Characterization of magnetic nanoparticles with potential applications in cancer hyperthermia

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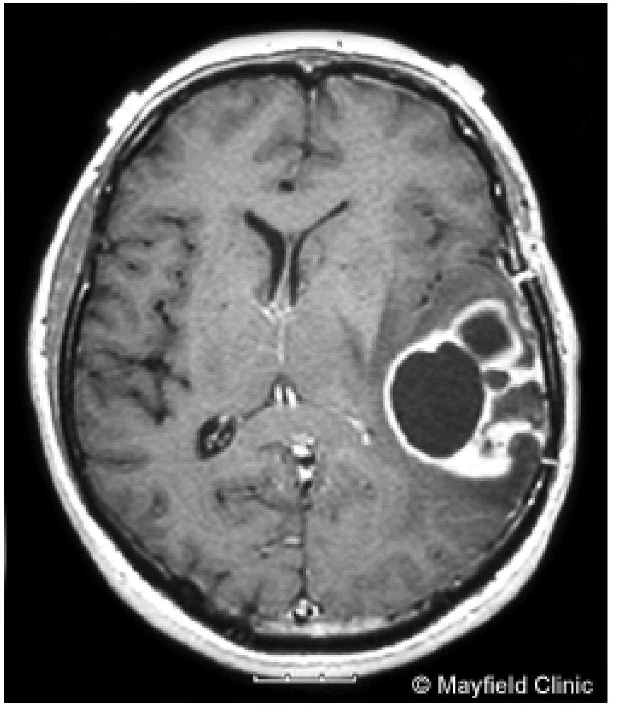
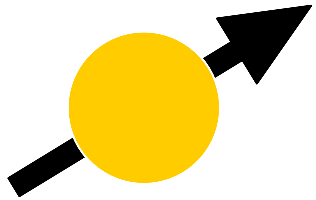
- **Hyperthermia** – artificial heating of tumor cells, long studied as an alternative or supplement to chemotherapy
- Externally applied heat damages healthy tissue
- **Magnetic nanoparticles** (MNPs) heated inside the body by the application of an alternating magnetic field
- Triggers cell death with only 4-5 degrees heating

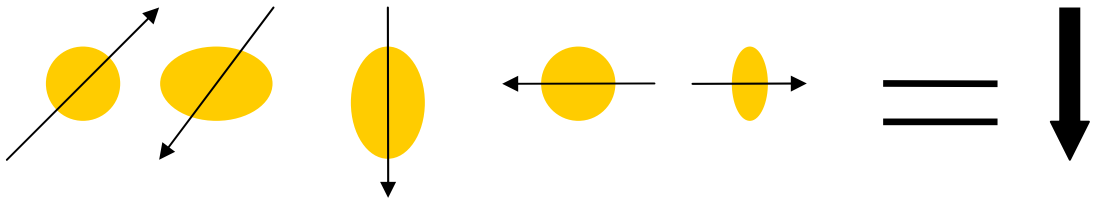


A glioblastoma tumor in the parietal lobe. Metastatic brain cancers could potentially be treated by MNP hyperthermia.

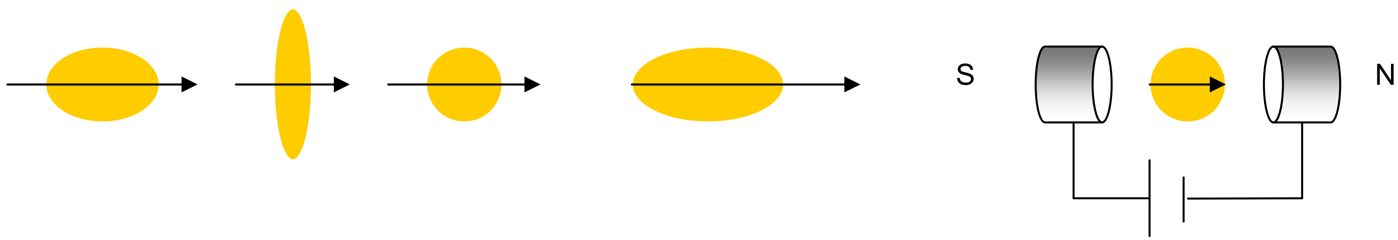
Image: Mayfield clinic



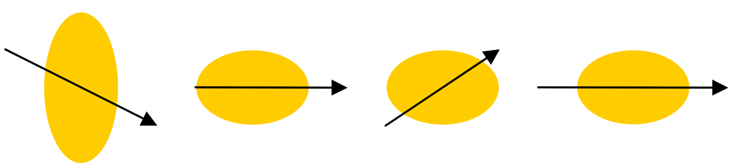
MNPs each have a net magnetic dipole from the effects of the internal electronic structure



Vector sum is the “magnetization”



