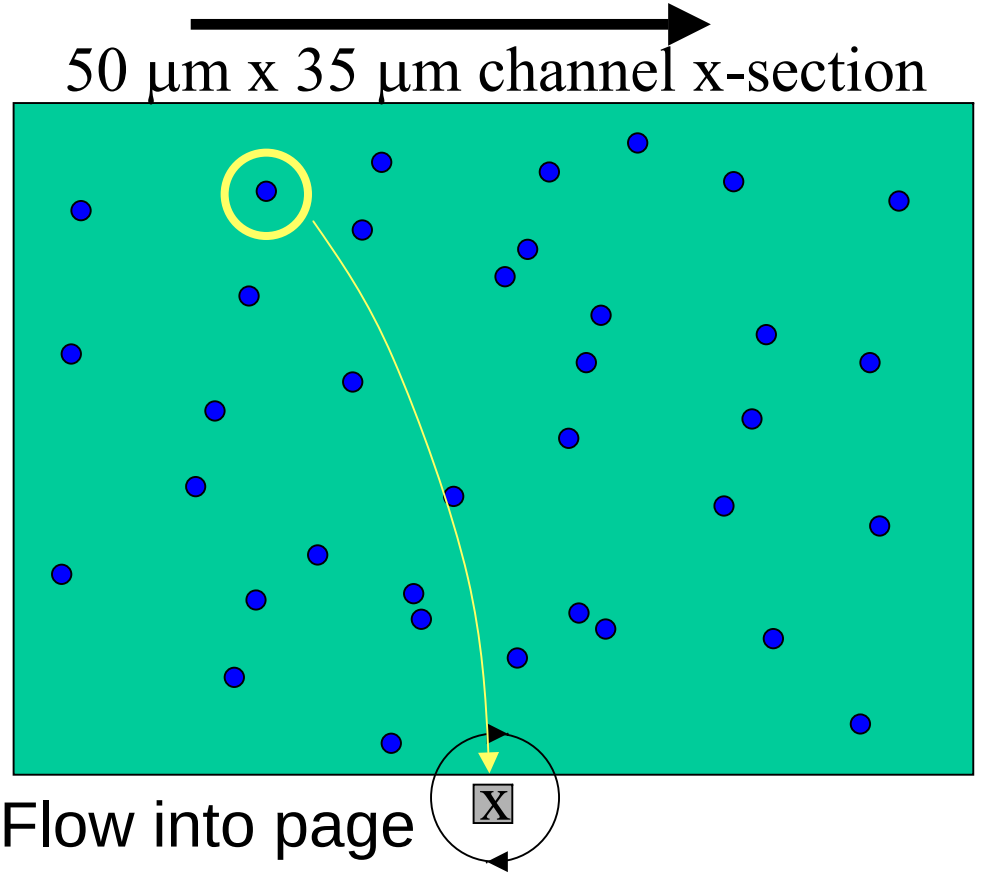
# Force on particle far from wire

$H_x = H_{external} = 100$ Oe




Initial $F_{mag}$ ~ 9 picoN
Initial $V_{terminal}$ ~ 1100 μm/sec
Characteristic time = 87 nsec
Max travel time = 0.03 sec.

Because the characteristic time is so much smaller than the total travel time of the particle, one can basically say that the particle trajectory follows the magnetic lines of force

Current = 10 mA

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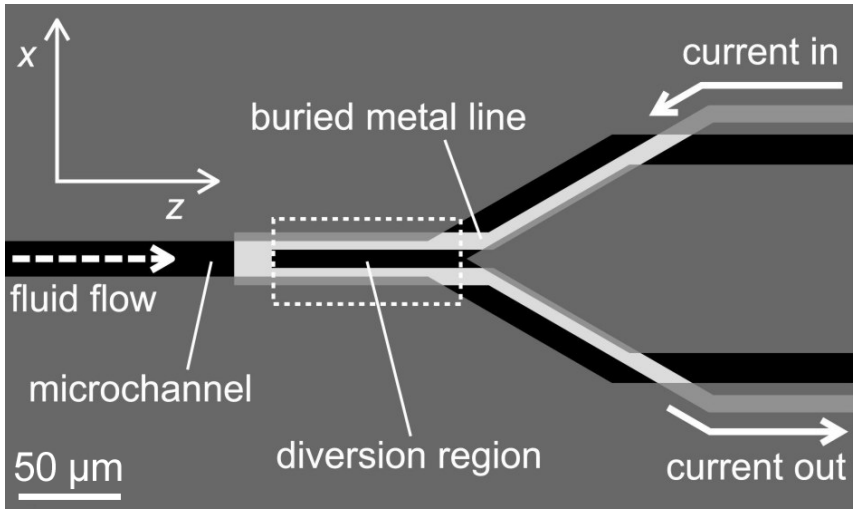
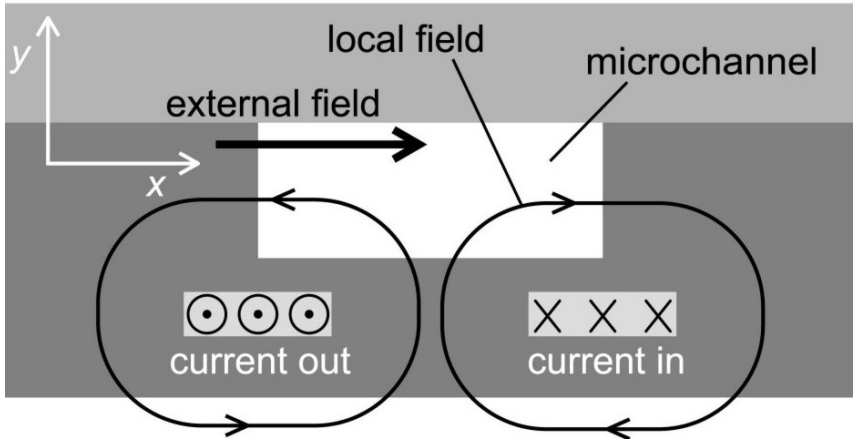
# Diverter Design and Fabrication




- A uniform external field magnetizes particles
- Current lines induce field gradients of $10^2$-$10^3$ T/m
- Resulting force diverts particles to a desired channel

# Theoretical Assessment

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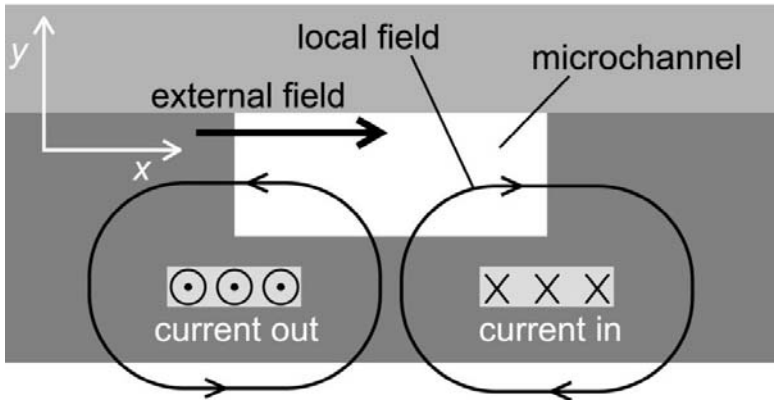
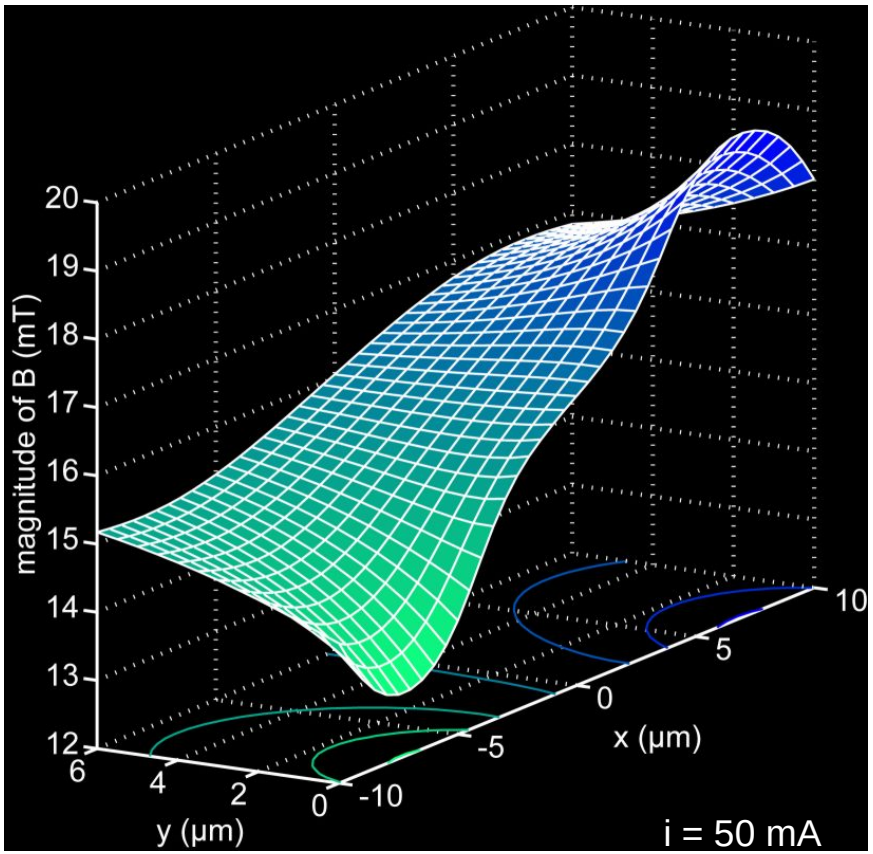
$$\mathbf{F}_{mag} = (\mathbf{m} \cdot \nabla)\mathbf{B}$$




