Nanotechnology for Imaging and Therapy: Advances in *in vivo* Magnetic Nanoparticle Sensing

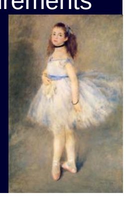
John B. Weaver
Department of Radiology
Geisel School of Medicine
Dartmouth College
and Dartmouth-Hitchcock Medical Center

Richard P. Feynman "There's Plenty of Room at the Bottom" (1959):

"The principles of physics, as far as I can see, do not speak against the possibility of maneuvering things atom by atom." … "Consider the possibility that we too can make a thing very small which does what we want – that we can manufacture an object that maneuvers at that level!"

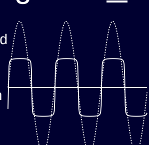
Outline

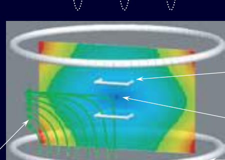
Sensitive Detection
Magnetic Nanoparticle Imaging MPI
MSB Spectroscopy
MSB Measurements
for Inflammation/Immune Monitoring:
- Molecular Concentration Measurements (*in vivo* ELISA)
- Phagocytic Activity - cell uptake
- Temperature



Disclosures:
- IP
- NIH/NCI 1U54CA151662 CCNE

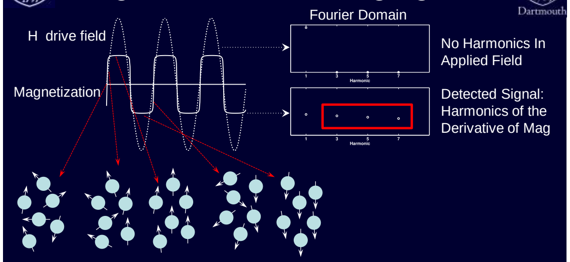
Magnetic Particle Imaging, MPI



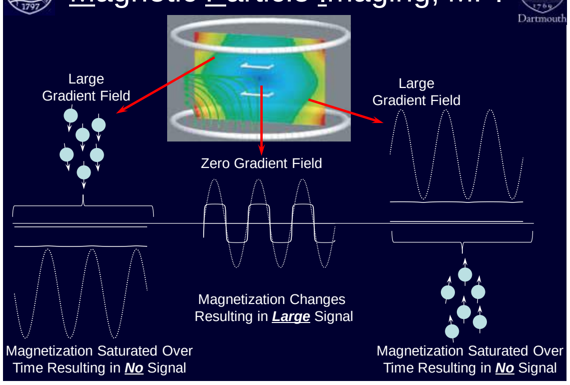


Gleich B, Weizenecker J. Tomographic imaging using the nonlinear response of magnetic particles. *Nature* 2005, **435**(7046): 1214-1217.

Magnetic Particle Imaging, MPI



Magnetic Particle Imaging, MPI



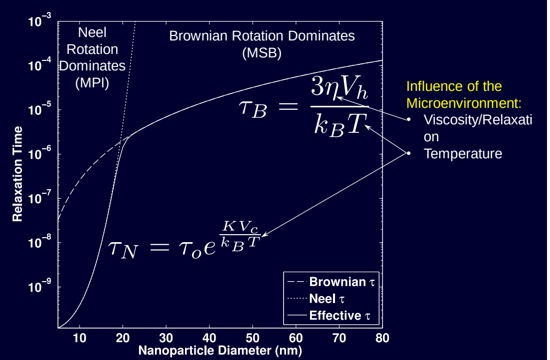
MPI - Magnetic Particle Imaging:

- High Sensitivity by Detecting Harmonics
- Localization by Saturating Nanoparticles Outside Field-Free Point

Development Focused on:

- Low Noise Electronics - Good Filters
- Large Field Gradients*
- Nanoparticles with High Saturation & Neel Relaxation

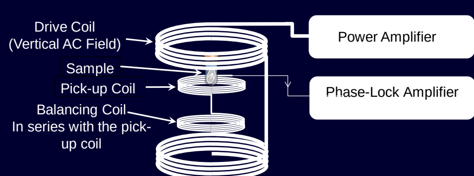
Relaxation Mechanisms



Magnetic Particle Spectroscopy

MSB Magnetic Spectroscopy of Brownian Motion

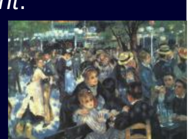
1) Measures Harmonics – MPI Detection Sensitivity with
2) Larger Nanoparticles that Rotate Via Brownian Motion so the Signal Reflects the Microenvironment

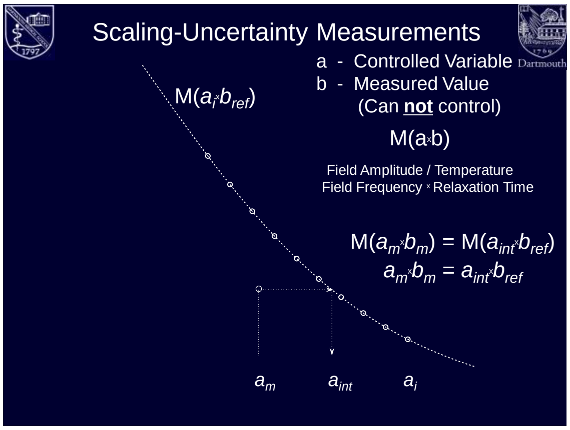


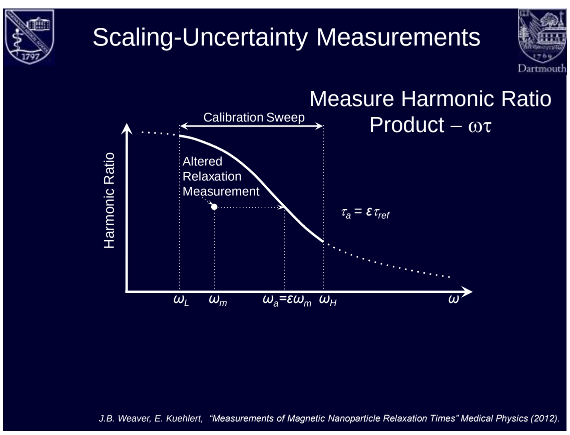
Scaling-Uncertainty Measurements

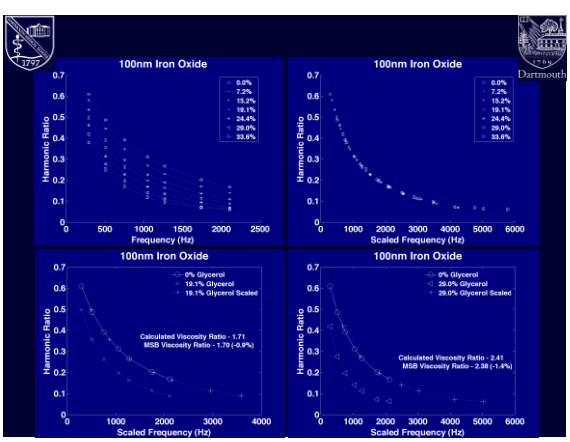
Measured quantity that is
monotonic function of the product of
1) an unknown and
*2) an user control*led quantity.

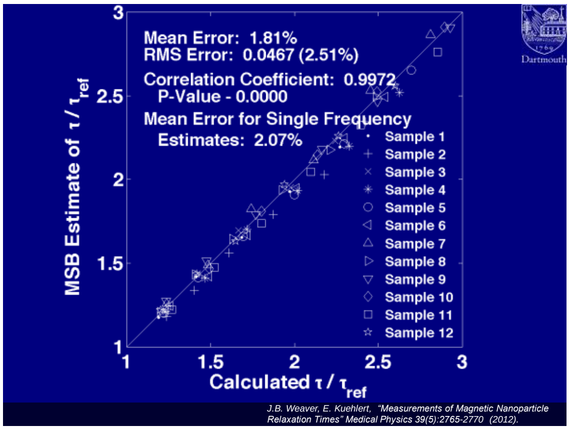
Need not characterize either
Functional form or *Environment*.



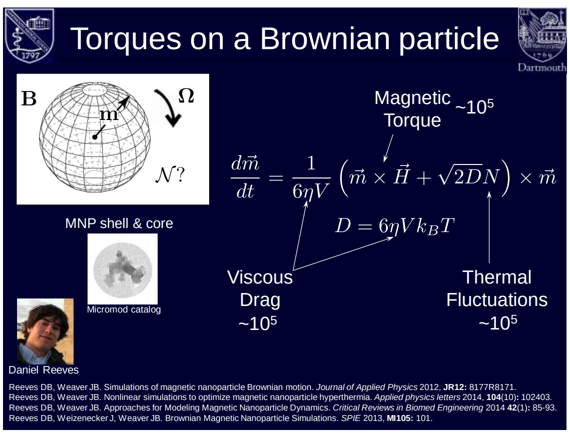

Scaling-Uncertainty Measurements
a - Controlled Variable
b - Measured Value
(Can not control)
M(a·b)
Field Amplitude / Temperature
Field Frequency × Relaxation Time
M(a_i·b_ref)
M(a_m·b_m) = M(a_int·b_ref)
a_m·b_m = a_int·b_ref
a_m
a_int
a_i
Dartmouth


Scaling-Uncertainty Measurements
Measure Harmonic Ratio
Product – ωτ
Calibration Sweep
Harmonic Ratio
Altered
Relaxation
Measurement
τ_a = ετ_ref
ω_L
ω_m
ω_a=εω_m
ω_H
ω
J.B. Weaver, E. Kuehlert, "Measurements of Magnetic Nanoparticle Relaxation Times" Medical Physics (2012).
Dartmouth

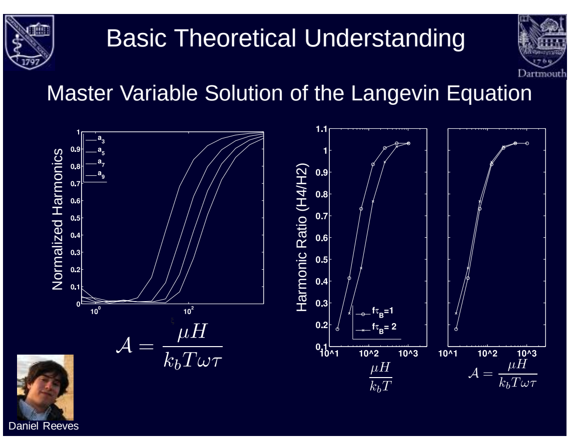

100nm Iron Oxide
Harmonic Ratio
Frequency (Hz)
Scaled Frequency (Hz)
0.0%
7.2%
15.2%
19.1%
24.4%
29.0%
33.6%
0% Glycerol
19.1% Glycerol
19.1% Glycerol Scaled
Calculated Viscosity Ratio - 1.71
MSB Viscosity Ratio - 1.70 (-0.9%)
29.0% Glycerol
29.0% Glycerol Scaled
Calculated Viscosity Ratio - 2.41
MSB Viscosity Ratio - 2.38 (-1.4%)
Dartmouth



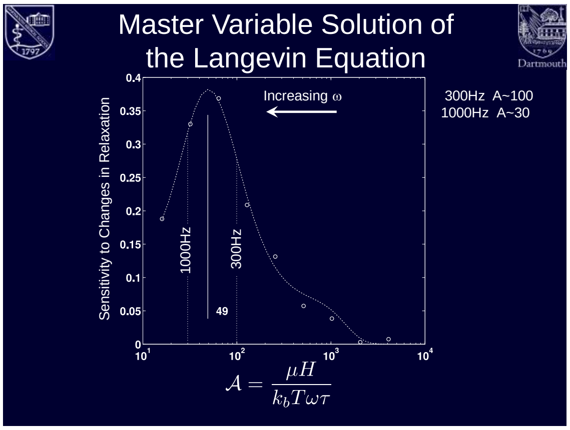
Mean Error: 1.81%
RMS Error: 0.0467 (2.51%)
Correlation Coefficient: 0.9972
P-Value - 0.0000
Mean Error for Single Frequency
Estimates: 2.07%
Sample 1
Sample 2
Sample 3
Sample 4
Sample 5
Sample 6
Sample 7
Sample 8
Sample 9
Sample 10
Sample 11
Sample 12
MSB Estimate of τ / τref
Calculated τ / τref
Dartmouth
J.B. Weaver, E. Kuehlert, "Measurements of Magnetic Nanoparticle Relaxation Times" Medical Physics 39(5):2765-2770 (2012).