The dipoles align in the presence of a field applied by an electromagnet



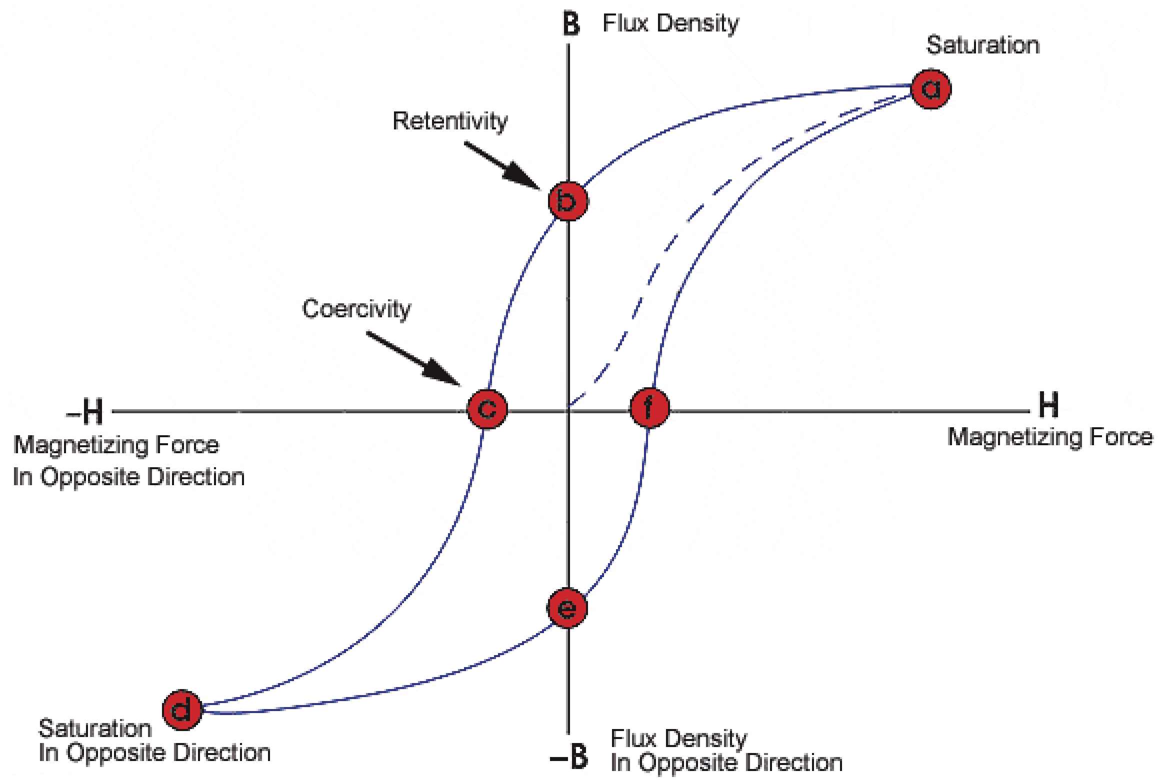
There is some tendency for the dipoles to “stick” in one direction after the electromagnet is turned off

Hysteresis loops

Gives magnetization as a function of applied field and magnetic history ("hysteresis") of the material

"Sticking" effect in dipoles causes open loop

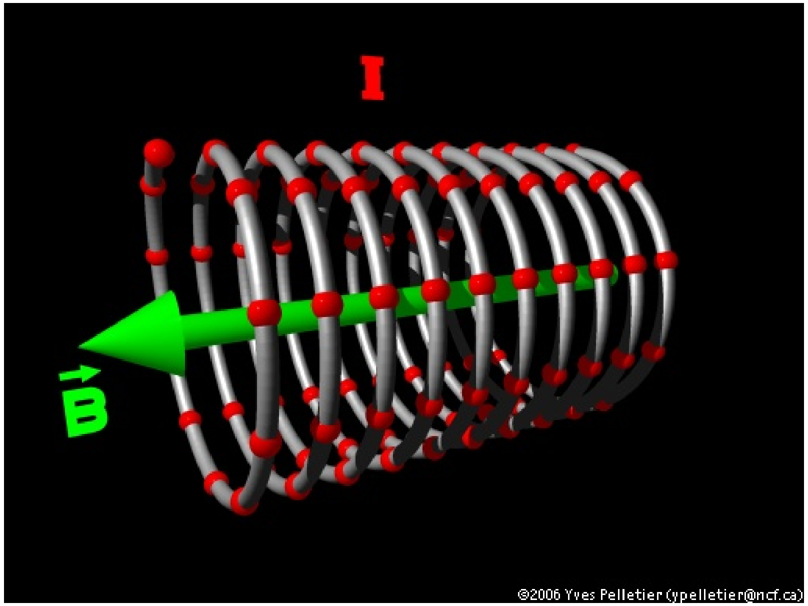
Area inside loop is equal to energy loss, most in the form of **heat,** an important design consideration for hyperthermia



Shape exaggerated for magnetic nanoparticle

Technical challenges

- Instrumental – large solenoid needed to deliver alternating magnetic fields (kHz), with huge power consumption (MW)

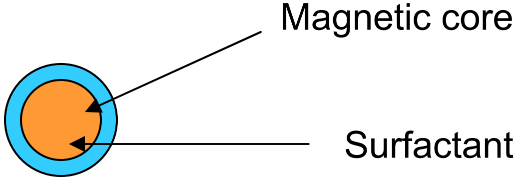


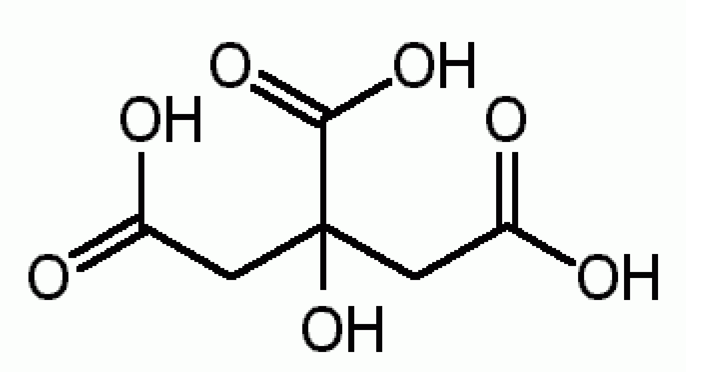
- Biomedical – must be able to target to cancerous cells
  - Biocompatible

- Chemical – narrow size and shape distribution, scalable

Technical challenges – Chemical

–Magnetic, electrostatic, and intermolecular forces may cause clumping and settling out of solution