Zborowski *et al*., J. Magn. Magn. Mater. **194**, 224 (1999)

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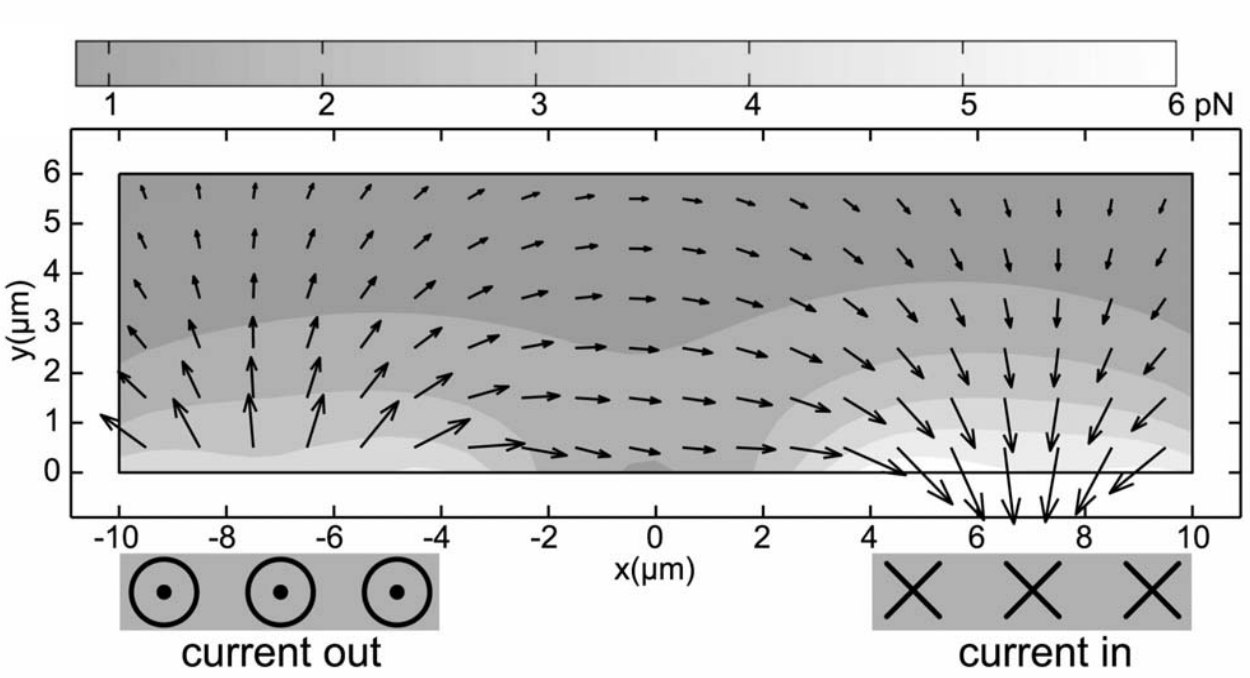
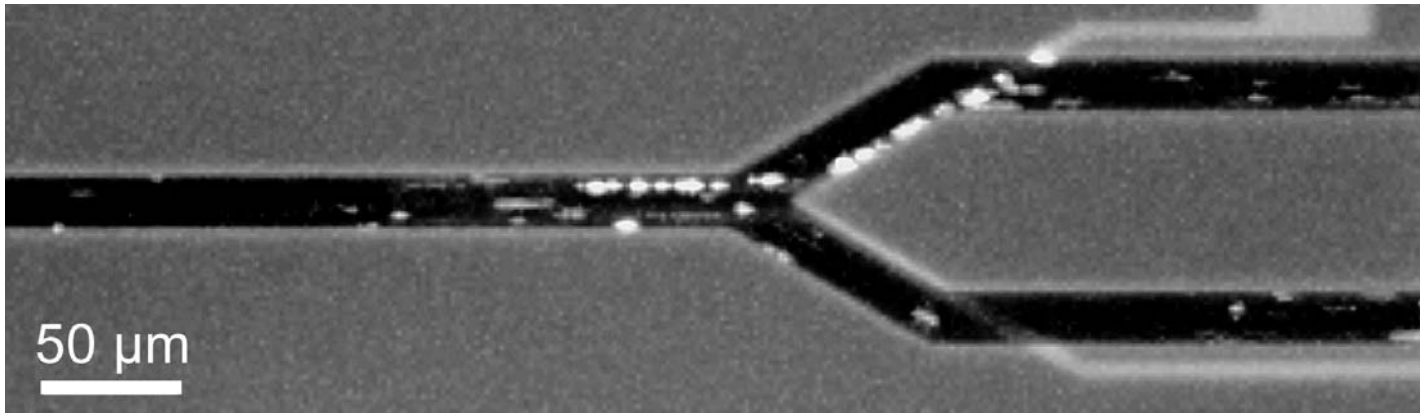
# Theoretical Assessment

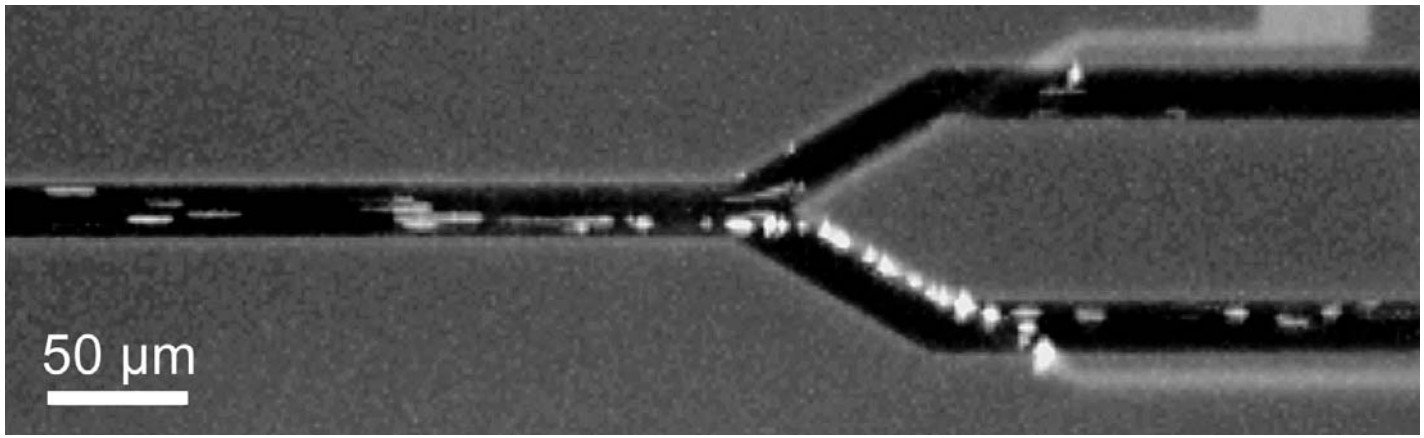
$$\mathbf{F}_{mag} = \frac{V\chi}{2\mu_0}\nabla B^2$$