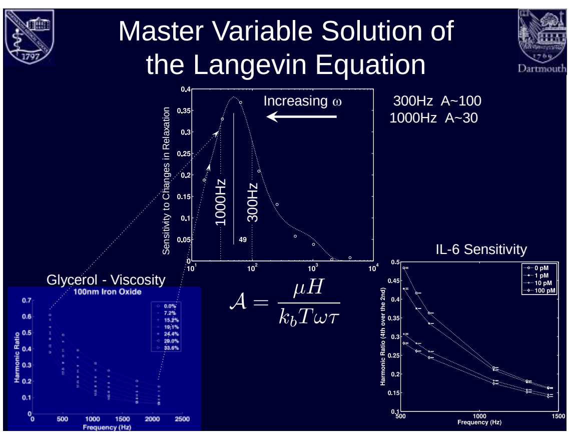


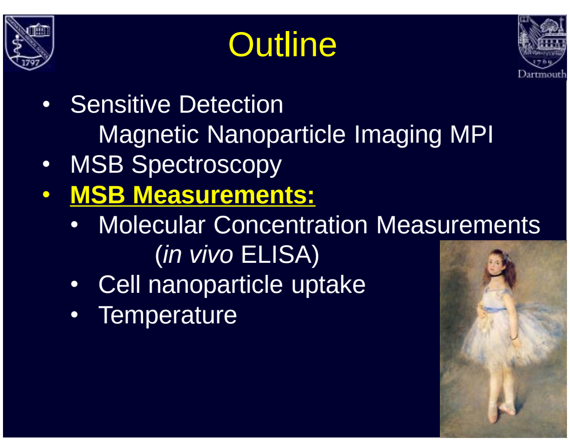
Torques on a Brownian particle
B
m
Ω
𝒩?
MNP shell & core
Micromod catalog
Magnetic Torque ~10^5
$\frac{d\vec{m}}{dt} = \frac{1}{6\eta V}\left(\vec{m} \times \vec{H} + \sqrt{2D}N\right) \times \vec{m}$
$D = 6\eta V k_B T$
Viscous Drag ~10^5
Thermal Fluctuations ~10^5
Daniel Reeves
Reeves DB, Weaver JB. Simulations of magnetic nanoparticle Brownian motion. Journal of Applied Physics 2012, JR12: 8177R8171.
Reeves DB, Weaver JB. Nonlinear simulations to optimize magnetic nanoparticle hyperthermia. Applied physics letters 2014, 104(10): 102403.
Reeves DB, Weaver JB. Approaches for Modeling Magnetic Nanoparticle Dynamics. Critical Reviews in Biomed Engineering 2014 42(1): 85-93.
Reeves DB, Weizenecker J, Weaver JB. Brownian Magnetic Nanoparticle Simulations. SPIE 2013, MI105: 101.
Dartmouth



Basic Theoretical Understanding
Master Variable Solution of the Langevin Equation
Normalized Harmonics
a_3
a_5
a_7
a_9
$\mathcal{A} = \frac{\mu H}{k_b T \omega \tau}$
Harmonic Ratio (H4/H2)
$f\tau_B$=1
$f\tau_B$= 2
$\frac{\mu H}{k_b T}$
$\mathcal{A} = \frac{\mu H}{k_b T \omega \tau}$
Daniel Reeves
Dartmouth


Master Variable Solution of the Langevin Equation
Increasing ω
300Hz A~100
1000Hz A~30
Sensitivity to Changes in Relaxation
1000Hz
300Hz
49
$\mathcal{A} = \frac{\mu H}{k_b T \omega \tau}$
Dartmouth


Master Variable Solution of the Langevin Equation
Increasing ω
300Hz A~100
1000Hz A~30
Sensitivity to Changes in Relaxation
1000Hz
300Hz
49
$\mathcal{A} = \frac{\mu H}{k_b T \omega \tau}$
Glycerol - Viscosity
100nm Iron Oxide
Harmonic Ratio
Frequency (Hz)
IL-6 Sensitivity
0 pM
1 pM
10 pM
100 pM
Dartmouth


Outline
• Sensitive Detection
Magnetic Nanoparticle Imaging MPI
• MSB Spectroscopy
• MSB Measurements:
• Molecular Concentration Measurements (in vivo ELISA)
• Cell nanoparticle uptake
• Temperature
Dartmouth

Biological Markers

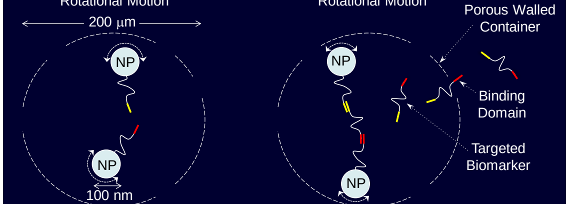
Immunotherapy effectiveness:
- Cytokine signaling changes – canine model TNFγ [1]

Infection Markers:
- Increased cytokine signaling
- Increased phagocytic activity
- Increased metabolic activity (Increased temperature)

Maekawa N, Konnai S, Ikebuchi R, Okagawa T, Adachi M, Takagi S, Kagawa Y, Nakajima C, Suzuki Y, Murata S. Expression of PD-L1 on Canine Tumor Cells and Enhancement of IFN-γ Production from Tumor-Infiltrating Cells by PD-L1 Blockade. *PloS one* 2014, **9**(6): e98415

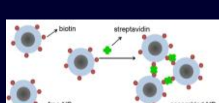
in vivo ELISA

Microscopic probes to measure quantitative concentrations *in vivo* over time

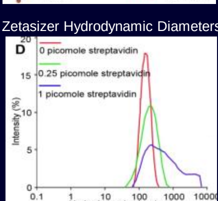


1. A.M. Rauwerdink, J.B. Weaver, "Measurement of Molecular Binding Using The Brownian Motion of Magnetic Nanoparticle Probes" Applied Physics Letters 96, 033702 (2010).
2. A.M. Rauwerdink, J.B. Weaver, "Concurrent quantification of nanoparticle bound states", Medical Physics 38(3):1136-1140, (2011).
3. J.B. Weaver, E. Kuehlert, "Measurements of Magnetic Nanoparticle Relaxation Times" Medical Physics 39(5):2765-2770 May (2012).
4. X. Zhang, D.B. Reeves, I.M. Perreard, W.C. Kett , K.E. Griswold, B. Gimi, John B. Weaver "Molecular Sensing with Magnetic Nanoparticles Using Magnetic Spectroscopy of Nanoparticle Brownian Motion" Biosensors and Bioelectronics **50**:441–446 (2013).

Concentration Measurements



Zetasizer Hydrodynamic Diameters



Electron Microscopy

0 pmole

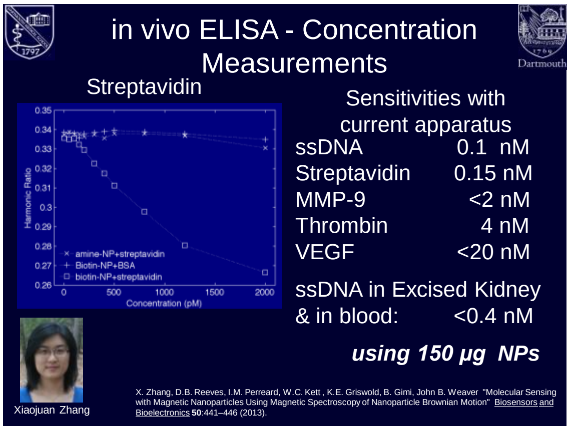
0.25 pmole

1.0 pmole

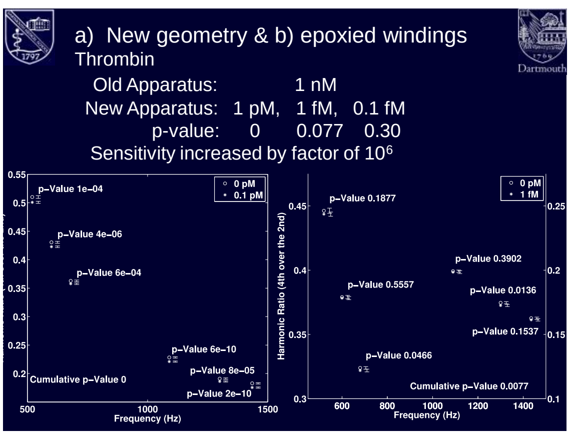
Increasing amount of streptavidin

Xiaojuan Zhang

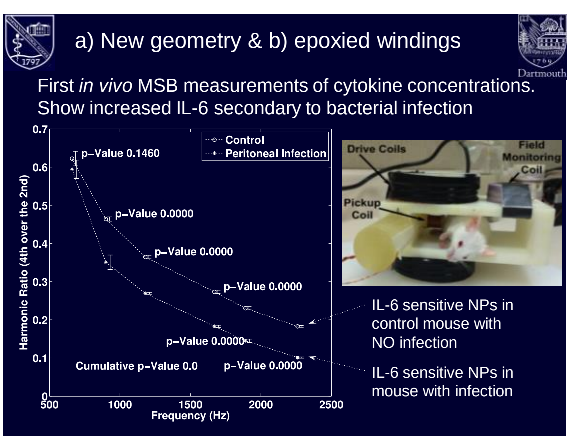
X. Zhang, D.B. Reeves, I.M. Perreard, W.C. Kett , K.E. Griswold, B. Gimi, John B. Weaver "Molecular Sensing with Magnetic Nanoparticles Using Magnetic Spectroscopy of Nanoparticle Brownian Motion" Biosensors and Bioelectronics **50**:441–446 (2013).