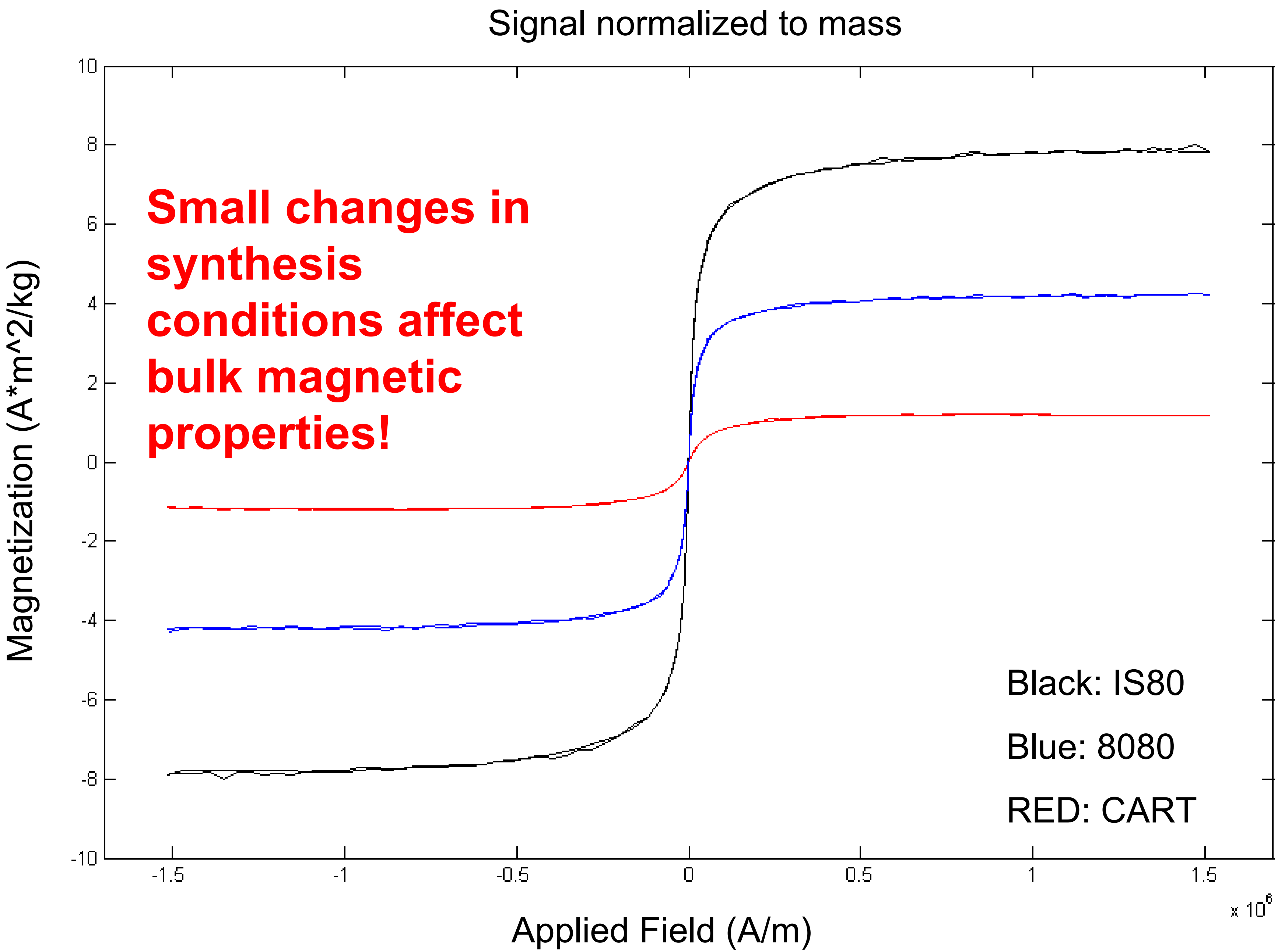


Citric acid surfactant

–A surfactant is needed to stabilize the MNPs by electrostatic or steric repulsion

