13th International Conference on the
SCIENTIFIC AND CLINICAL
APPLICATIONS OF
MAGNETIC CARRIERS

LONDON, UNITED KINGDOM
JUNE 14-17, 2022

UCL
Nguyen T. K. Thanh
London, U.K.

FH KREMS
Wolfgang Schutt
Krems, Austria

IMC

Cleveland Clinic
Maciej Zborowski
Cleveland, Ohio, U.S.A.

UBC
Urs Hafeli
Vancouver, BC, Canada
The cover image was captured using a TEM at 40,000x magnification during work on the synthesis of iron oxide nanoflowers with outstanding heating efficiencies (ILP of 8.4 nH m^2/kgFe, or SAR = 2426 ± 76 W/gFe) measured at a frequency of 488 kHz and a field strength of 25 kA m^−1. Each flower contains approximately 50 coalesced nanoparticles. (Storozhuk, L., Besenhard M. O., Moudrikouidis, S., LaGrow, A. P., Lees, M.R., Tung, L. D., Gavriilidis, A., Thanh, N. T. K* (2021) Simple and Fast Polyol Synthesis of Stable Iron Oxide Nanoflowers with Exceptional Heating Efficiency. Journal of Applied Materials and Interface. 13: 45870–45880). The work has become a finalist for 2022 The Royal Society of Chemistry Emerging Technologies Competition in Health category.

References:
Welcome Message

It is our great pleasure to welcome you all to the 13th International Conference on the Scientific and Clinical Applications of Magnetic Carriers. We are happy that it is now once again possible to have this wonderful meeting in-person to discuss our recent achievements in research on magnetic particles and their applications.

London is an excellent location to host such a conference and we are very fortunate that the selected venue, University College London, or UCL for short, is located right in the heart of the city. This allows easy access to a great variety of historical landmarks and areas around the city in reasonable time.

Unfortunately, the COVID-19 pandemic is not yet over, so while our conference will be held in person, we are basing our plans on you having received your vaccinations and booster shots, all of us wearing masks during the conference, and following all the local and UK national requirements regarding meetings and gatherings. Also, if you feel unwell during the conference or demonstrate COVID-19 symptoms, please perform a lateral flow test, and stay home if you are positive.

At our conference location, University College London (UCL), we will have a large auditorium so we can be well spaced out during the talks. In addition, the spaces for poster sessions, lunches and breaks are extensive enough for social distancing, and we also have a large outside space available.

We welcome you for a successful and interesting conference!

Your organizers,

Urs Hafeli, University of British Columbia, Vancouver, Canada,
Nguyen T. K. Thanh, University College London, UK,
Maciej Zborowski, Cleveland Clinic Foundation, Cleveland, USA,
Wolfgang Schutt, IMC Krems, Austria & Rostock, Germany.
Social Program

It has been said that science may never come up with a better system for communication than the coffee break. But why not also extend our social interactions beyond the conference venue? In this way, we will have fun, enjoy London, and get to know each other better.

Tuesday, June 14
After the end of the first poster session, we will have a reception in the Wilkins Terrace, with lots of food and drinks. This traditional get-together is generously sponsored by nanotherics. Enjoy!

Wednesday, June 15
At the end of the day, beer and Pretzels will be offered following the end of the second poster session. This is graciously supported by micromod Partikeltechnology GmbH.

Thursday, June 16
During the day, there will be a spouse tour. This tour is complimentary and always fun. Spouses will meet at 9:00 at the registration desk in the UCL Wilkins building, in the North Cloisters. Spouses will be back at UCL latest at 17:15.

The traditional boat trip along the river Thames is generously sponsored by Imagion Biosystems. We will start at 17:30 with a double decker bus ride to Butlers Wharf Pier, board at 18:15 and cast off at 18:30 – please be on time! During the trip, we will enjoy a wonderful dinner, picturesque views of London and as always, a great time. The New Orleans style jazz band "The Blind Tigers" will keep us on our feet and is generously sponsored by chemicell. Our boat, the 'Dixie Queen' will be back at a different pier, the Tower Millennium Pier at 22:30. The buses will bring us back to UCL from there.

