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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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.
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)
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
Magnetic capture is a common approach

- Add special magnetic particles to container
Magnetic capture is a common approach

- Add special magnetic particles to container
- Allow specific binding of labels to cell
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
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
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
GMR Sensing of Magnetic Picodroplets

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

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

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

• Channel passes over sensing GMRs
Idealized Spin Valve Transfer Curve

Resistance $\propto R_0 + \sin \theta$
Resistance when labels are present

Resistance $\propto R_0 + \sin \theta$

Signal is resistance difference

Resistance with labels

Field (Oe)
Simulation using “Amperes” magnetic modeling software

$H_x$ in Sensor Plane, Flowing Ferrofluid Plug

$H_{\text{applied}} = 15$ Oersted

Plug dimensions: 13 $\mu$m wide 18 $\mu$m deep 85 $\mu$m long

FerroTec 307 10nm ferrite particles $\sim$1% by volume

Effective GMR sensor area

X direction, $\parallel$ GMR sense axis, $\parallel$ direction of flow

GMR signal ($\text{mV}$) vs. $x$ ($\mu$m)
Direct Flow Velocity Monitoring

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

Velocity determined by cross-correlating the signals from two bridges
Detection of single ~5 micron beads in flow
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<sup>TM</sup>)
Homogeneous 1-µm shell, \( \chi = 0.18 \)
Homogeneous 200-nm shell, \( \chi = 0.2 \)
(Micromod nanomag-D, \( \chi = 2 \))
Model: fractional field change vs. distance

Relative change in $H_x$

Homogeneous 1-µm shell, $\chi = 0.18$
Field vs. position (time) for 2.8 micron Dynal Bead

Stray field vs. longitude in 100 Oe Hx

Hx (Oe)

Altitude (µm)

microns
Stray field vs. longitude in 100 Oe Hx

Field vs. position (time) for 2.8 micron Dynal Bead
Detection of labels and cells in small channels is magnetically easy
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

old design

12 µm x 15 µm channel x-section

3 µm x 15 µm detector area

GMR detector
Challenges

new design

50 µm x 35 µm channel x-section

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?

2 µm x 2 µm detector area

GMR detector
Simple situation: qualitative force calc.

\[ H_x = H_{\text{external}} = 100 \text{ Oe} \]

50 \( \mu \text{m} \) x 35 \( \mu \text{m} \) channel x-section

1 \( \mu \text{m} \) diameter
Paramagnetic
Small wire x-section
\( H_{\text{external}} \) across channel
\( H_{\text{external}} \) parallel \( H_{\text{wire}} \)

Current into plane
1 \( \mu \text{m} \) x 1 \( \mu \text{m} \) wire
under channel center
Simple situation: qualitative force calc.

\[ H_x = H_{\text{external}} = 100 \text{ Oe} \]

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

1 \( \mu \)m diam. Particles paramagnetic
Small wire x-section
\( H_{\text{external}} \) across channel
\( H_{\text{external}} \) parallel \( H_{\text{wire}} \)

Current into plane
1 \( \mu \)m x 1 \( \mu \)m wire
under channel center
Quantitative Theoretical Assessment

Equation of motion

\[
m\frac{dv}{dt} = -3\pi \eta av + F_{mag}
\]

Integrate to get velocity

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

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
**Equation of motion**

\[
m \frac{dv}{dt} = -3\pi \eta a v + F_{\text{mag}}
\]

For a given \( F_{\text{mag}} \), one can calculate:
- “terminal velocity”
- “characteristic time”

**Integrate to get velocity**

\[
v(t) = \frac{F_{\text{mag}}}{3\pi \eta a} \left( 1 - e^{-\frac{3\pi \eta a}{m} t} \right)
\]
Quantitative Theoretical Assessment

\[ m \frac{dv}{dt} = -3\pi \eta a v + F_{mag} \]

\[ v(t) = \frac{F_{mag}}{3\pi \eta a} \left( 1 - e^{-\frac{3\pi \eta a}{m} t} \right) \]
Force on particle far from wire

\[ H_x = H_{\text{external}} = 100 \text{ Oe} \]

Initial \( F_{\text{mag}} \approx 9 \text{ picoN} \)
Initial \( V_{\text{terminal}} \approx 1100 \mu\text{m/sec} \)
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
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
\[ F_{\text{mag}} = (\mathbf{m} \cdot \nabla)\mathbf{B} \]

Theoretical Assessment

\[ F_{mag} = \frac{V \chi}{2 \mu_0} \nabla B^2 \]

\[ i = 50 \text{ mA}; B_{ext} = 16 \text{ mT}; \chi = 0.1; a = 1 \mu\text{m} \]
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

Top view

Channel: 400 µm long

Electrical current

Flow

X-sections

H_{ext}
Sorting cells from labels

$H_x = H_{\text{external}} = 100 \text{ Oe}$

50 $\mu$m x 35 $\mu$m channel x-section

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

Flow into page

1 $\mu$m x 1 $\mu$m wire under channel center
Sorting cells from labels

\[ H_x = H_{\text{external}} = 100 \text{ Oe} \]

50 \( \mu \text{m} \) x 35 \( \mu \text{m} \) channel x-section

Attract all objects to one wire

Flow into page

Current into plane
1 \( \mu \text{m} \) x 1 \( \mu \text{m} \) wire under channel center
Sorting cells from labels

\[ H_x = H_{\text{external}} = 100 \text{ Oe} \]

50 \( \mu \text{m} \times 35 \mu \text{m} \) channel x-section

Selectively pull cells to another wire

Flow into page

1 \( \mu \text{m} \times 1 \mu \text{m} \) wire under channel center
Cell sorter, director, and detector
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.
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

- Electrical connections
- PDMS Fluidic connections
- Optical access
Dice, mount on circuit board, wire bond
Ready to use fluidic / GMR chip
Die-Holding Printed Circuit Board

Design Basics

24 pin surface mount edge connector

Narrow die area for fitting between in the excitation magnet gap

“Diving Board”

Wire bonds are potted such that sense pad is still exposed
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
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
New low profile fabrication process design

a) Close up of metal layers
Fabrication Challenges: Stress (and strain) management
Possible Advantages of Magnetic Cytometer

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

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