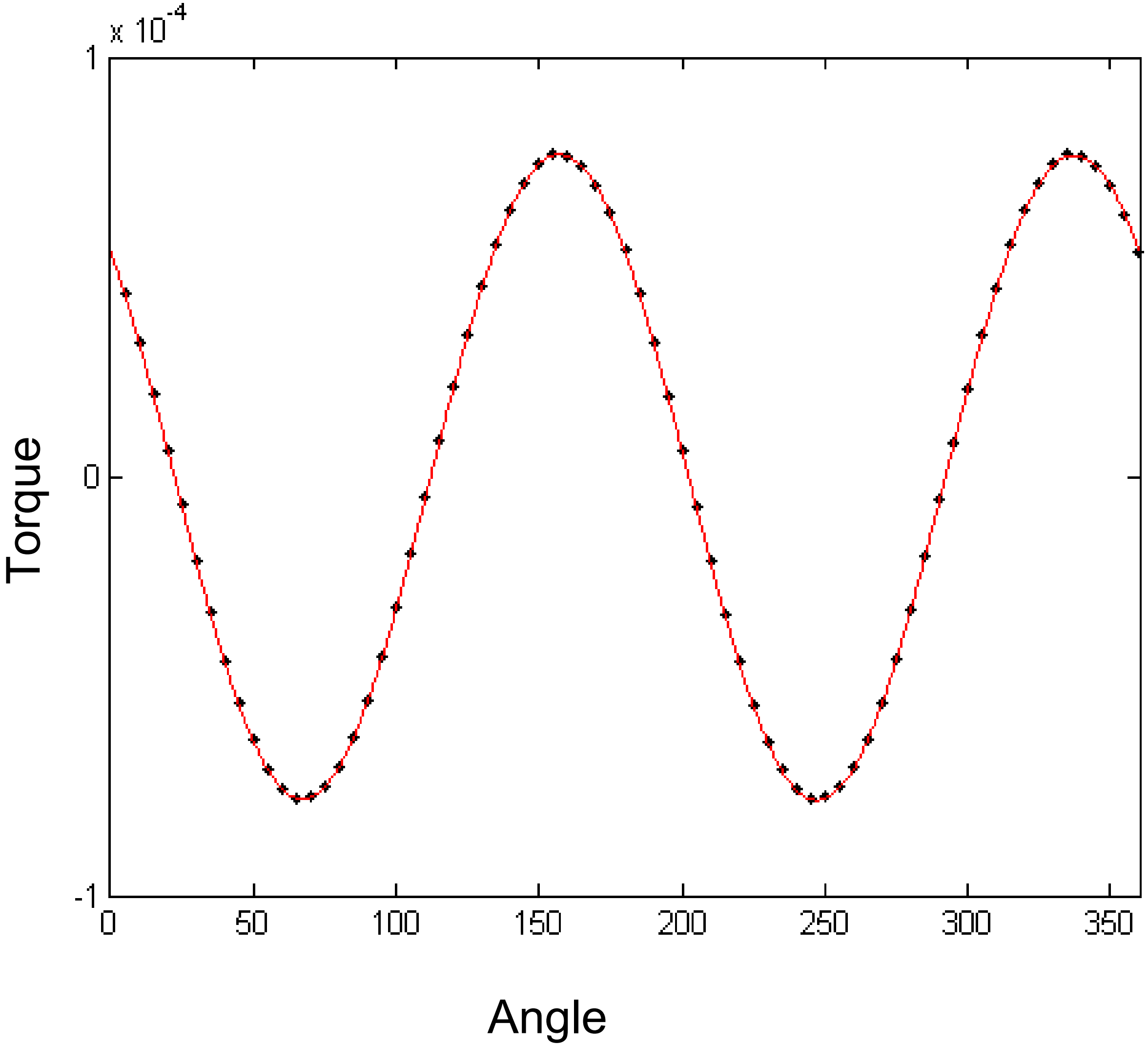
Synthesis

- Three iron oxide nanoparticle systems synthesized at the University of Kentucky by coprecipitation of Fe^{+3} and Fe^{+2} in ammonium hydroxide
- Iron oxide is biocompatible
- “CART” sample reduced in the presence of citric acid at room temperature
- “IS80” sample reduced in the presence of citric at 80°C
- “8080” made by a two step synthesis; first reduced in NH_4OH at 80°C then reduced in citric acid



Signal normalized to mass
Small changes in synthesis conditions affect bulk magnetic properties!
Magnetization (A*m^2/kg)
10
8
6
4
2
0
-2
-4
-6
-8
-10
-1.5
-1
-0.5
0
0.5
1
1.5
x 10^6
Applied Field (A/m)
Black: IS80
Blue: 8080
RED: CART

Torque curves



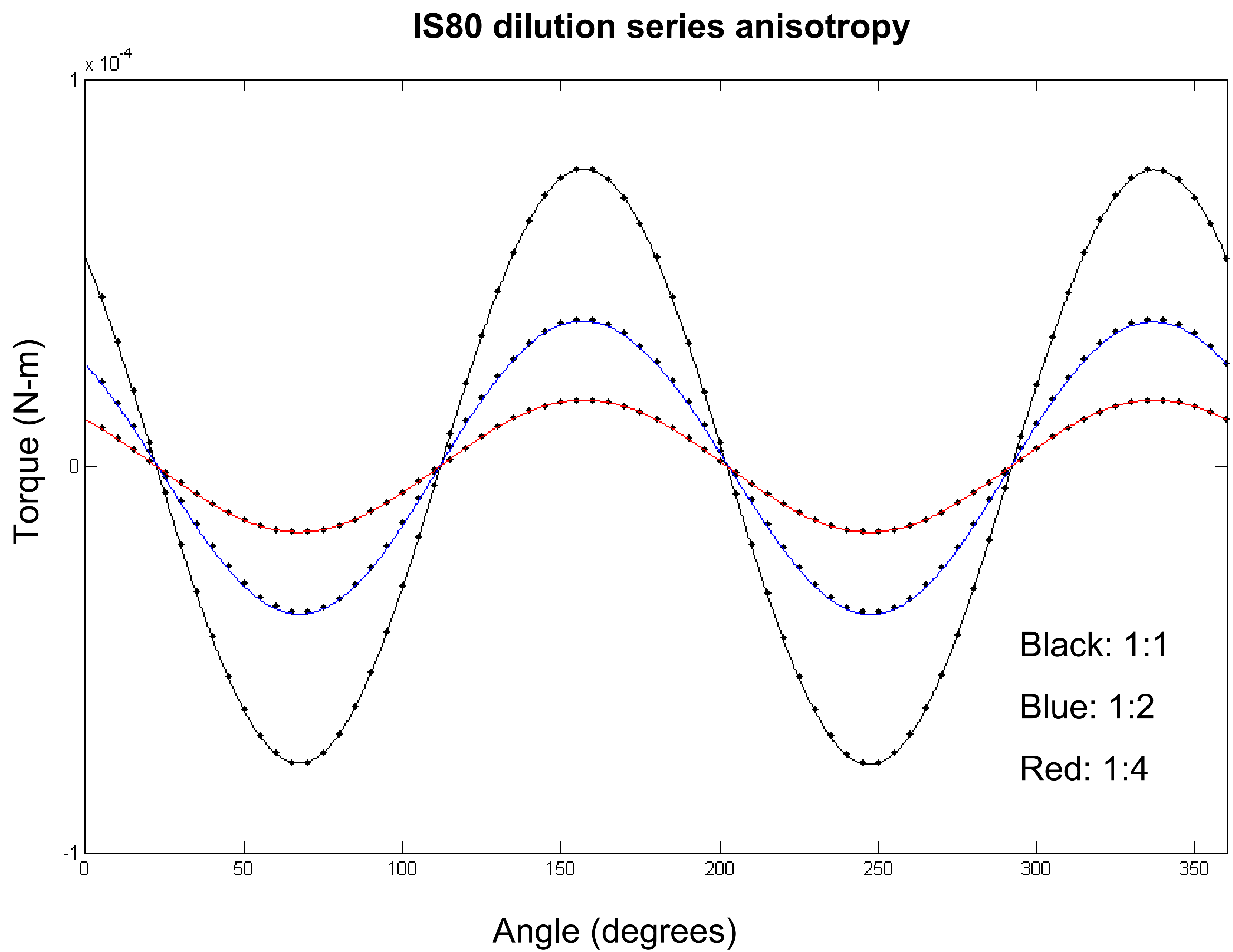
$T = M_T * H * \sin(\Theta_m - \Theta_H)$