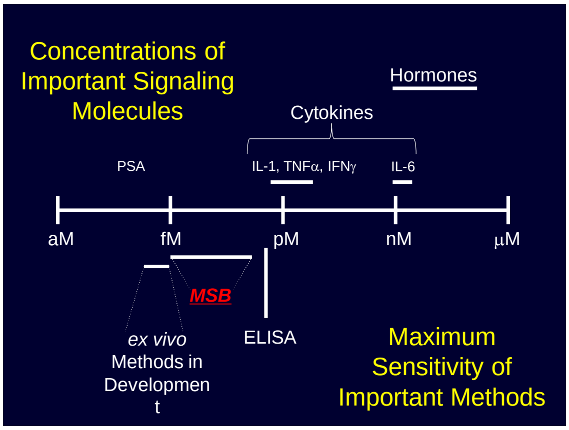
in vivo ELISA - Concentration Measurements
Streptavidin
Sensitivities with current apparatus
ssDNA 0.1 nM
Streptavidin 0.15 nM
MMP-9 <2 nM
Thrombin 4 nM
VEGF <20 nM
ssDNA in Excised Kidney & in blood: <0.4 nM
using 150 µg NPs
Xiaojuan Zhang
X. Zhang, D.B. Reeves, I.M. Perreard, W.C. Kett, K.E. Griswold, B. Gimi, John B. Weaver "Molecular Sensing with Magnetic Nanoparticles Using Magnetic Spectroscopy of Nanoparticle Brownian Motion" Biosensors and Bioelectronics 50:441–446 (2013).
Harmonic Ratio
Concentration (pM)
amine-NP+streptavidin
Biotin-NP+BSA
biotin-NP+streptavidin



a) New geometry & b) epoxied windings
Thrombin
Old Apparatus: 1 nM
New Apparatus: 1 pM, 1 fM, 0.1 fM
p-value: 0 0.077 0.30
Sensitivity increased by factor of 10^6
0 pM
0.1 pM
p–Value 1e–04
p–Value 4e–06
p–Value 6e–04
p–Value 6e–10
p–Value 8e–05
p–Value 2e–10
Cumulative p–Value 0
Frequency (Hz)
Harmonic Ratio (4th over the 2nd)
0 pM
1 fM
p–Value 0.1877
p–Value 0.3902
p–Value 0.5557
p–Value 0.0136
p–Value 0.1537
p–Value 0.0466
Cumulative p–Value 0.0077
Frequency (Hz)

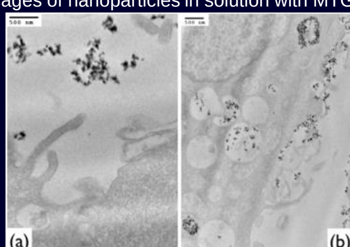


a) New geometry & b) epoxied windings
First in vivo MSB measurements of cytokine concentrations.
Show increased IL-6 secondary to bacterial infection
Control
Peritoneal Infection
p–Value 0.1460
p–Value 0.0000
p–Value 0.0000
p–Value 0.0000
p–Value 0.0000
Cumulative p–Value 0.0
p–Value 0.0000
Harmonic Ratio (4th over the 2nd)
Frequency (Hz)
Drive Coils
Field Monitoring Coil
Pickup Coil
IL-6 sensitive NPs in control mouse with NO infection
IL-6 sensitive NPs in mouse with infection



in vitro Cell Uptake

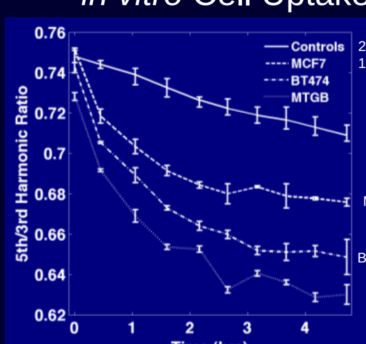
TEM images of nanoparticles in solution with MTG-B cells.



(a) 5 minutes (b) 5 hours
post addition of nanoparticles
Nanoparticles are (a) outside cells (b) in vesicles and on cell surface.

Adam M. Rauwerdink (& J.B. Weaver)
Andrew J. Giustini (& P.J. Hoopes)

in vitro Cell Uptake



290 Hz
16 mT/μ_0

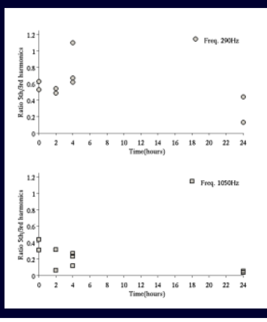
MCF-7 Uptake
less than
BT-474 Uptake [1]

[1] Steinhauser, I., Spankuch, B., Strebhardt, K., Langer, K., 2006. Biomaterials 27, 4975-4983.

A.J. Giustini, I.M. Perreard, A.M. Rauwerdink, P.J. Hoopes, J.B. Weaver, "Noninvasive assessment of magnetic nanoparticle-cancer cell interactions" Integrative Biology 4:1283-8 (2012).

in vivo Tumor Uptake Studies

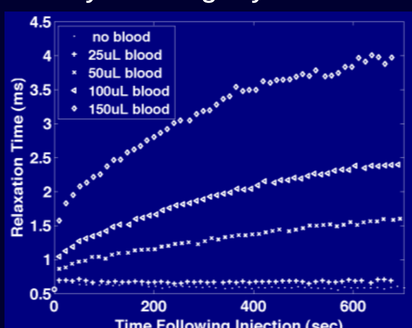
Harmonic Ratio vs Incubation Time in Tissue



1. Direct Injection
2. Incubation
3. Tumor Excision
4. Tumor Division
5. MSB Measurement
6. Pathology

Adam M. Rauwerdink (& J.B. Weaver)
Andrew J. Giustini (& P.J. Hoopes)

Activity of Phagocytes in Blood



Daniel Reeves, Irina Perrard, Xiaojuan Zhang (& J.B. Weaver)
Seiko T. Brown (& S. N. Fiering)

Ovarian Cancer Early Detection

Method: 24 hrs post ip NP inj. in mice

P53/Kras Tg | **WT Control**

Increased uptake by ovarian cancer

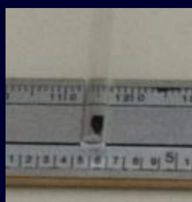
Uniform Signal

Contralateral **AdvCre** **Contralateral** **AdvCre**

J.B. Weaver, U.K. Scarlett, A.M. Rauwerdink, S.N. Fiering, J.R. Conejo-Garcia, "Potential Ovarian Cancer Screening Method: Immunologically Targeted Nanoparticles Detected with Magnetic Spectroscopy of Nanoparticle Brownian Motion" RSNA 2011 11034641 (LL-PHS-TU7B).

Identify Surgical Site Infections

UHMWP Temperature Probe Material from Anna Samia's lab, Case Western Reserve



Small (Neel Relaxing) Nanoparticles Embedded in UHMWP

- Solid (large signal)
- Biologically inert
- Localized
- Mean Error 0.4º

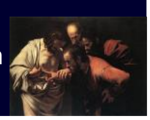
Anna Samia Case Western Reserve University

Conclusions:

- **MSB can monitor local immune/inflammatory responses**
  - **Cytokine concentrations**
  - **Phagocytic activity - cell uptake**
  - **Temperature.**
- **MSB Sensitivity can be further optimized.**

We believe that the potential applications are many and diverse:

- **Cancer therapy monitoring**
- **Early infection identification**
- **Early cancer detection**

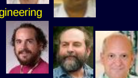


Current NP Students
Yipeng Shi, Physics

Microbiology and Immunology
Prof. Steven Fiering
Prof. Brent Berwin

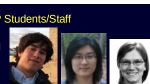
Radiology
Prof. Barjor Gimi
Venkata Nemani

Thayer School of Engineering
Prof. Ryan Halter
Prof. Alex Hartov
Prof. Keith Paulsen

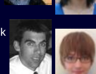


Surgery
Prof. P.Jack Hoopes
Dr. Sohail Mirza

Former Weaver NP Students/Staff
Dr. Daniel Reeves
Dr. Xiaojuan Zhang
Dr. Irina Perreard



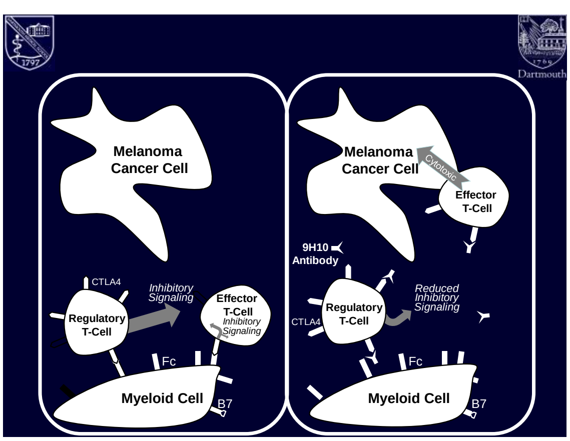
Dr. Adam Rauwerdink
Esra Kuehlert

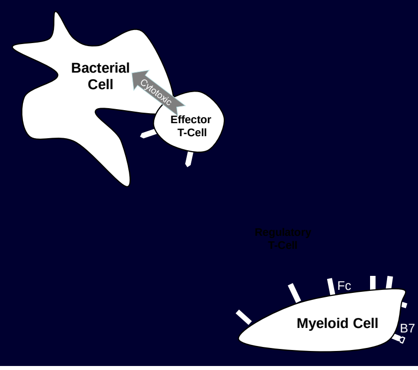


Richard P. Feynman "There's Plenty of Room at the Bottom" (1959):

"The principles of physics, as far as I can see, do not speak against the possibility of maneuvering things atom by atom." … "Consider the possibility that we too can make a thing very small which does what we want – that we can manufacture an object that maneuvers at that level!"