i=50 mA; $B_{ext}$=16 mT; $\chi$=0.1; a=1 μm

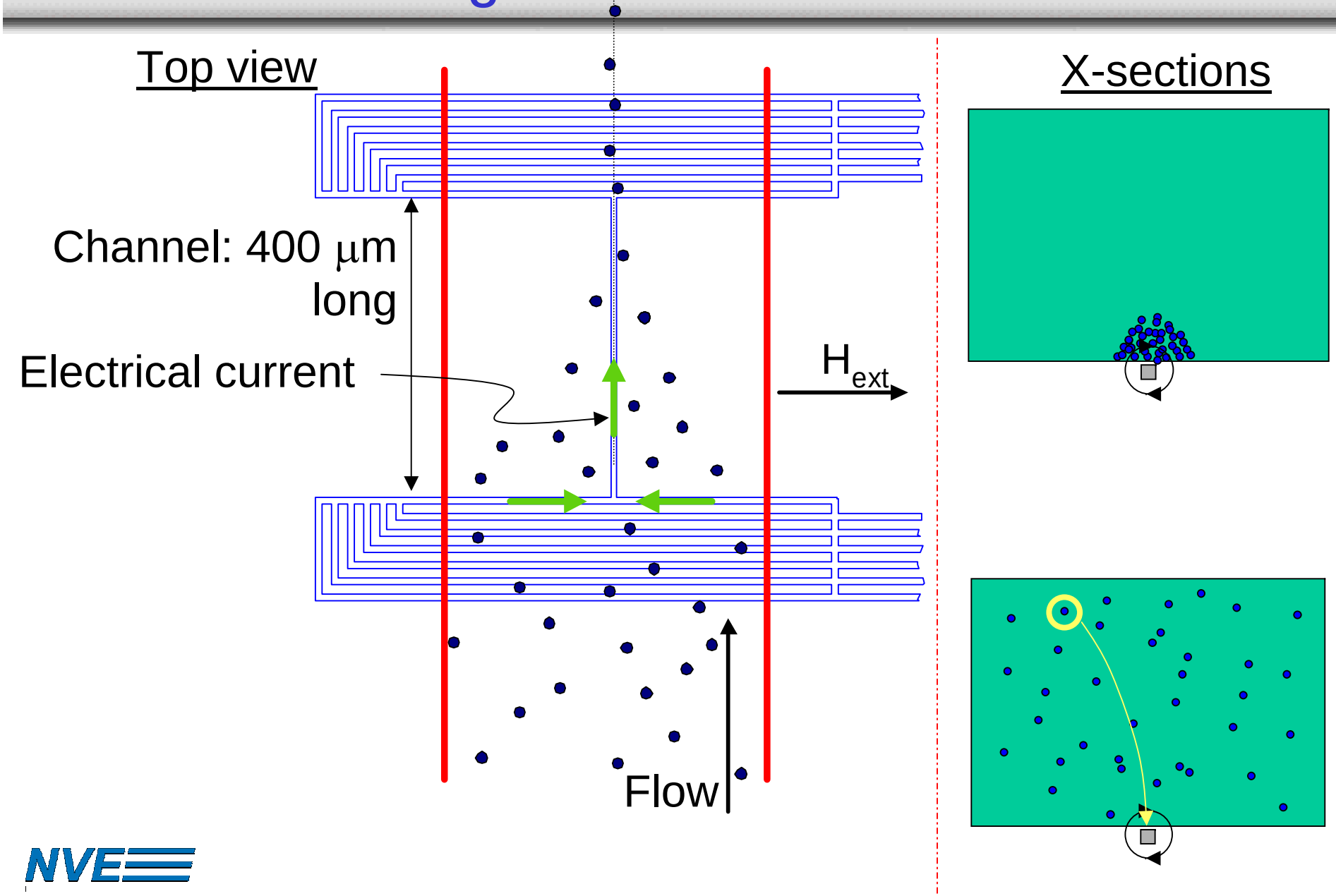
# Magnetic Flow Sorting Experiments



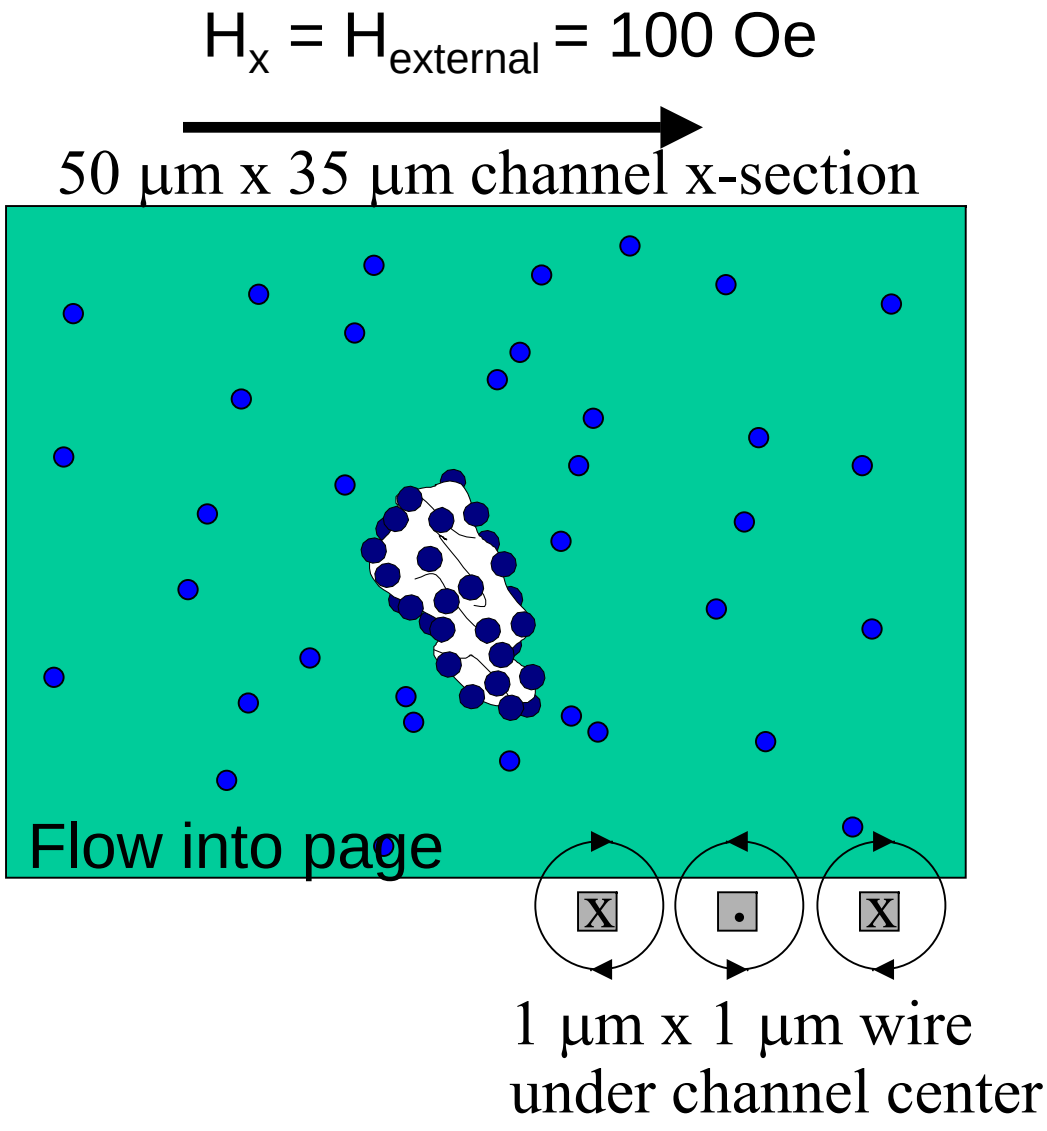




- Bangs Labs, 28% magnetite, 1 µm
- Flow rate: 6 nL/min
- 85% of the beads in desired channel

# Single-wire attractor



# Sorting cells from labels




How do you know if a detected magnetic object is a cell or an unbound label?

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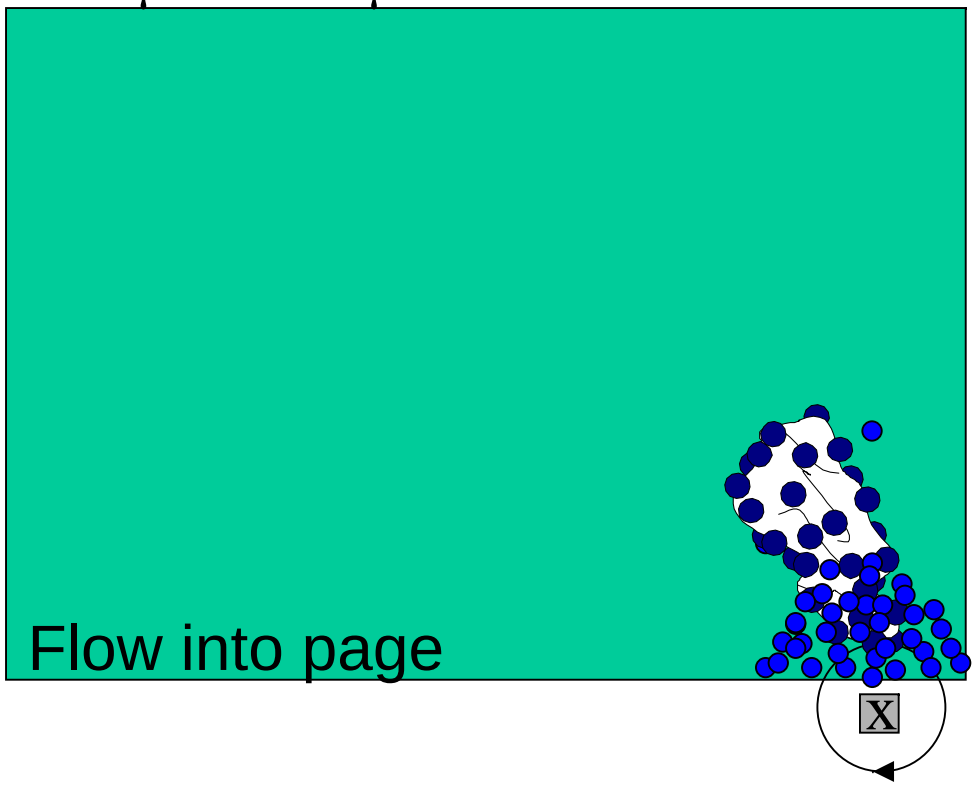
# Sorting cells from labels