M_T = total magnetization, the vector sum of the parallel and perpendicular signals

H = applied field

Θ_M = magnetization angle = $\tan^{-1}(Y/X)$

Θ_H = field angle, determined by physical orientation of magnet



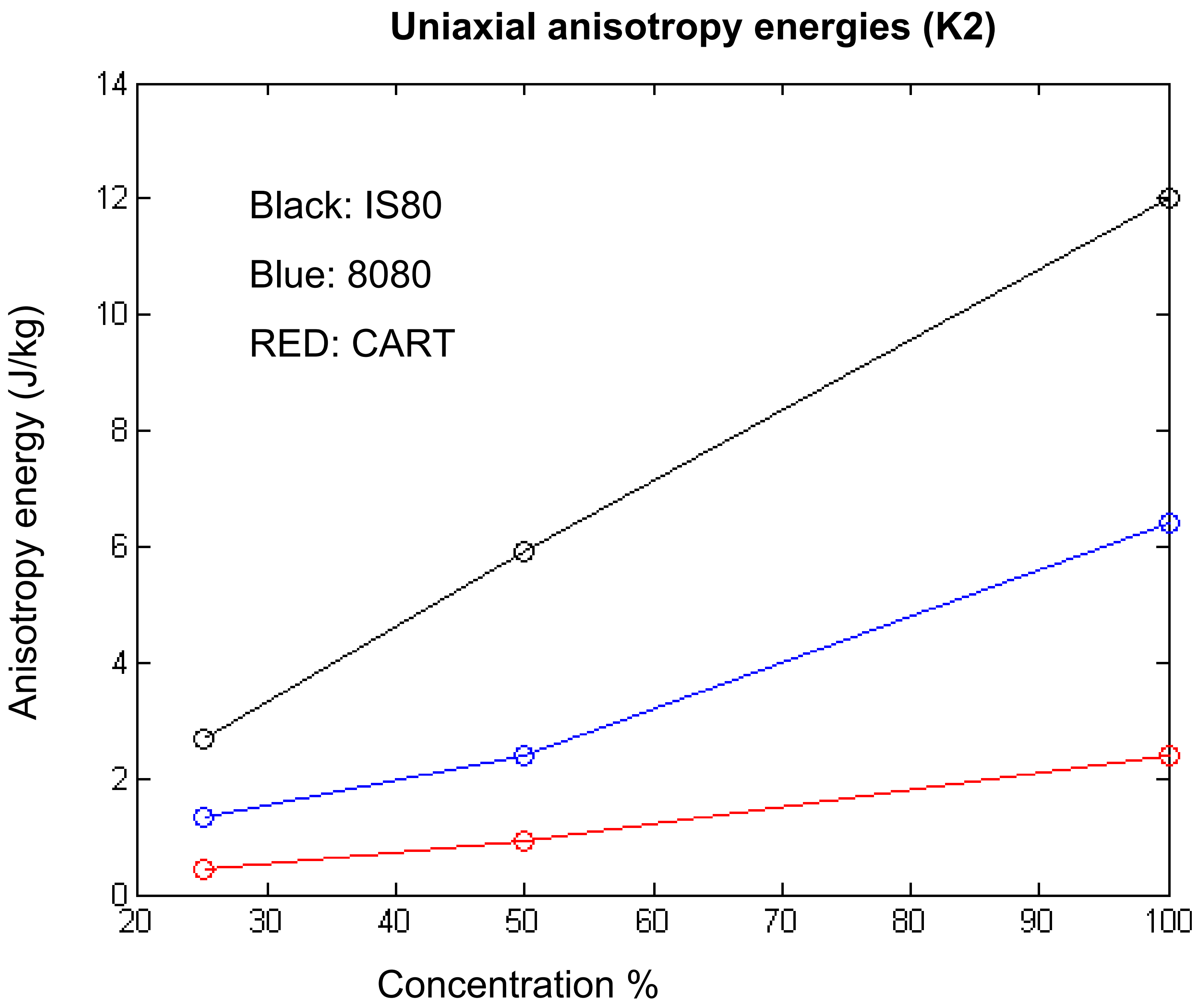
IS80 dilution series anisotropy
x 10^-4
1
0
-1
Torque (N-m)
0
50
100
150
200
250
300
350
Angle (degrees)
Black: 1:1
Blue: 1:2
Red: 1:4