1) NIH - Centers for Cancer Nanotechnology Excellence 1U54CA151662-01
2) Norris Cotton Cancer Center
3) Department of Radiology


Melanoma
Cancer Cell
CTLA4
Inhibitory
Signaling
Effector
T-Cell
Inhibitory
Signaling
Regulatory
T-Cell
Fc
Myeloid Cell
B7
Melanoma
Cancer Cell
Cytotoxic
Effector
T-Cell
9H10
Antibody
Reduced
Inhibitory
Signaling
Regulatory
T-Cell
CTLA4
Fc
Myeloid Cell
B7



MSB Applications:

MSB[1] (or MPS) employs the signal used in MPI to characterize the microenvironment:

- Temperature[1-4]
- Viscosity[5, 6]
- Cell Phagocytic Activity[7]
- Signaling Molecules[8, 9]
- Local Matrix Rigidity[10, 11]

1. John B. Weaver, Adam M. Rauwerdink, Hansen EW. Magnetic nanoparticle temperature estimation. ***Med Phys*** 2009, **36**(5)**:** 1822-1829.
2. Perreard I, Reeves D, Zhang X, Kuehlert E, Forauer E, Weaver J. Temperature of the magnetic nanoparticle microenvironment: estimation from relaxation times. *PMB* 2014, **59**(5)**:** 1109.
3. Rauwerdink AM, Hansen EW, Weaver JB. Nanoparticle temperature estimation in combined ac and dc magnetic fields. *PMB* 2009, **54**(19)**:** L51-55.
4. Reeves DB, Weaver JB. Temperature measurements using static field magnetic particle spectroscopy. Magnetic Particle Imaging (IWMPI), 2013 International Workshop on; 2013 23-24 March 2013; 2013. p. 1-1.
5. Rauwerdink AM, Weaver JB. Viscous effects on nanoparticle magnetization harmonics. *J. of Mag and Mag Materials* 2010, **322**(6)**:** 609-613.
6. Rauwerdink AM, Weaver JB. Harmonic phase angle as a concentration-independent measure of nanoparticle dynamics. *Med Phys* 2010, **37**(6)**:** 2587-2592.
7. Giustini AJ, Perreard I, Rauwerdink AM, Hoopes PJ, Weaver JB. Noninvasive assessment of magnetic nanoparticle–cancer cell interactions. *Integrative Biology* 2012, **4**(10)**:** 1283-1288.
8. Zhang X, Reeves D, Shi Y, Gimi B, Nemani K, Perreard IM, Toraya-Brown S, Fiering S, Weaver JB. Toward Localized In Vivo Biomarker Concentration Measurements. *Magnetics, IEEE Transactions on* 2015, **51**(2)**:** 1-4.
9. Zhang X, Reeves DB, Perreard IM, Kett WC, Griswold KE, Gimi B, Weaver JB. Molecular sensing with magnetic nanoparticles using magnetic spectroscopy of nanoparticle Brownian motion. *Biosensors and Bioelectronics* 2013, **50**(0)**:** 441-446.
10. Weaver JB, Rauwerdink AM, Perreard I, Kilfoyle R. Micro-rheology: evaluating the rigidity of the microenvironment surrounding antibody binding sites. *SPIE Medical Imaging* 2010, **7626-54:** 1-8.
11. Weaver JB, Rauwerdink KM, Rauwerdink AM, Perreard IM. Magnetic spectroscopy of nanoparticle Brownian motion measurement of microenvironment matrix rigidity. *Biomedizinische Technik/Biomedical Engineering* 2013, **58**(6)**:** 547-550.

Microenvironment Sensing

- Temperature[1,2,19]
- Viscosity[3,6]
- Molecular Binding[4,5]
- Cell Uptake & Compartmentalization[8,9,15]
- Imaging[10,11,14,20]
- Molecular Concentrations[12,13,21,22]
- Heating Mechanisms & Modeling[16]
- Matrix Rigidity[17]
- NP Quantitation[18]

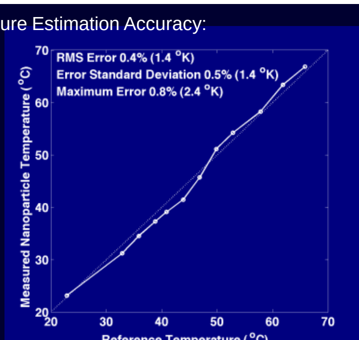
Applications we are pursuing in temporal order:

- Monitor Temperature During Hyperthermia Treatment
- Ovarian Cancer Screening
- *in vivo* ELISA for Immunotherapy Monitoring
- Early Identification of Surgical Site Infections

Conclusions:

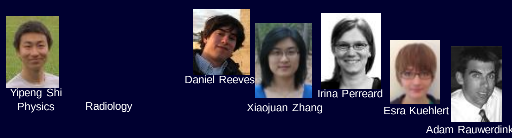
- **NP signals can be localized using a perpendicular magnetization induced by a static perpendicular field.**
- **Gradients in:**
  - **a) in-line and b) perpendicular fields can be used to achieve excellent conditioning (condition numbers <10).**
  - **In-line geometry is fast but requires larger dynamic fields**
  - **Perpendicular geometry requires small dynamic fields but is slower**
- **pMPI is worth further study**

Temperature Estimation Accuracy:



1. John B. Weaver, Adam M. Rauwerdink, Hansen EW. Magnetic nanoparticle temperature estimation. ***Med Phys*** 2009, **36**(5)**:** 1822-1829.
2. Perreard I, Reeves D, Zhang X, Kuehlert E, Forauer E, Weaver J. Temperature of the magnetic nanoparticle microenvironment: estimation from relaxation times. *PMB* 2014, **59**(5)**:** 1109.
3. Rauwerdink AM, Hansen EW, Weaver JB. Nanoparticle temperature estimation in combined ac and dc magnetic fields. *PMB* 2009, **54**(19)**:** L51-55.
4. Reeves DB, Weaver JB. Temperature measurements using static field magnetic particle spectroscopy. Magnetic Particle Imaging (IWMPI), 2013 International Workshop on; 2013 23-24 March 2013; 2013. p. 1-1.

1) NIH - Centers for Cancer Nanotechnology Excellence 1U54CA151662-01
2) Norris Cotton Cancer Center, Prouty Funds
3) Department of Radiology

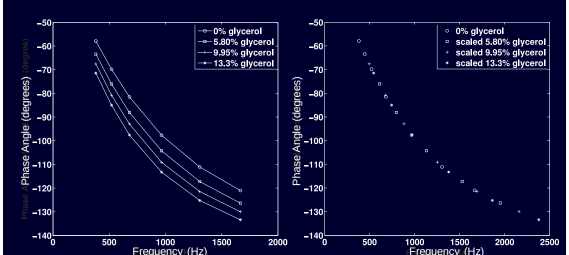


Current Weaver NP Postdocs/Students

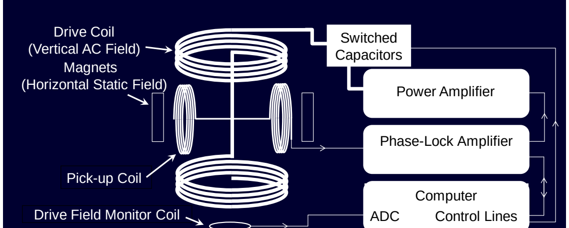
Former Weaver NP Students

1) NIH - Centers for Cancer Nanotechnology Excellence 1U54CA151662-01
2) Norris Cotton Cancer Center, Prouty Grant
3) Department of Radiology

Phase Angle Scaling with Viscosity



New Apparatus Geometry



D.B. Reeves, J.B. Weaver, "Magnetic nanoparticle sensing: decoupling the magnetization from the excitation field", J. Phys. D: Appl. Phys. 47:045002 (8pp) (2014).

a) New geometry & b) epoxied windings

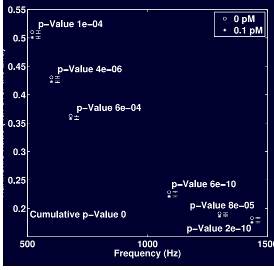
Thrombin

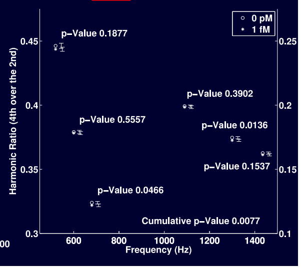
Old Apparatus: 1 nM

New Apparatus: 1 pM, 1 fM, 0.1 fM

p-value: 0 0.077 0.30

Sensitivity increased by factor of 10^6





Perpendicular Apparatus Geometry 2nd Gen

D.B. Reeves, J.B. Weaver, "Magnetic nanoparticle sensing: decoupling the magnetization from the excitation field", J. Phys. D: Appl. Phys. 47:045002 (8pp) (2014).

Daniel Reeves

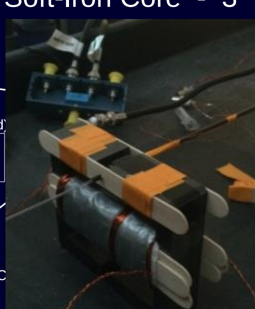
Perpendicular Apparatus Geometry With Soft-Iron Core - 3rd Gen

Drive Coil (Vertical AC Field)

Magnets (Horizontal Static Field)

Pick-up Coil

Drive Field Monitor C



wer Amplifier

-Lock Amplifier

Computer

Control Lines

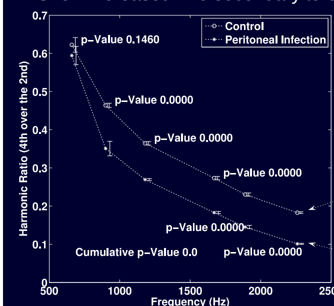
Apparatus Comparison

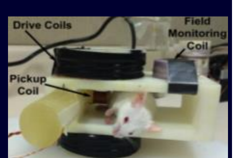
Generation	1	2	3
Feedthrough	2.5 nV	0.3 nV	0.04 nV
Standard Deviation in Feedthrough	0.2 nV	0.02 nV	0.006 nV
Sensitivity (grams iron)	90 µg[1]	100 ng[2]	< 10 ng
Concentration Sensitivity (Molar)	1 nM[1]	1 fM ?	