$H_x = H_{external} = 100$ Oe

50 μm x 35 μm channel x-section




Attract all objects to one wire

Current into plane
1 μm x 1 μm wire
under channel center

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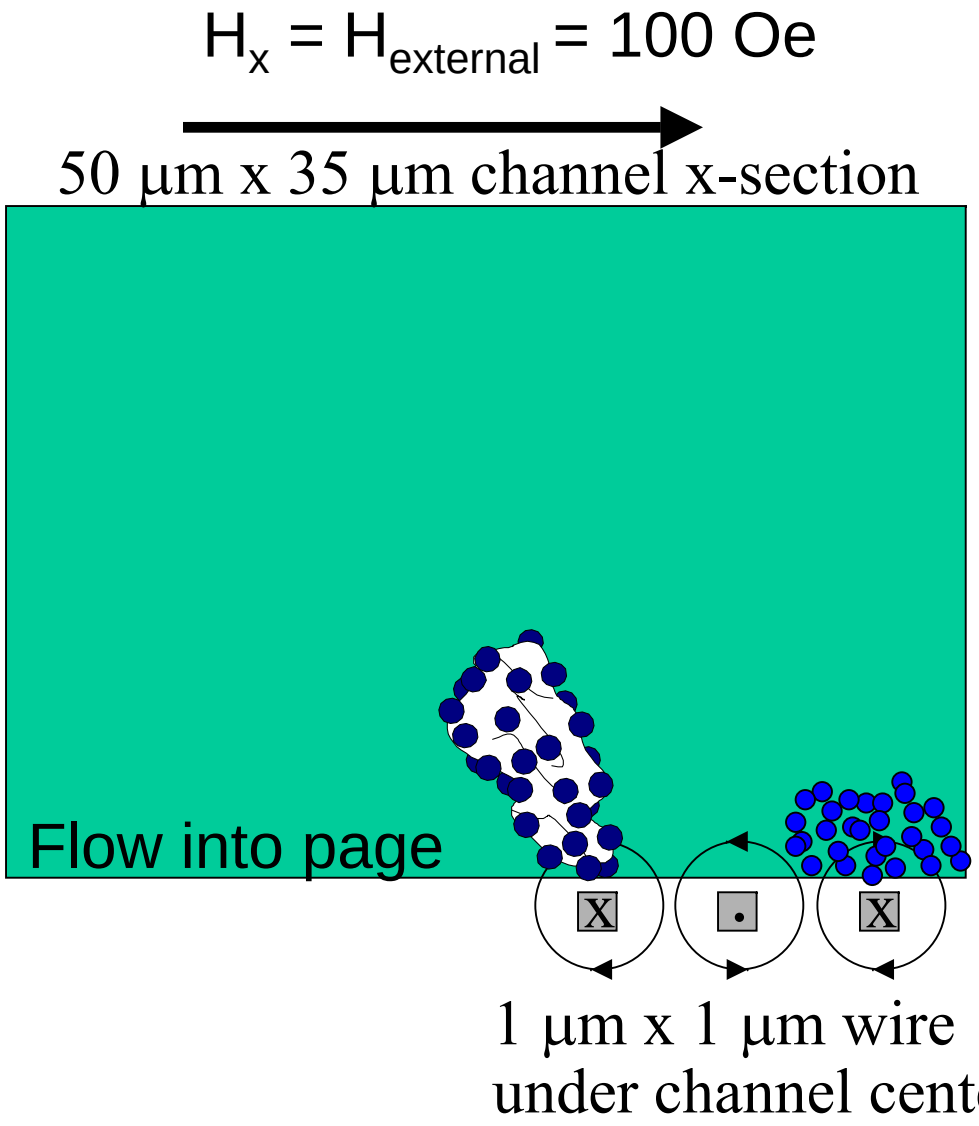
# Sorting cells from labels




Selectively pull cells to another wire

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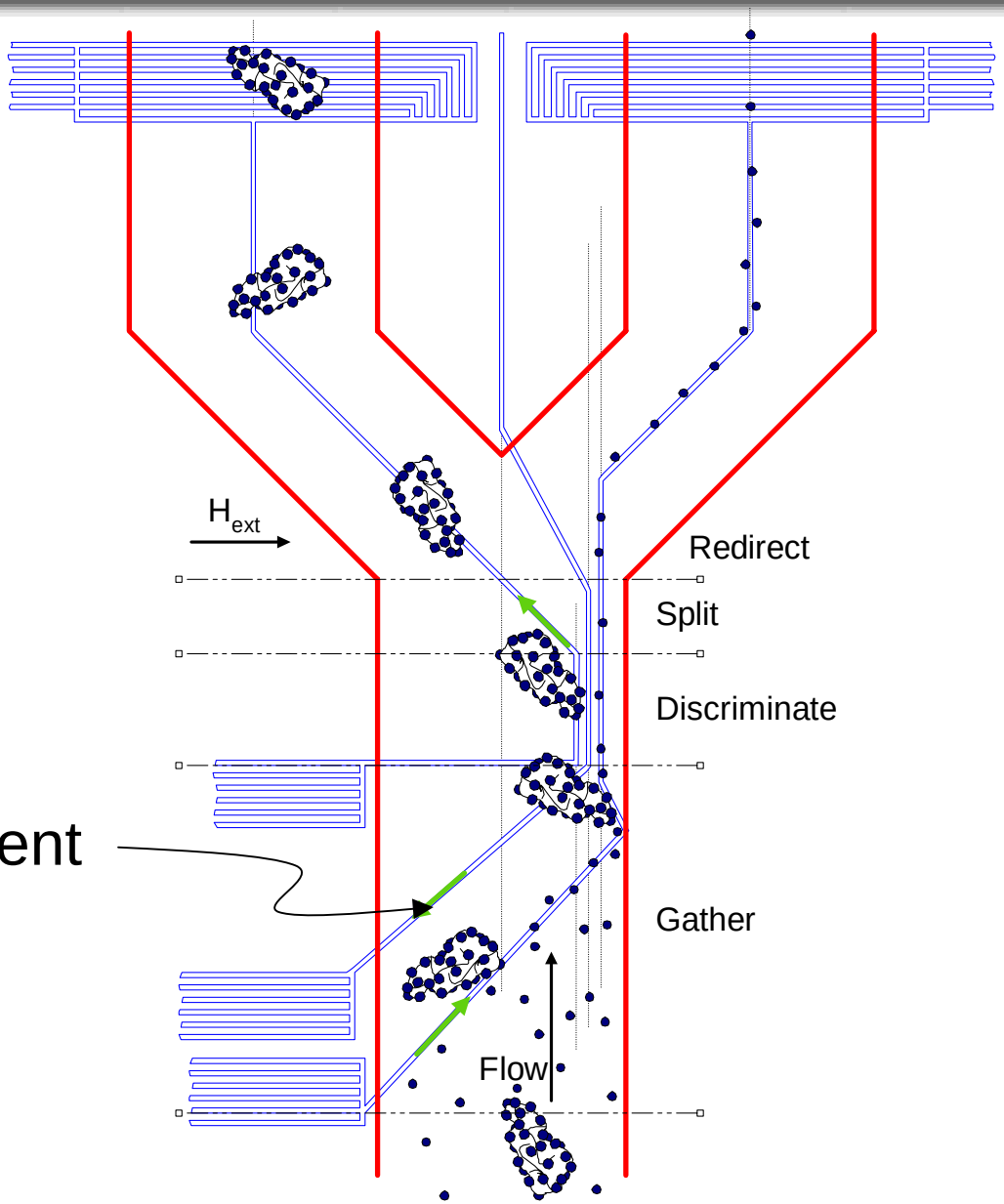
# Cell – Label splitter