Torque curve model fitting

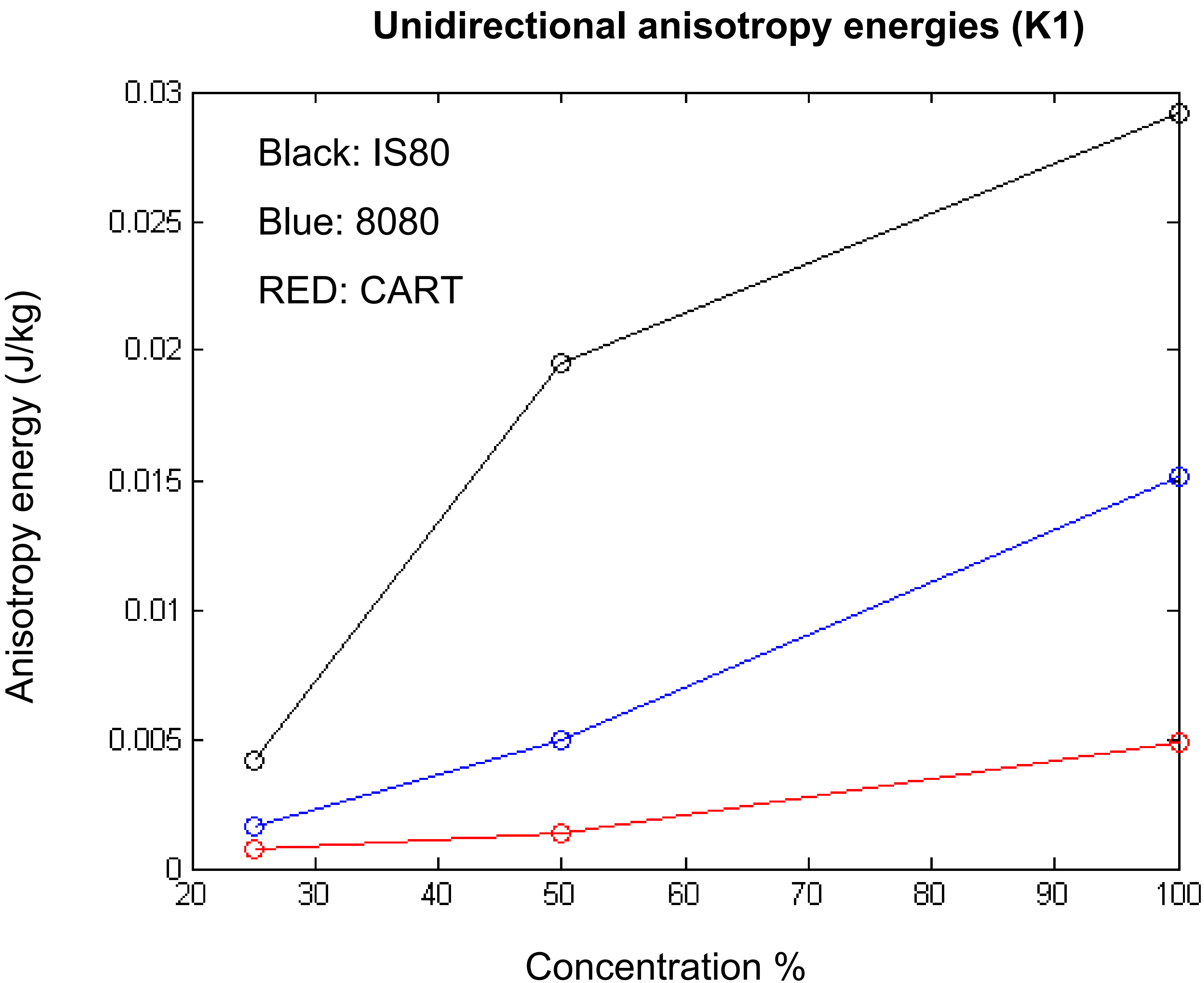
$K_1 * \sin(\Theta) + K_2 * \sin(2\Theta) + K_4 * \sin(4\Theta)$….

- K_1 = unidirectional anisotropy constant
- K_2 = uniaxial anisotropy constant
- K_4 = bidirectional anisotropy constant

We can "pull out" quantitative information about the behavior of magnetic nanoparticles in solution from the model coefficients

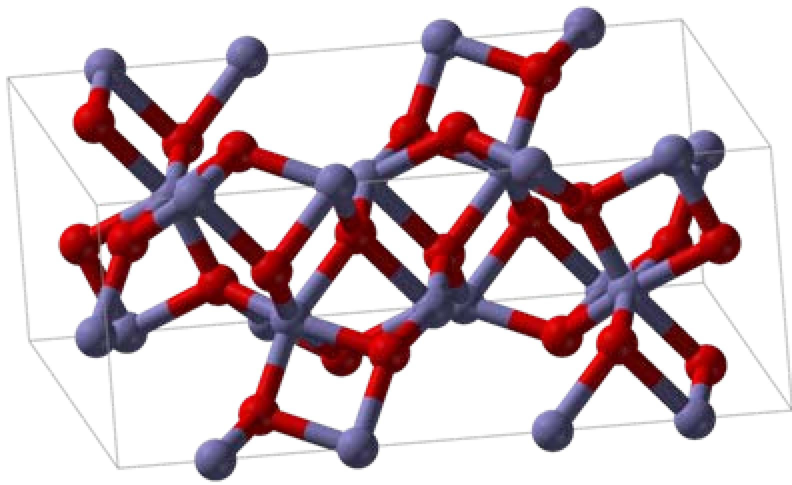


Uniaxial anisotropy energies (K2)
Black: IS80
Blue: 8080
RED: CART
Anisotropy energy (J/kg)
0
2
4
6
8
10
12
14
20
30
40
50
60
70
80
90
100
Concentration %


Unidirectional anisotropy energies (K1)
Black: IS80
Blue: 8080
RED: CART
Anisotropy energy (J/kg)
0.03
0.025
0.02
0.015
0.01
0.005
0
20
30
40
50
60
70
80
90
100
Concentration %

Why are there different signal strengths for equal masses of magnetic material?