1) X. Zhang, D.B. Reeves, I.M. Perreard, W.C. Kett , K.E. Griswold, B. Gimi, John B. Weaver "Molecular Sensing with Magnetic Nanoparticles Using Magnetic Spectroscopy of Nanoparticle Brownian Motion" Biosensors and Bioelectronics **50**:441–446 (2013).
2) Zhang X, Reeves DB, Shi Y, Gimi B, Nemani KV, Perreard IM, Toraya-Brown S, Fiering S, Weaver JB. Toward Localized in vivo Biomarker Concentration Measurements. IEEE transactions on magnetics 2015.

a) New geometry & b) epoxied windings

First *in vivo* MSB measurements of cytokine concentrations.
Show increased IL-6 secondary to bacterial infection

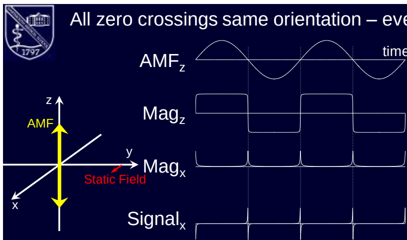




IL-6 sensitive NPs in control mouse with NO infection

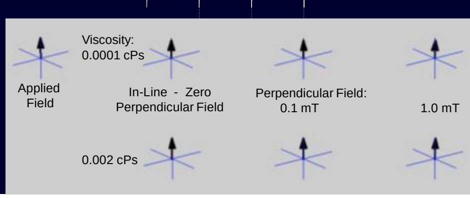
IL-6 sensitive NPs in mouse with infection

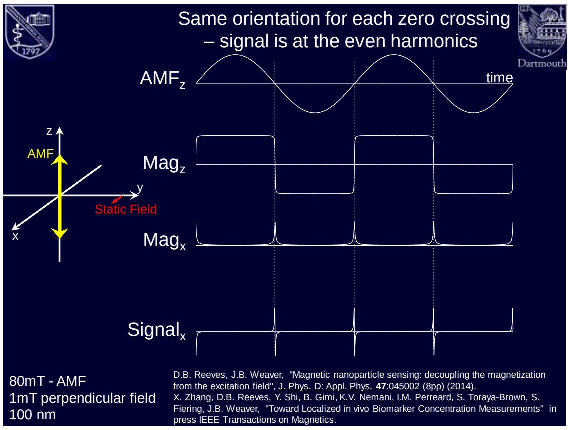
All zero crossings same orientation – even harmonics

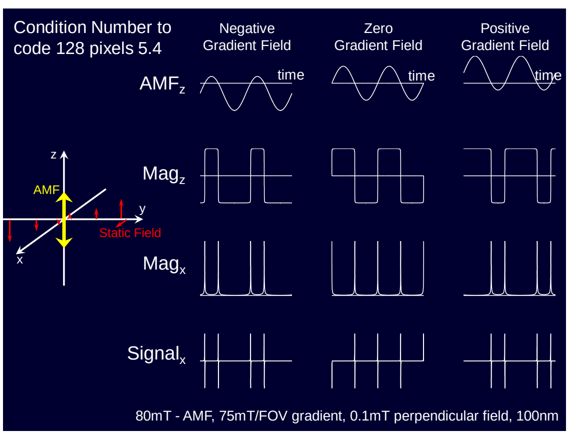


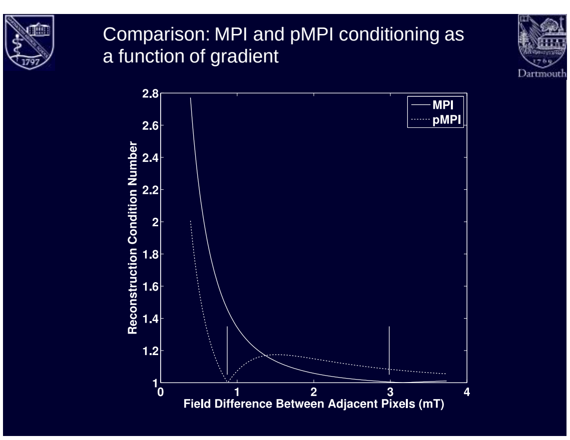
80mT - AMF
1mT perpendicular field
100 nm

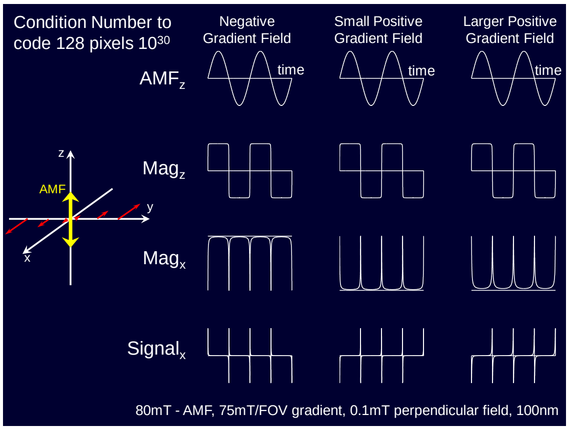
D.B. Reeves, J.B. Weaver, "Magnetic nanoparticle sensing: decoupling the magnetization from the excitation field", J. Phys. D: Appl. Phys. **47**:045002 (8pp) (2014).

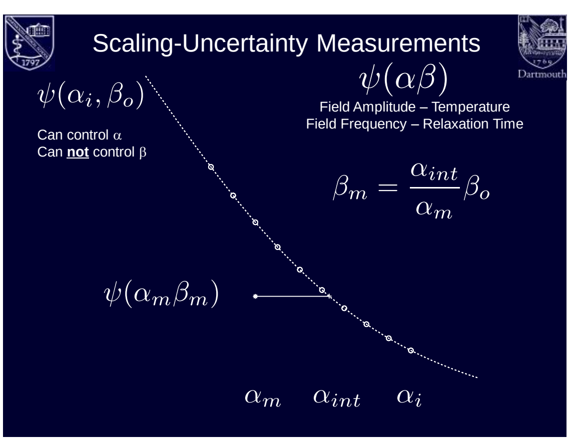



Same orientation for each zero crossing – signal is at the even harmonics
AMFz
time
Magz
Magx
Signalx
z
AMF
y
Static Field
x
80mT - AMF
1mT perpendicular field
100 nm
D.B. Reeves, J.B. Weaver, "Magnetic nanoparticle sensing: decoupling the magnetization from the excitation field", J. Phys. D: Appl. Phys. 47:045002 (8pp) (2014).
X. Zhang, D.B. Reeves, Y. Shi, B. Gimi, K.V. Nemani, I.M. Perreard, S. Toraya-Brown, S. Fiering, J.B. Weaver, "Toward Localized in vivo Biomarker Concentration Measurements" in press IEEE Transactions on Magnetics.
Dartmouth


Condition Number to code 128 pixels 5.4
Negative Gradient Field
Zero Gradient Field
Positive Gradient Field
AMFz
time
Magz
Magx
Signalx
z
AMF
y
Static Field
x
80mT - AMF, 75mT/FOV gradient, 0.1mT perpendicular field, 100nm

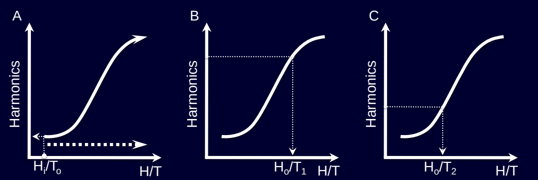

Comparison: MPI and pMPI conditioning as a function of gradient
MPI
pMPI
Reconstruction Condition Number
Field Difference Between Adjacent Pixels (mT)
Dartmouth


Condition Number to code 128 pixels 10^{30}
Negative Gradient Field
Small Positive Gradient Field
Larger Positive Gradient Field
AMF_z
time
time
time
Mag_z
Mag_x
$Signal_x$
z
y
x
AMF
80mT - AMF, 75mT/FOV gradient, 0.1mT perpendicular field, 100nm


Scaling-Uncertainty Measurements
$\psi(\alpha_i, \beta_o)$
Can control α
Can **not** control β
$\psi(\alpha\beta)$
Field Amplitude – Temperature
Field Frequency – Relaxation Time
$\beta_m = \frac{\alpha_{int}}{\alpha_m}\beta_o$
$\psi(\alpha_m \beta_m)$
α_m α_{int} α_i
1797
Dartmouth

Temperature Measurement:

Magnetization a function of μH/kT: $M = M_S\left[coth\left(\frac{\mu H_0}{kT}\right)+\left(\frac{\mu H_0}{kT}\right)^{-1}\right]$

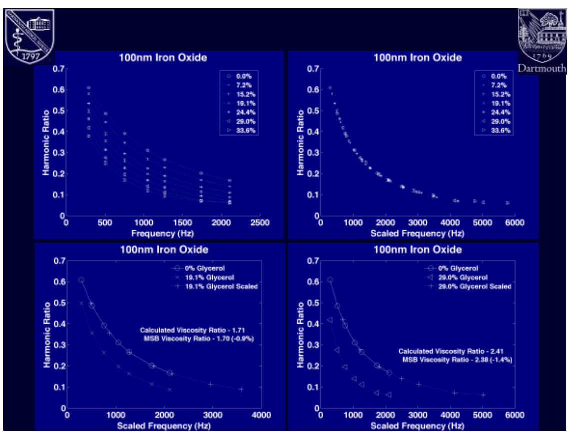


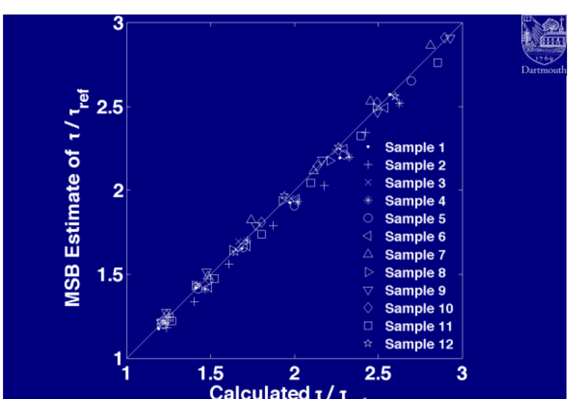
A: Change drive amplitude, H_i, at constant temperature, T_o, to generate calibration curve

B: First measurement at a selected drive field, H_o, yields a value of H_o/T_1 from which the current temperature, T_1, can be found

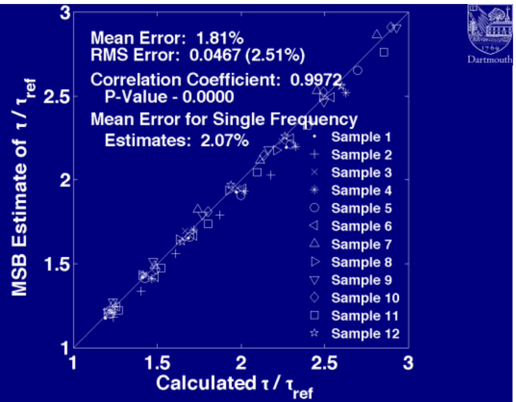
C: Subsequent measurements at the selected drive field yield values of H_o/T_2 from which the current temperature, T_2, can be found

J.B. Weaver, A.M. Rauwerdink, E.W. Hansen, "Magnetic Nanoparticle Temperature Estimation", Medical Physics 36(5):1822-1829 (2009).





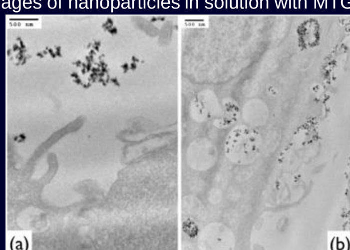
J.B. Weaver, E. Kuehlert, "Measurements of Magnetic Nanoparticle Relaxation Times" Medical Physics 39(5):2765-2770 (2012).



J.B. Weaver, E. Kuehlert, "Measurements of Magnetic Nanoparticle Relaxation Times" Medical Physics 39(5):2765-2770 (2012).

in vitro Cell Uptake

TEM images of nanoparticles in solution with MTG-B cells.

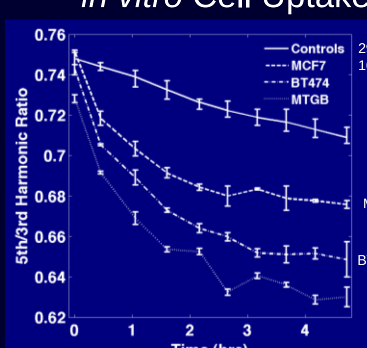


(a) 5 minutes (b) 5 hours
post addition of nanoparticles

Nanoparticles are (a) outside cells (b) in vesicles and on cell surface.