Electrical current

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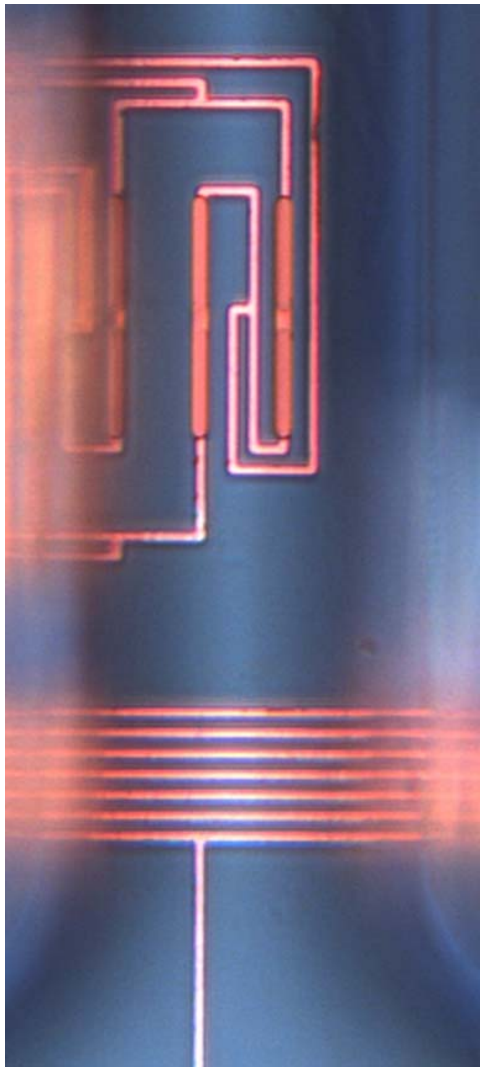
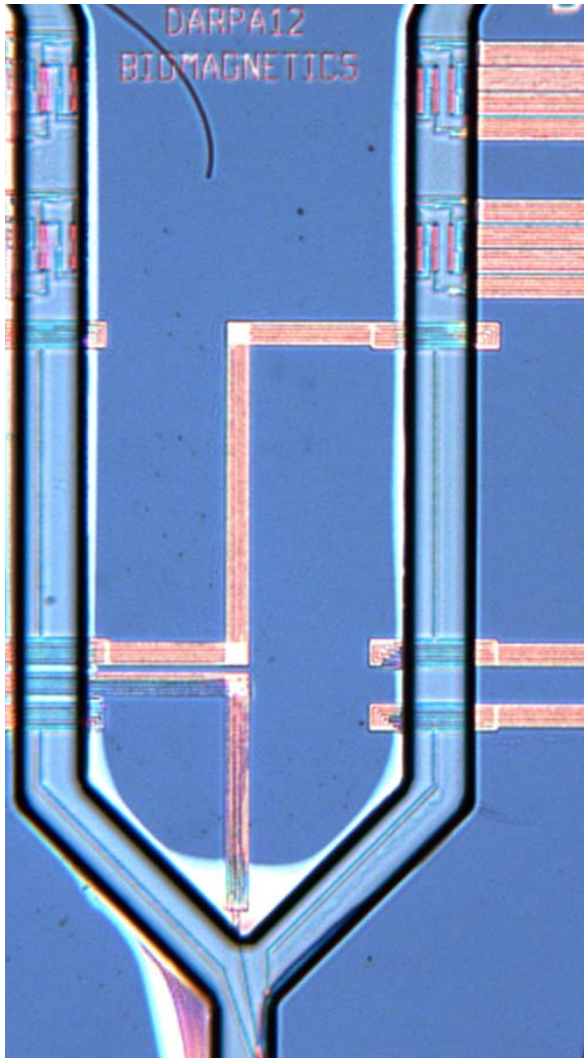
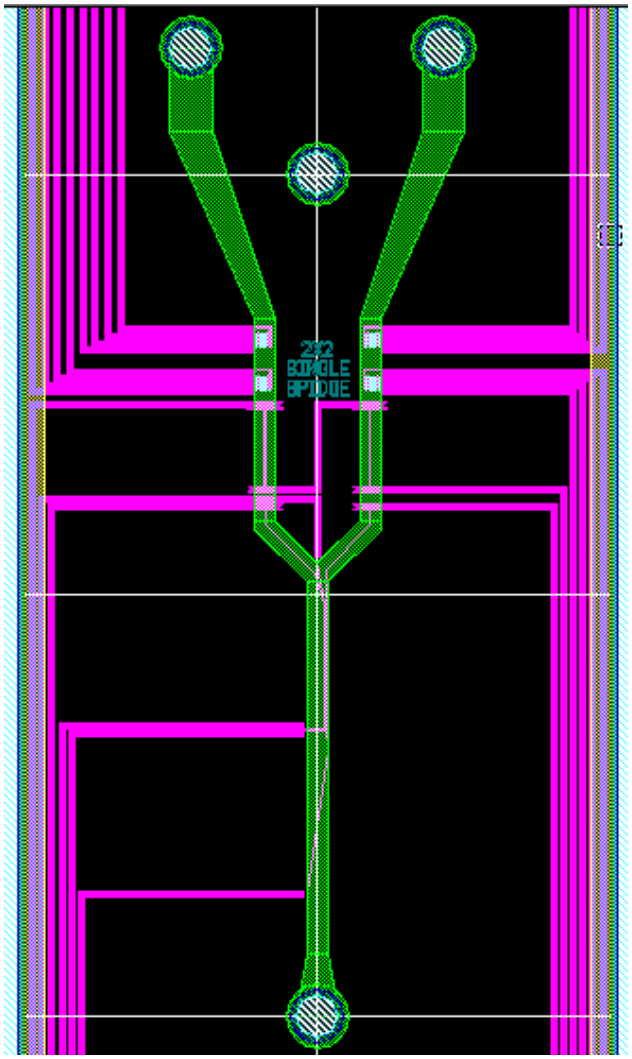
# Cell sorter, director, and detector



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# Fluid dynamics

This talk has largely ignored the fluid dynamics. However, they are very important!

Mostly, a detailed account would show that there are additional tools that can be designed in to aid in sorting and detecting.

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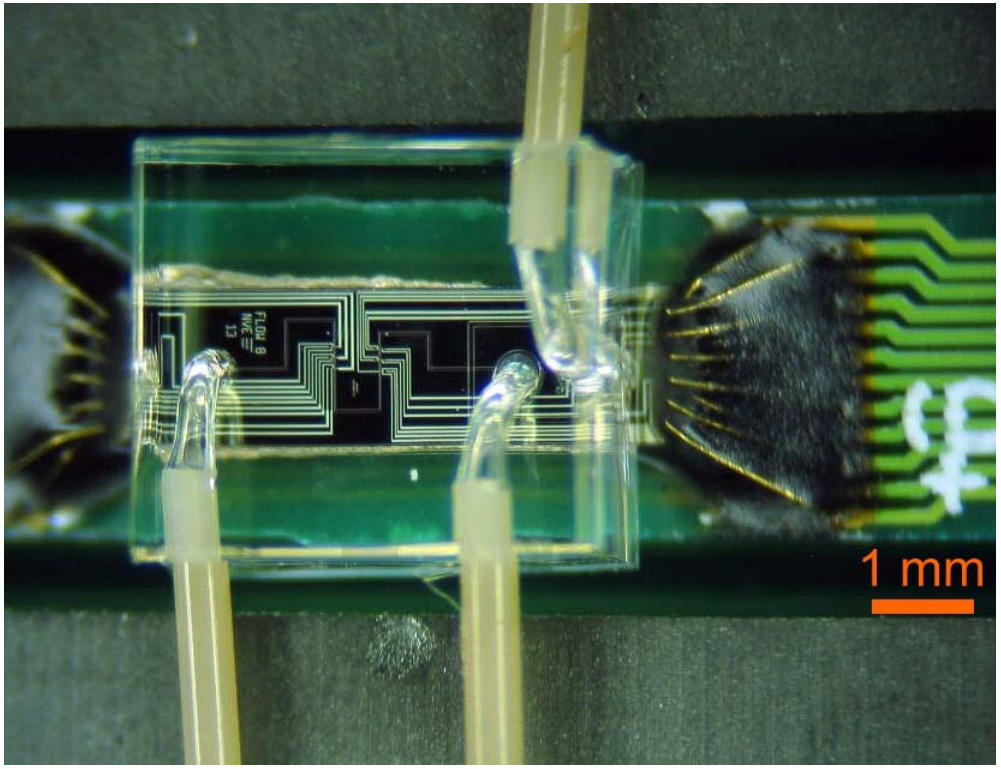
# Magnetic design consistency

- The magnetic biasing field must work for both manipulation and detection: desire large magnetizing field, but not saturating the sensors