- Crystallinity – easy axis of magnetization



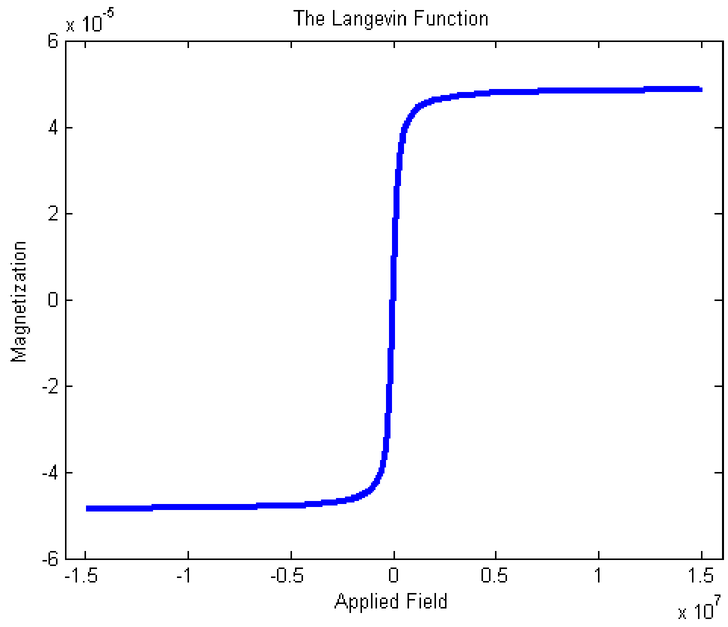
Left: the crystalline structure of Fe_3O_4

- Size effects – fewer surface spins

- Collective behavior – reduces magnetization energy

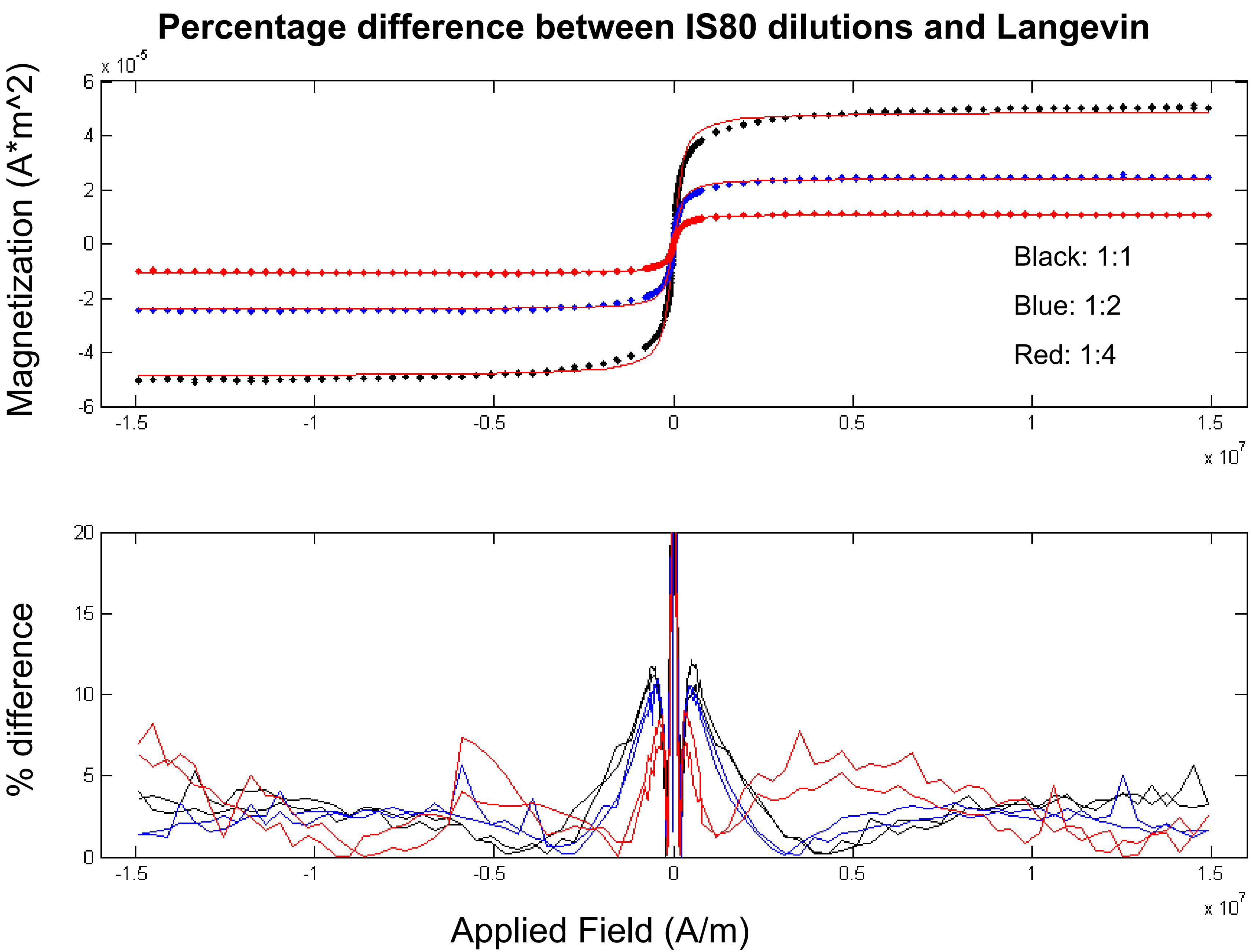
Hysteresis loop model fitting

- **The Langevin Function:**
- M = N*μ*(coth(μ*H/ kb*T) – 1/(μ*H/ kbT))
- N = number of atoms per unit volume
- μ = magnetic moment per particle
- H = applied magnetic field
- Kb = Boltzmann's constant
- T = measurement temperature