Adam M. Rauwerdink (& J.B. Weaver)
Andrew J. Giustini (& P.J. Hoopes)

in vitro Cell Uptake



290 Hz
16 mT/μ_0

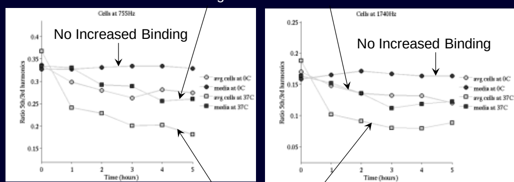
MCF-7 Uptake
less than
BT-474 Uptake [1]

[1] Steinhauser, I., Spankuch, B., Strebhardt, K., Langer, K., 2006. Biomaterials 27, 4975-4983.

A.J. Giustini, I.M. Perreard, A.M. Rauwerdink, P.J. Hoopes, J.B. Weaver, "Noninvasive assessment of magnetic nanoparticle-cancer cell interactions" Integrative Biology 4:1283-8 (2012).

Cells Uptake Measurements

Protein Binding Cell Surface and in Media

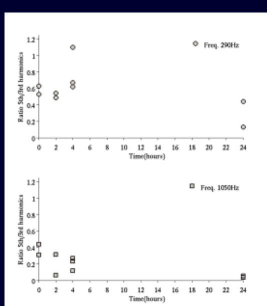


Invagination & Protein Binding

Cool Cells to Eliminate Invagination

in vivo Tumor Uptake Studies

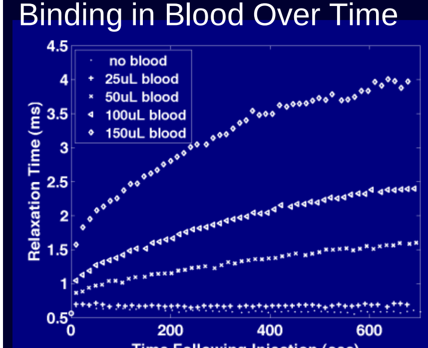
Harmonic Ratio vs Incubation Time in Tissue



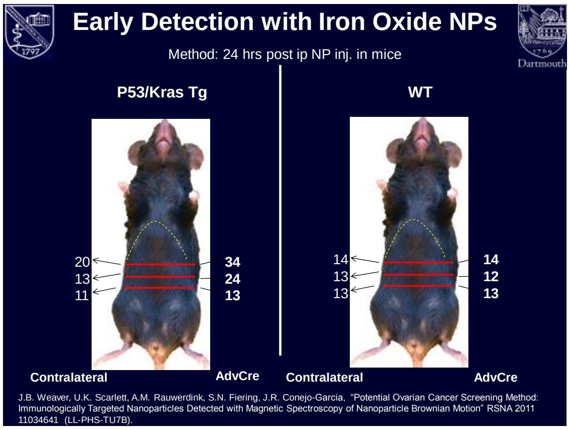
1. Direct Injection
2. Incubation
3. Tumor Excision
4. Tumor Division
5. MSB Measurement
6. Pathology

Adam M. Rauwerdink (& J.B. Weaver)
Andrew J. Giustini (& P.J. Hoopes)

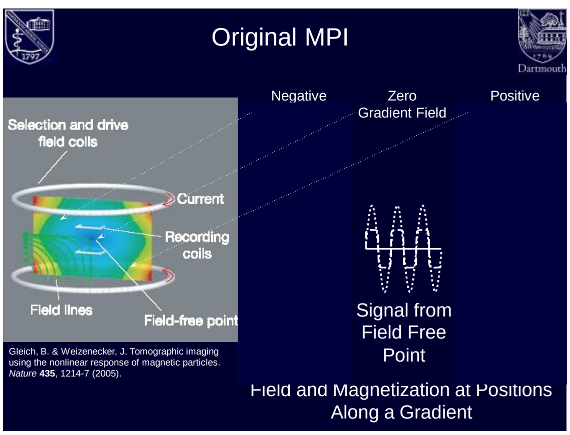
Binding in Blood Over Time



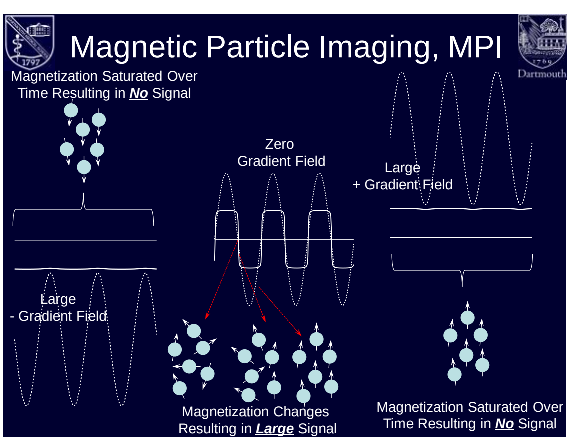
Daniel Reeves, Irina Perrard, Xiaojuan Zhang (& J.B. Weaver)
Seiko T. Brown (& S. N. Fiering)



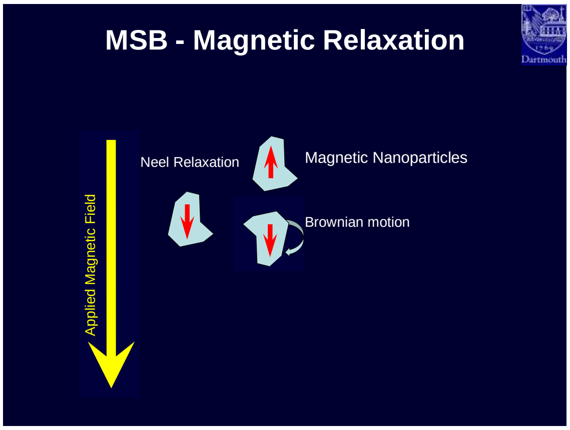
Early Detection with Iron Oxide NPs
Method: 24 hrs post ip NP inj. in mice
P53/Kras Tg
WT
20
13
11
34
24
13
14
13
13
14
12
13
Contralateral
AdvCre
Contralateral
AdvCre
J.B. Weaver, U.K. Scarlett, A.M. Rauwerdink, S.N. Fiering, J.R. Conejo-Garcia, "Potential Ovarian Cancer Screening Method: Immunologically Targeted Nanoparticles Detected with Magnetic Spectroscopy of Nanoparticle Brownian Motion" RSNA 2011 11034641 (LL-PHS-TU7B).

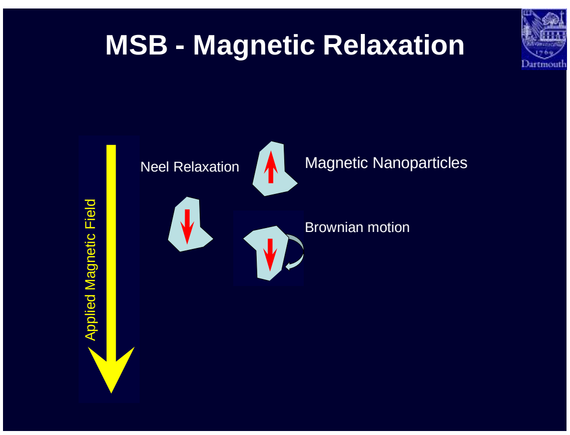


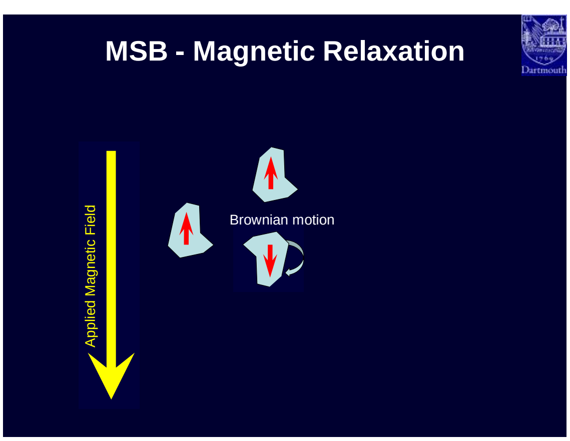
Original MPI
Negative
Zero
Gradient Field
Positive
Selection and drive field coils
Current
Recording coils
Field lines
Field-free point
Gleich, B. & Weizenecker, J. Tomographic imaging using the nonlinear response of magnetic particles. Nature 435, 1214-7 (2005).
Signal from Field Free Point
Field and Magnetization at Positions Along a Gradient

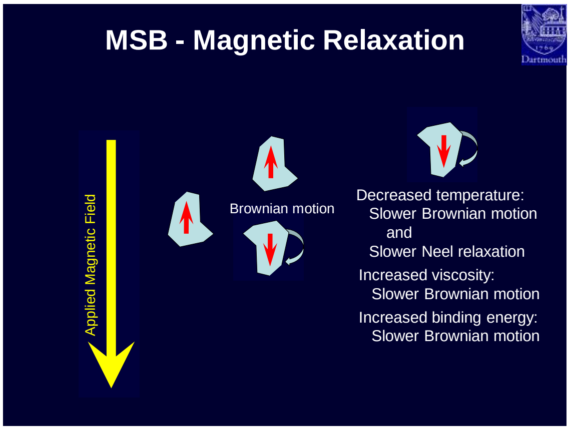


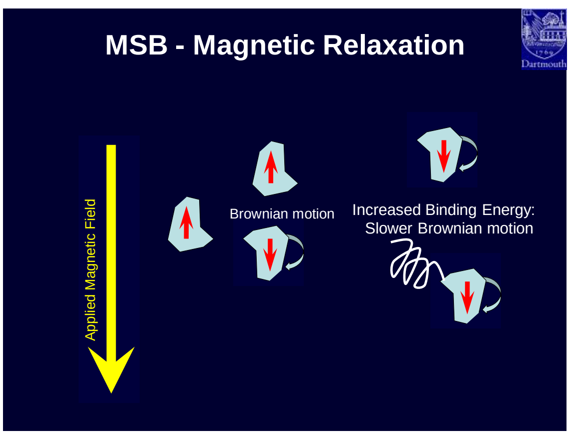
Magnetic Particle Imaging, MPI
Magnetization Saturated Over Time Resulting in No Signal
Zero
Gradient Field
Large
+ Gradient Field
Large
- Gradient Field
Magnetization Changes Resulting in Large Signal
Magnetization Saturated Over Time Resulting in No Signal