# Device Packaging with PDMS

IOWA STATE UNIVERSITY




- Electrical connections
- PDMS Fluidic connections
- Optical access

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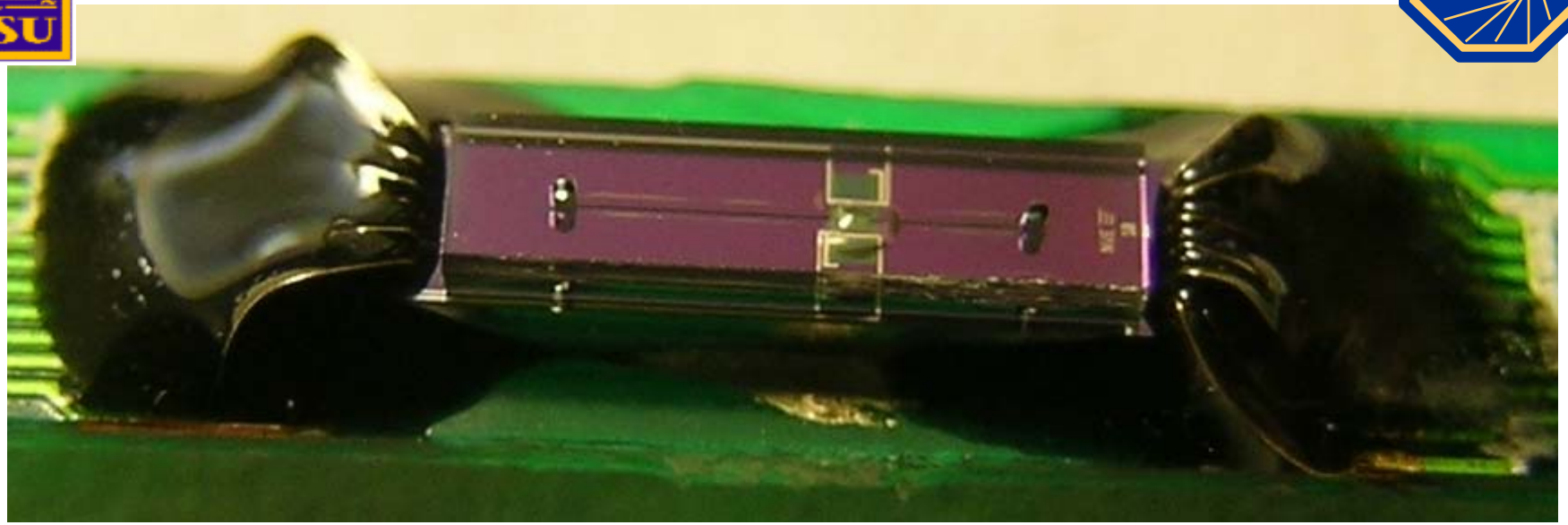
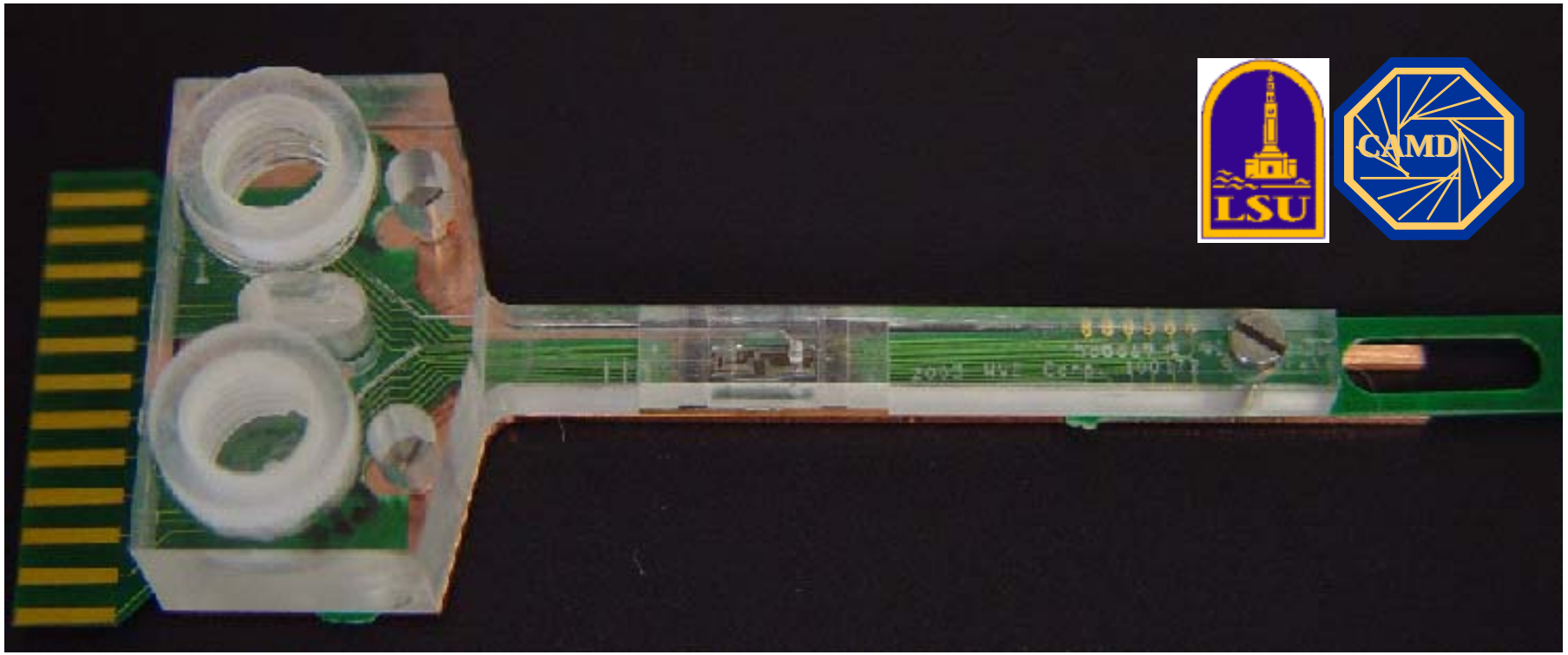
# Dice, mount on circuit board, wire bond



# Ready to use fluidic / GMR chip

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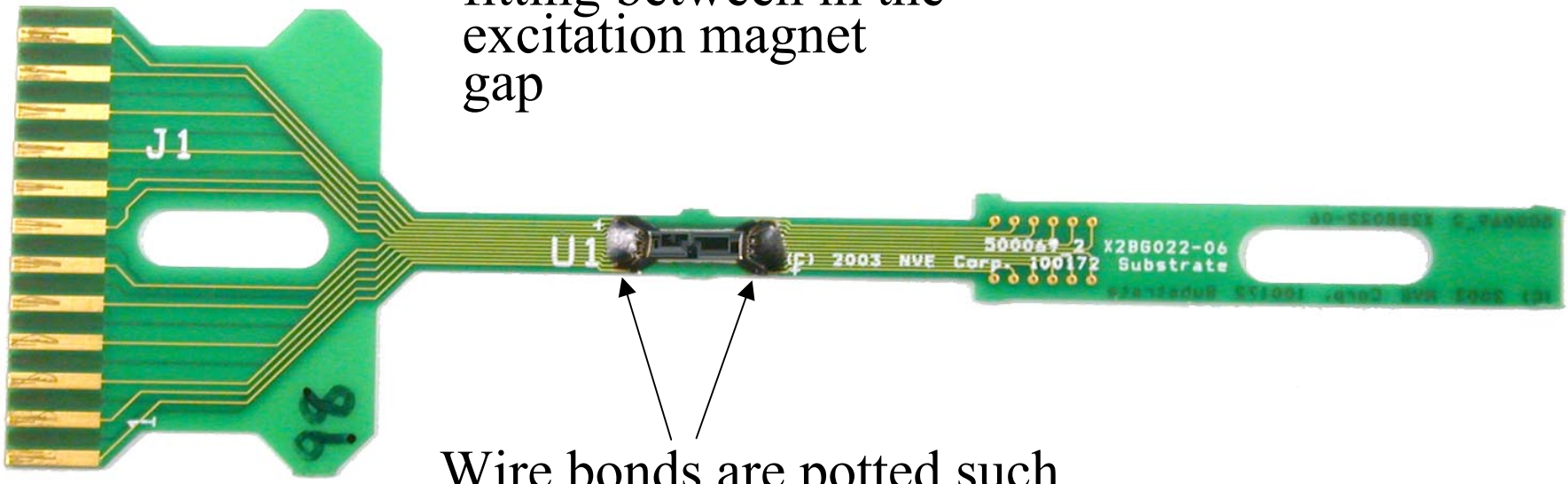
# Die-Holding Printed Circuit Board