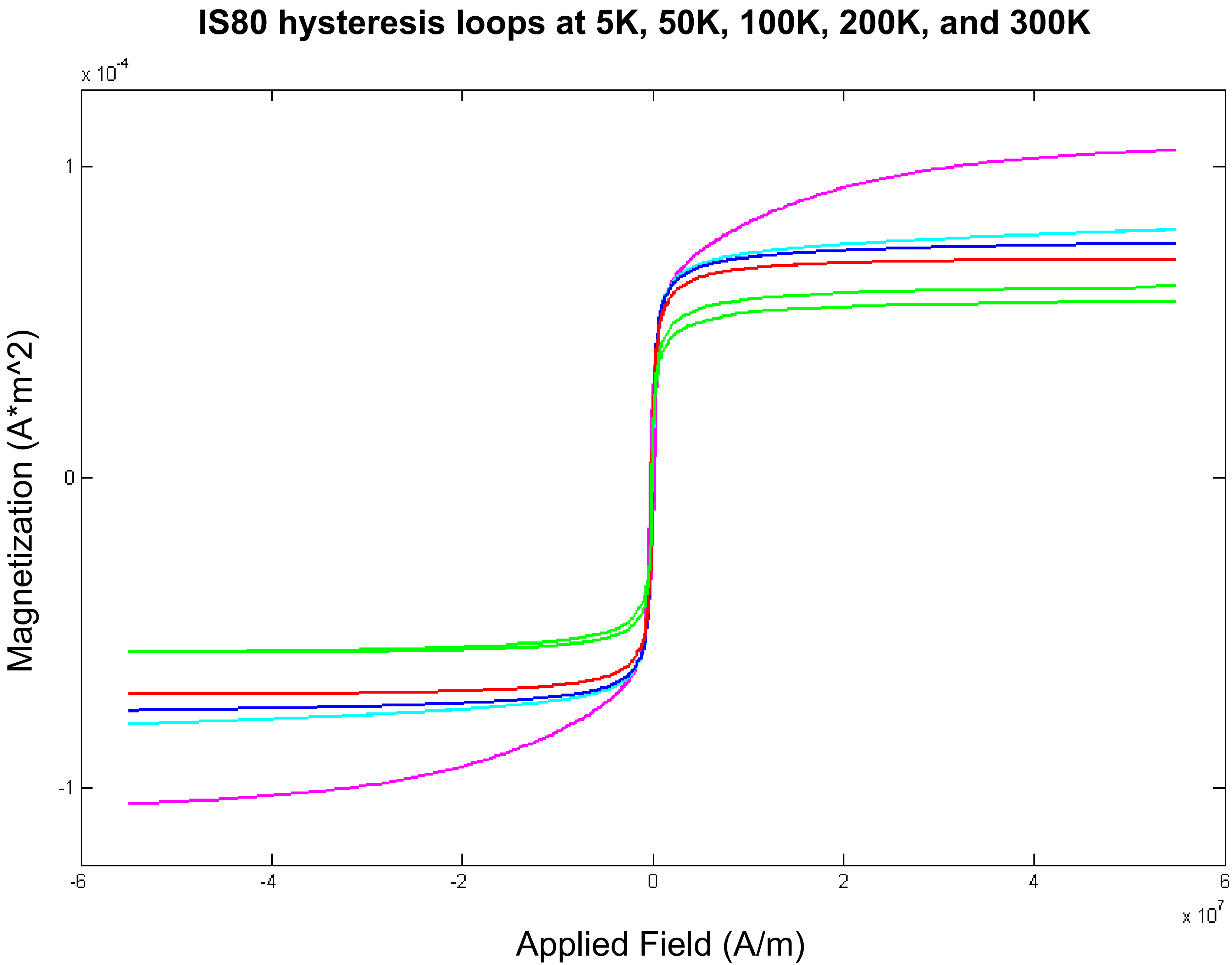


Models magnetic systems that are approximately paramagnetic

Deviation from Langevin function may indicate interparticle interactions



Percentage difference between IS80 dilutions and Langevin
Magnetization (A*m^2)
x 10^-5
6
4
2
0
-2
-4
-6
-1.5
-1
-0.5
0
0.5
1
1.5
x 10^7
Black: 1:1
Blue: 1:2
Red: 1:4
% difference
20
15
10
5
0
-1.5
-1
-0.5
0
0.5
1
1.5
x 10^7
Applied Field (A/m)


IS80 hysteresis loops at 5K, 50K, 100K, 200K, and 300K
x 10^-4
1
0
-1
Magnetization (A*m^2)
-6
-4
-2
0
2
4
6
x 10^7
Applied Field (A/m)

In review:

- **Minor changes in synthesis conditions can affect magnetic properties that change value as a MNP hyperthermia agent**
- **Collective behavior present in nanoparticles**

  --Relevant to functionalization of nanoparticles

  -Good candidate for SANS study

Thanks to:

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- Dr. Julie Borchers
- Dr. Andrew Jackson

Center for High Resolution Neutron Scattering

Questions?