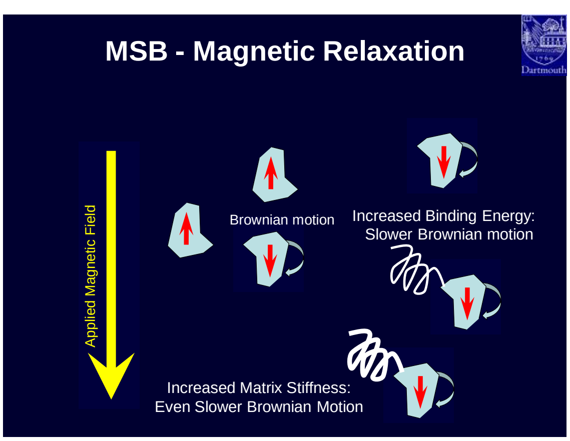

MSB - Magnetic Relaxation
Applied Magnetic Field
Neel Relaxation
Magnetic Nanoparticles
Brownian motion


MSB - Magnetic Relaxation
Applied Magnetic Field
Neel Relaxation
Magnetic Nanoparticles
Brownian motion


MSB - Magnetic Relaxation
Applied Magnetic Field
Brownian motion


MSB - Magnetic Relaxation
Applied Magnetic Field
Brownian motion
Decreased temperature:
Slower Brownian motion
and
Slower Neel relaxation
Increased viscosity:
Slower Brownian motion
Increased binding energy:
Slower Brownian motion


MSB - Magnetic Relaxation
Applied Magnetic Field
Brownian motion
Increased Binding Energy:
Slower Brownian motion


MSB - Magnetic Relaxation
Applied Magnetic Field
Brownian motion
Increased Binding Energy:
Slower Brownian motion
Increased Matrix Stiffness:
Even Slower Brownian Motion

Typical/Realistic Values

$$\boxed{I\dot{\mathbf{\Omega}}} = \boxed{\mathbf{m} \times \mathbf{B}} - \boxed{6\eta V \mathbf{\Omega}} + \boxed{\sqrt{2D}\mathcal{N}}$$

Moment of inertia and angular acceleration

Magnetic moment and magnetic field ~10^5

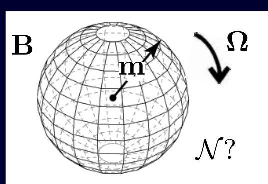
Viscosity volume and angular frequency ~10^5

Gaussian noise and Diffusion constant ~10^5

$$D = 6\eta V k_B T$$

$$\langle \mathcal{N}(t) \rangle = 0 \quad \langle \mathcal{N}_i(t)\mathcal{N}_j(t') \rangle = \delta_{ij}\delta(t - t')$$

Torques on a Brownian particle



MNP shell & core

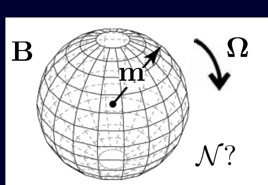
Micromod catalog

$$I\dot{\mathbf{\Omega}} = \mathbf{m} \times \mathbf{B} - 6\eta V \mathbf{\Omega} + \sqrt{2D}\mathcal{N}$$

Inertia | Magnetic Torque ~10^5 | Viscous Drag ~10^5 | Thermal fluctuations ~10^5

Reeves DB, Weaver JB. Magnetic nanoparticle sensing: decoupling the magnetization from the excitation field. J Phys D: Appl Phys 2014, 47: 045002 (045008pp)

Torques on a Brownian particle



MNP shell & core

Micromod catalog

$$I\dot{\mathbf{\Omega}} = \mathbf{m} \times \mathbf{B} - 6\eta V \mathbf{\Omega} + \sqrt{2D}\mathcal{N}$$

Daniel Reeves

Inertia | Magnetic Torque ~10^5 | Viscous Drag ~10^5 | Thermal fluctuations ~10^5

Reeves DB, Weaver JB. Simulations of magnetic nanoparticle Brownian motion. *Journal of Applied Physics* 2012, **JR12:** 8177R8171.
Reeves DB, Weaver JB. Nonlinear simulations to optimize magnetic nanoparticle hyperthermia. *Applied physics letters* 2014, **104**(10)**:** 102403.
Reeves DB, Weaver JB. Approaches for Modeling Magnetic Nanoparticle Dynamics. *Critical Reviews in Biomed Engineering* 2014 **42**(1)**:** 85-93.
Reeves DB, Weizenecker J, Weaver JB. Brownian Magnetic Nanoparticle Simulations. *SPIE* 2013, **MI105:** 101.

Equations Describing Nanoparticles Relaxing via the Brownian Mechanism

$$\frac{d\vec{m}}{dt} = \frac{1}{6\eta V}\left(\vec{m} \times \vec{H} + \sqrt{2D}N\right) \times \vec{m}$$

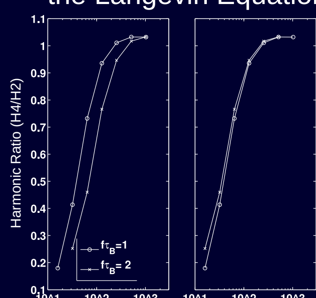
$$D = 6\eta V k_B T$$

1. Viscosity
2. Temperature

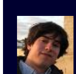

Daniel Reeves

Reeves DB, Weaver JB. Simulations of magnetic nanoparticle Brownian motion. *Journal of Applied Physics* 2012, **JR12:** 8177R8171.
Reeves DB, Weaver JB. Approaches for Modeling Magnetic Nanoparticle Dynamics. *Critical Reviews in Biomed Engineering* 2014 **42**(1)**:** 85-93.

Master Variable Solution of the Langevin Equation



$\frac{\mu H}{kT}$ $\quad \mathcal{A} = \frac{\mu H}{k_b T \omega \tau}$


Daniel Reeves

Equations Describing Nanoparticles Relaxing via the Brownian Mechanism

$$\frac{d\vec{m}}{dt} = \frac{1}{6\eta V}\left(\vec{m} \times \vec{H} + \sqrt{2D}N\right) \times \vec{m}$$

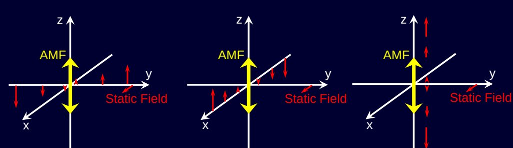
$$D = 6\eta V k_B T$$

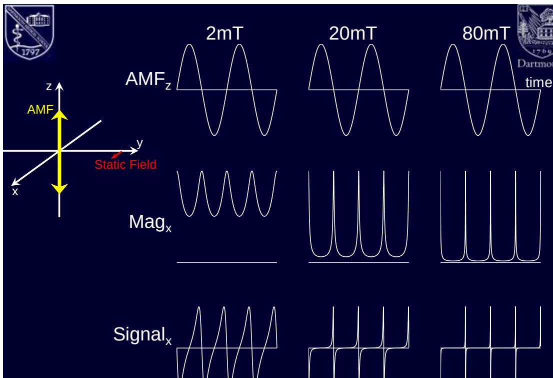
1. Viscosity
2. Temperature

Conclusions:

- Simulations show that NP signals can be localized using the perpendicular magnetization.

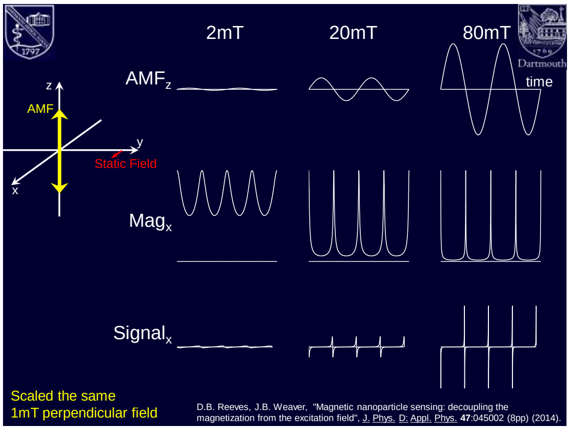
In-Line: Gradients in In-Line Fields



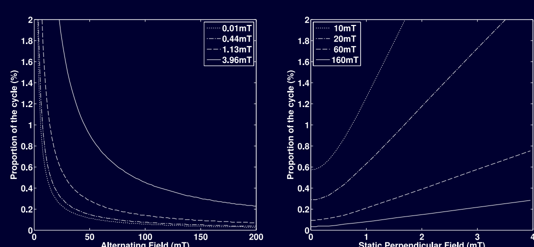


Scaled differently
1mT perpendicular field

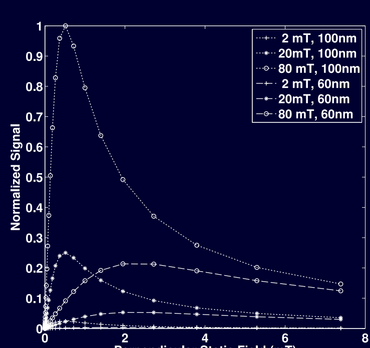
D.B. Reeves, J.B. Weaver, "Magnetic nanoparticle sensing: decoupling the magnetization from the excitation field", J. Phys. D: Appl. Phys. 47:045002 (8pp) (2014).



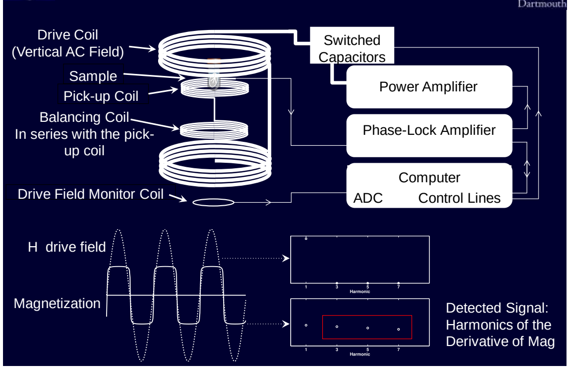
Signal Localization in Time



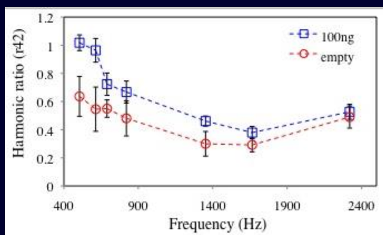
Signal Amplitude



Old Apparatus Geometry



a) New geometry & b) epoxied windings
Old Apparatus - 20 microgram of NPs
New Apparatus - 100 nanogram of NPs
Increase in sensitivity by factor of >200



P-value – 2x10^{-5} at 100ng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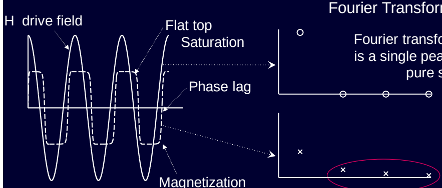
MSB - Magnetic Spectroscopy of Nanoparticle Brownian Motion

Fourier Transforms



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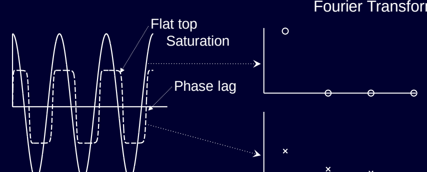