## “Diving Board”

Design Basics

24 pin surface mount edge connector

Narrow die area for fitting between in the excitation magnet gap




Wire bonds are potted such that sense pad is still exposed

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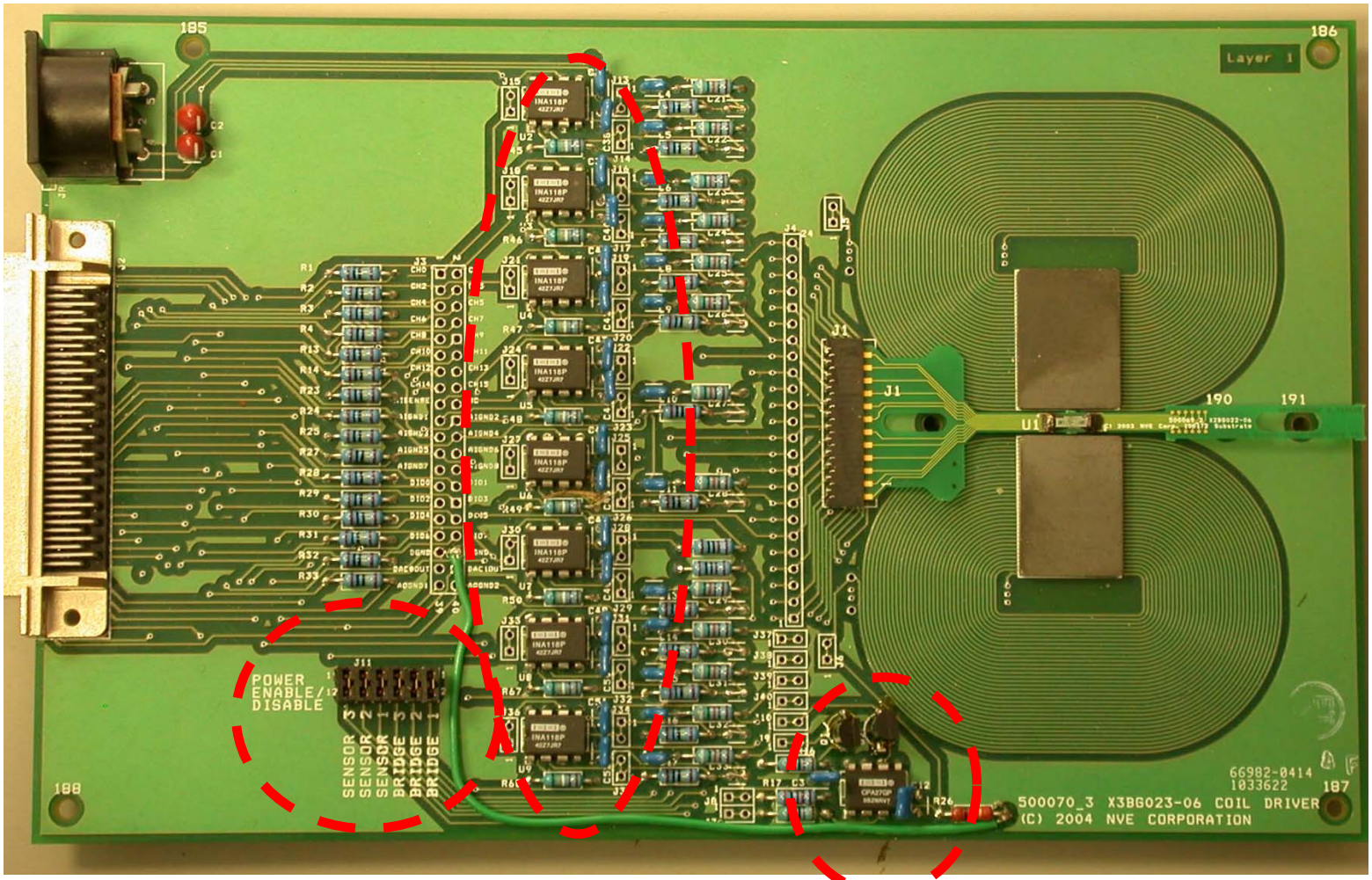
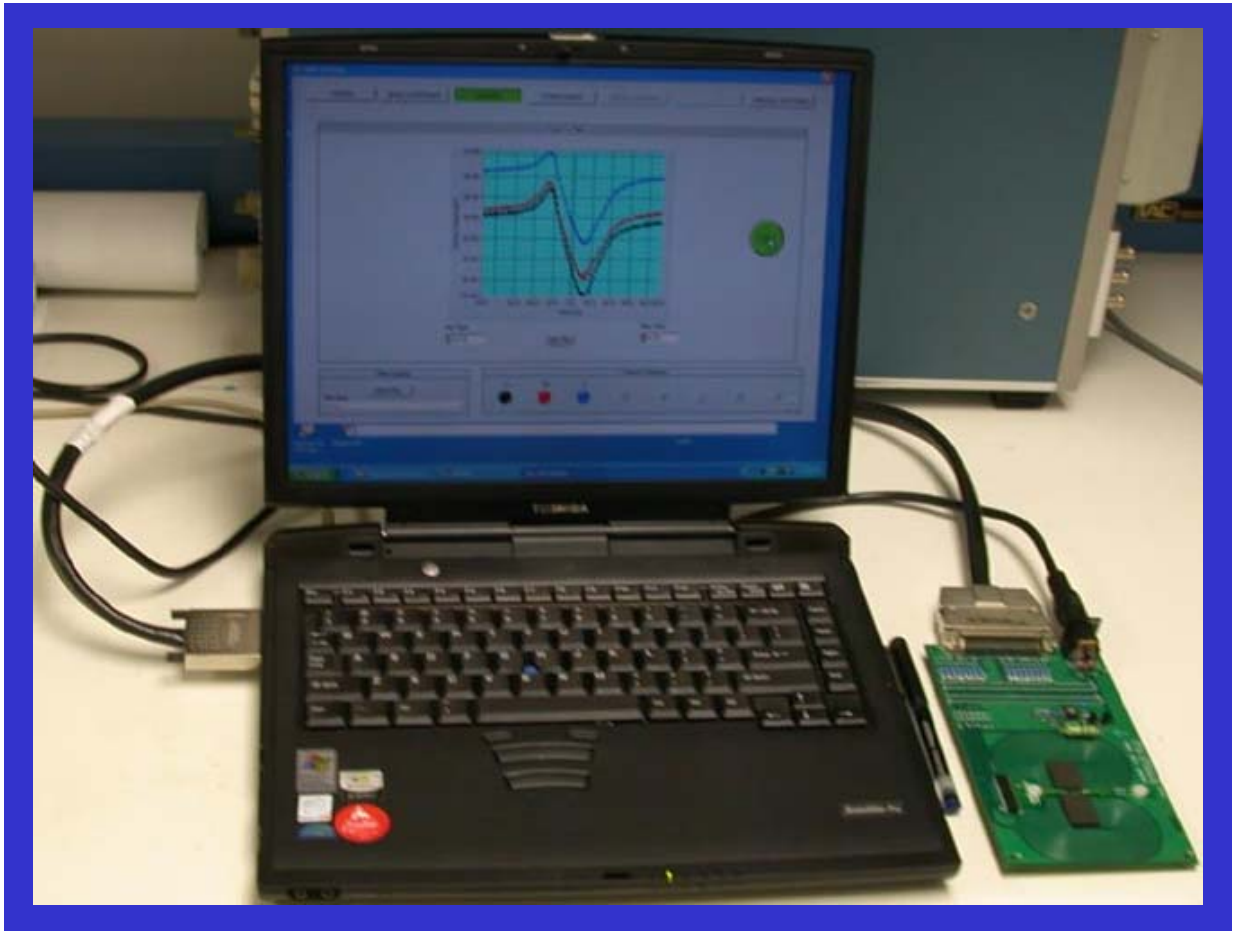
# Magnetic Excitation Module

- 8 On-board signal preamps
- Jumpers for sensor channels
- Jumpers for coil driver



# BioMagnetIC System



- A to D card in laptop
- Pocket-sized excitation module
- Disposable sensor cartridges
- Adaptable device development platform
- R vs. H plots
- Vout vs. time

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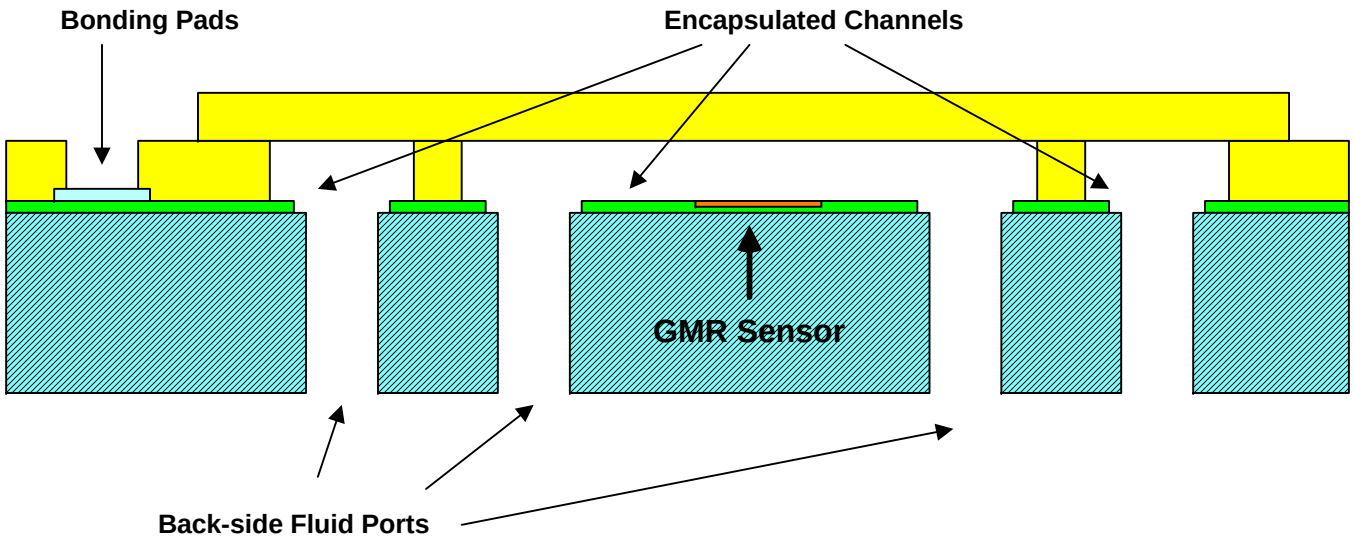
# New low profile fabrication process design

a) Motivation:
   1. Need wider channels to avoid plugging
   2. Lower surface topography for better flow and sealing
   3. Want thin cover for closest microscope working distance
   4. Improved manufacturability

b) Features
   1. Buried interconnects formed using damascene process
   2. Allows arbitrary channel width and alignment
   3. Much lower surface step height (<100 nm vs. 2000 nm)
   4. Thin passivation is viable (<100 nm)
   5. Facilitates electrodes for electrochemistry and applying electric forces
   6. Fluidic through-holes for better optical access and fluidics options