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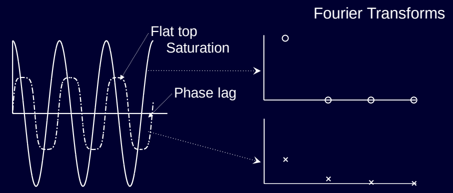

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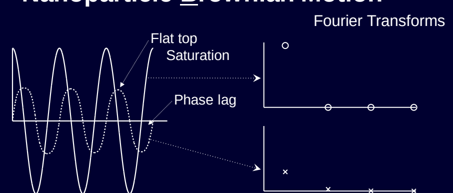

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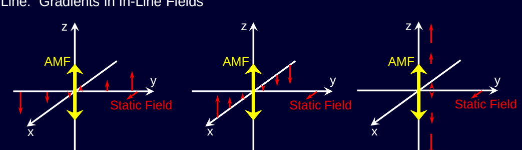
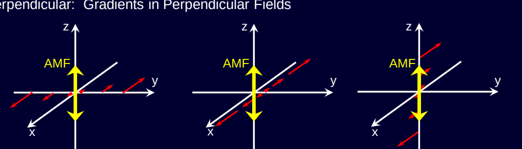
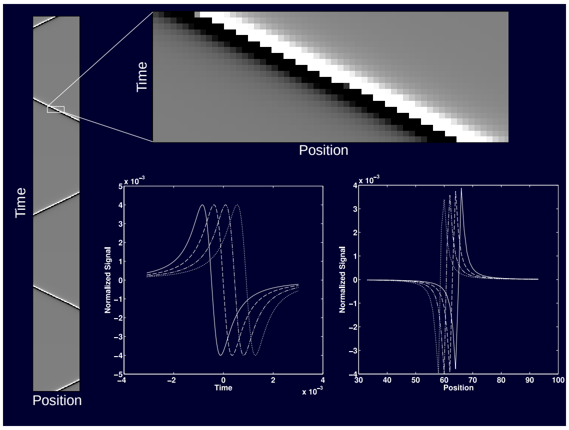
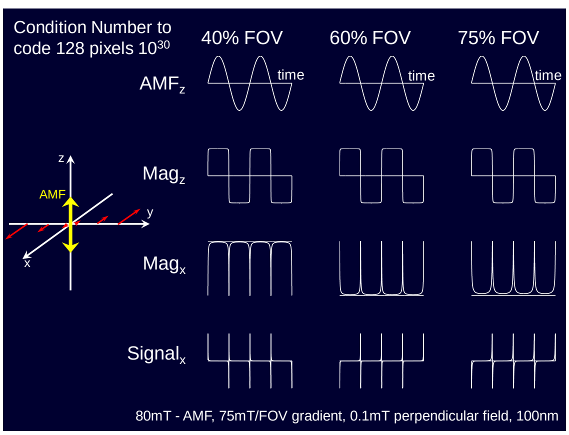
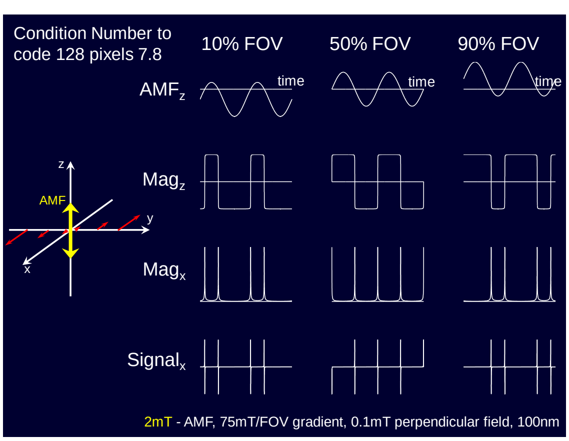


Perpendicular: Gradients in Perpendicular Fields




Time
Time
Position
Position
Normalized Signal
Time
Normalized Signal
Position


Condition Number to code 128 pixels 10^{30}
40% FOV
60% FOV
75% FOV
AMF_z
time
time
time
Mag_z
Mag_x
$Signal_x$
z
AMF
y
x
80mT - AMF, 75mT/FOV gradient, 0.1mT perpendicular field, 100nm


Condition Number to code 128 pixels 7.8
10% FOV
50% FOV
90% FOV
AMF_z
time
time
time
Mag_z
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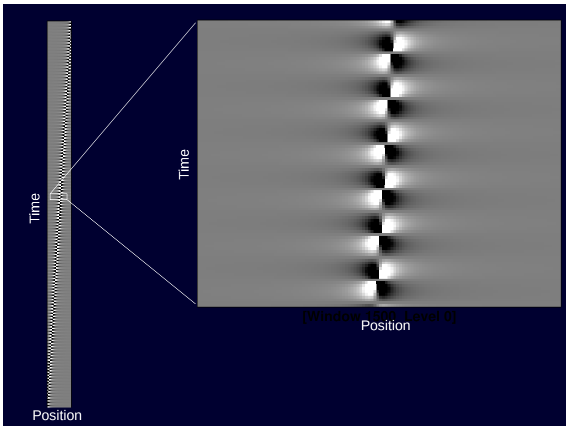
z
AMF
y
x
2mT - AMF, 75mT/FOV gradient, 0.1mT perpendicular field, 100nm



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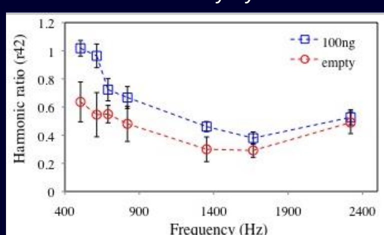

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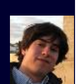

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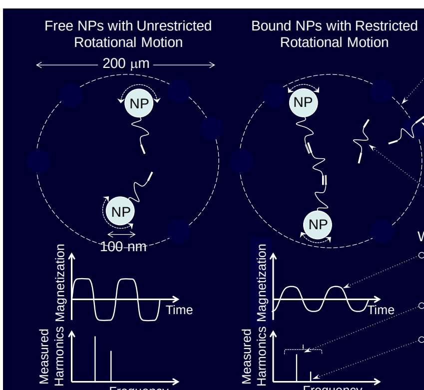


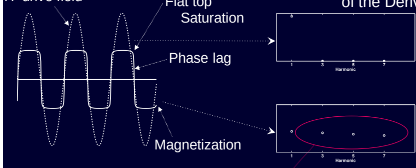
With Binding:
- Transition to Saturation Smoother
- Harmonics All Decrease
- Higher Harmonics Decrease More Than Lower Harmonics

***In vivo* ELISA**

Rauwerdink & Weaver, Applied Physics Letters 96, 033702 (2010).
Rauwerdink & Weaver, Medical Physics 38(3):1136-1140, (2011).
Weaver & Kuehlert, Medical Physics 39(5):2765-2770 (2012).

Signal Generation in Spectroscopy and MPI

Signal: Fourier Transforms of the Derivative



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MSB - Magnetic Spectroscopy of Nanoparticle Brownian Motion

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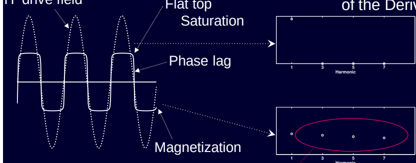

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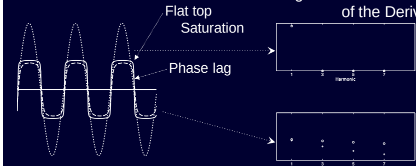

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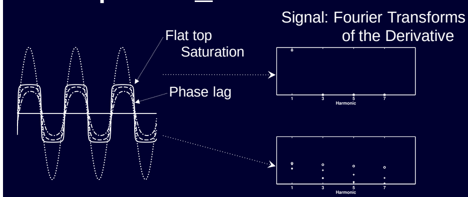

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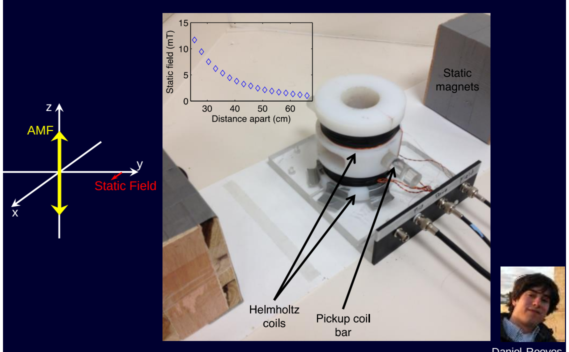

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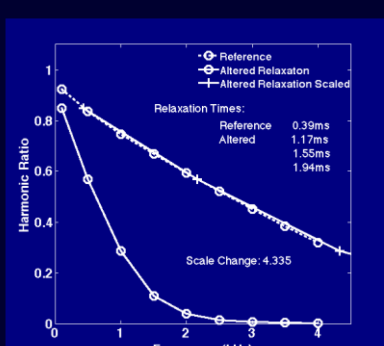
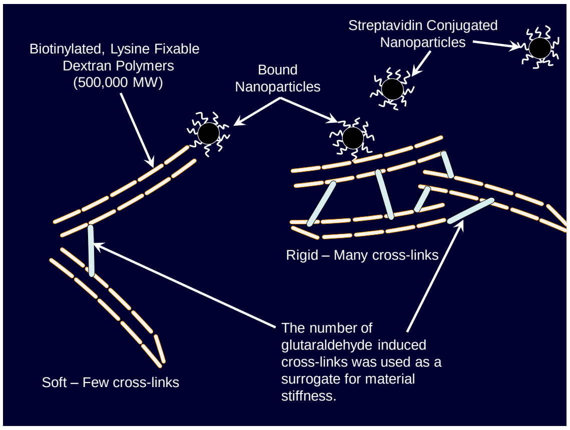
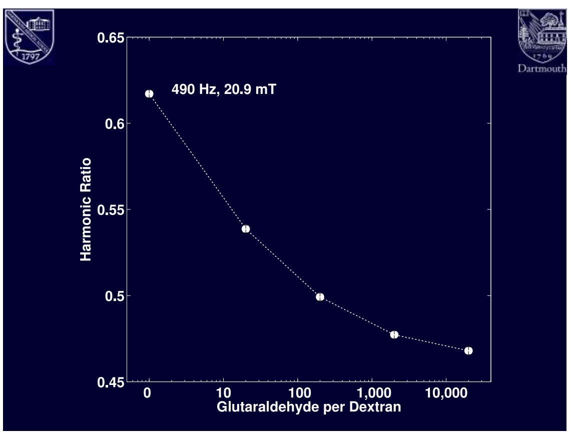



Streptavidin Conjugated Nanoparticles
Biotinylated, Lysine Fixable Dextran Polymers (500,000 MW)
Bound Nanoparticles
Rigid – Many cross-links
The number of glutaraldehyde induced cross-links was used as a surrogate for material stiffness.
Soft – Few cross-links


490 Hz, 20.9 mT
Harmonic Ratio
0.65
0.6
0.55
0.5
0.45
0
10
100
1,000
10,000
Glutaraldehyde per Dextran
Dartmouth
1797
1769