# New low profile fabrication process design

a) Fluidic Through-holes

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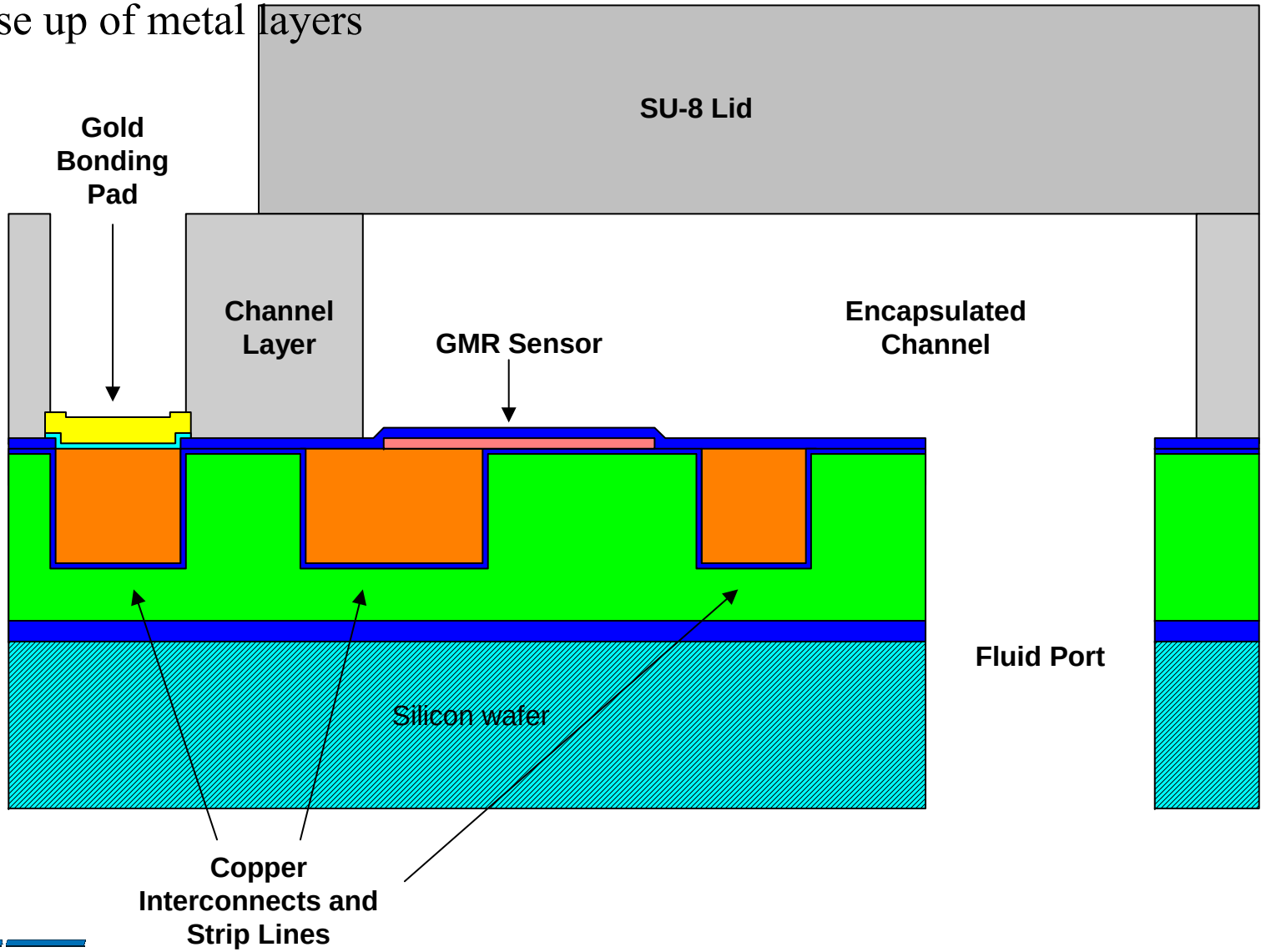
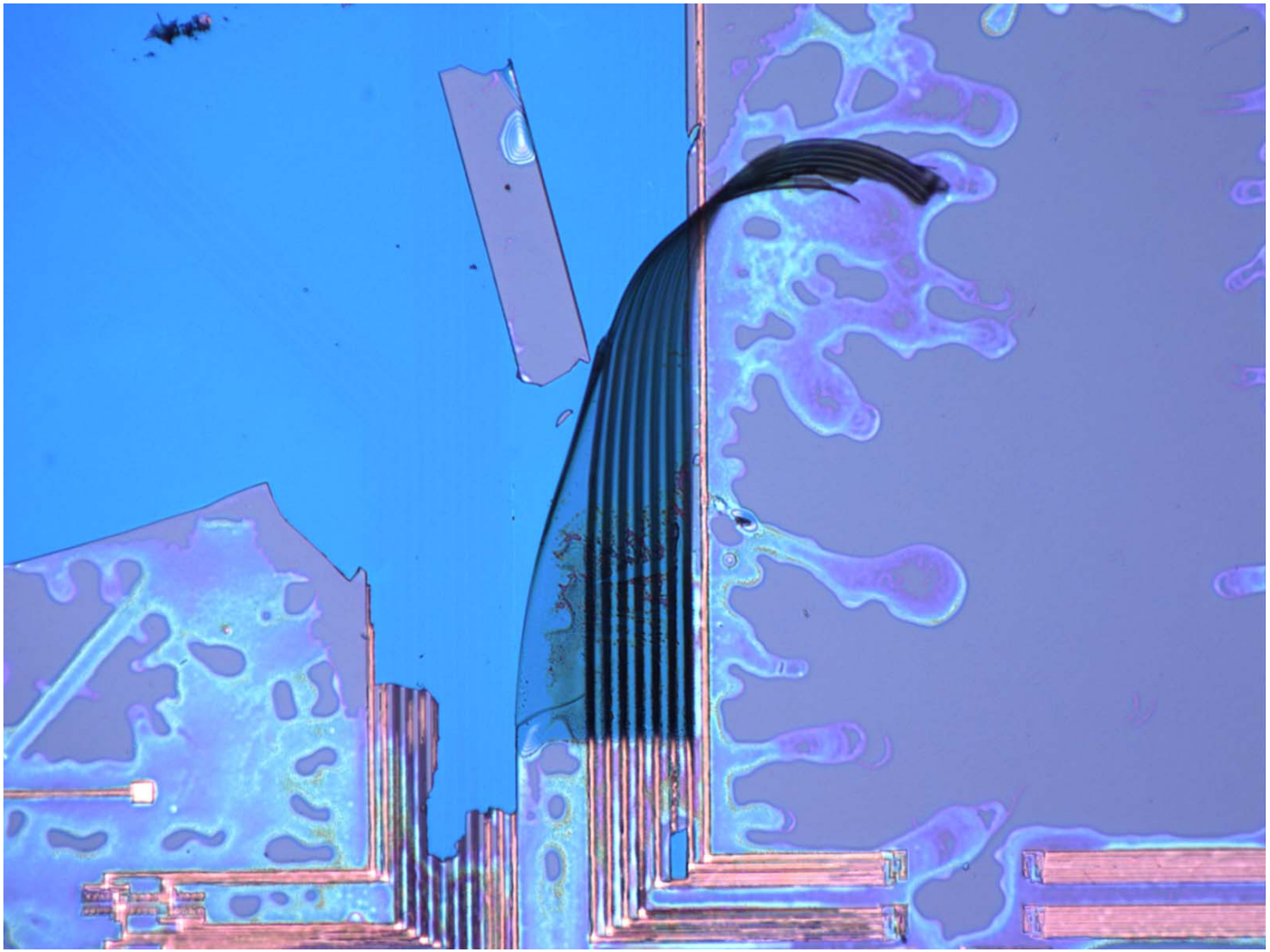
# New low profile fabrication process design

a) Close up of metal layers



# Fabrication Challenges: Stress (and strain) management



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# Possible Advantages of Magnetic Cytometer

- Portable high performance bioanalytical system for military
- Many parallel channels are possible: higher throughput
- More affordable laboratory system

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# Summary

- Detection of flowing magnetic objects is feasible
- Sorting and redirecting in microfluidic channels works well
- Magnetic flow cytometer requires wider (unplugged) channels, which introduces new challenges for detection
- Magnetic focusing alone may suffice
- Fabrication of new designs is in progress

www.nve.com/~markt/biomagnetics

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