Friday, June 17
The meeting will come to an end at 17:00. Please take the opportunity to explore the English capital on your own after the end of the conference!
## 13th International Conference on the Scientific and Clinical Applications of Magnetic Carriers - London, UK

**Tuesday, June 14, 2022**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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</thead>
<tbody>
<tr>
<td>12:00</td>
<td>Registration desk opens in the Wilkins Building, North Cloisters</td>
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<tr>
<td>13:00</td>
<td>Opening Session - Cruciform Building, Auditorium B304 - LT1</td>
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<tr>
<td></td>
<td>Parkin, Ivan: Opening of the conference and welcome address by Prof. Ivan Parkin, the Dean of UCL MAPS (Faculty of Math Applied Phys Sci)</td>
</tr>
<tr>
<td>13:10</td>
<td>Hafeli, Urs: Short review of the last 4 years of magnetic carriers research</td>
</tr>
<tr>
<td>13:30</td>
<td>Session 1: Nanoparticle Synthesis I</td>
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<tr>
<td></td>
<td>Ablets, Yevhen: Synthesis and properties of Fe3N nanoparticles as alternative material for magnetic fluid hyperthermia</td>
</tr>
<tr>
<td>13:45</td>
<td>Bertuit, Enzo: Structure-Property-Function Relationships of Iron Oxide Multi-Core Nanoflowers in Magnetic Hyperthermia and Photothermia</td>
</tr>
<tr>
<td>14:00</td>
<td>Beauchamp, Maximilian: Novel Reactor Concepts for the Reproducible and Scalable Synthesis of Fine-Tuned Magnetic Nanoparticles</td>
</tr>
<tr>
<td>14:15</td>
<td>Bleul, Regina: Micromixer synthesis for optimized manufacturing of single-core magnetic nanoparticles with tailored properties for versatile biomedical and clinical applications</td>
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</tr>
<tr>
<td>14:30</td>
<td>Coffee break - Wilkins Building North &amp; South Cloisters and Upper Terrace</td>
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<tr>
<td>15:15</td>
<td>Durhuus, Frederik: Simulated clustering dynamics of magnetic nanoparticles</td>
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<td>15:30</td>
<td>Mefford, Thompson: Synthesis of polymer modified substituted ferrite nanoparticles guided by density functional theory and machine learning</td>
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<td>15:45</td>
<td>Roca, Alejandro: Fe3O4 Nanocubes as Multifunctional Theranostic Agents</td>
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<td>16:00</td>
<td>Zabow, Gary: Micropatterning Magnetic Microparticles</td>
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<td>16:15</td>
<td>Zolochevskaya, Kristina: Interaction of Ferritin Derivatives with Lysozyme, Amyloid Fibils</td>
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<tr>
<td>16:30</td>
<td>Discussion with speakers from the Nanoparticle Synthesis session: Do we really still need new magnetic nanoparticle types?</td>
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<tr>
<td>18:30</td>
<td>Reception in the Wilkins Building Upper Terrace with drinks and snacks. Generously sponsored by nanotherics!</td>
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**Wednesday, June 15, 2022**

<table>
<thead>
<tr>
<th>Time</th>
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<tr>
<td>08:30</td>
<td>Registration desk opens in the Wilkins Building, North Cloisters</td>
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<tr>
<td>09:15</td>
<td>Session 3: Magnetic Imaging / MPI / MRI I</td>
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<tr>
<td></td>
<td>Schier, Peter: Quantitative Imaging of Magnetic Nanoparticles in Large Body Regions using Nonlinear Magnetorelaxometry</td>
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<tr>
<td>09:30</td>
<td>Rinaldi-Ramos, Carlos: Labeling T cells with a new tracer tailored for sensitive tracking using magnetic particle imaging (MPI)</td>
</tr>
<tr>
<td>09:45</td>
<td>Kim, Hohyeon: MRI image-based cancer hyperthermia therapy</td>
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<tr>
<td>10:00</td>
<td>Coffee break - Wilkins Building North Cloisters, JBR and Upper Terrace</td>
</tr>
<tr>
<td>10:45</td>
<td>Marotta, Robert: Establishment of metabolic tracer based magnetic particle imaging</td>
</tr>
<tr>
<td>11:00</td>
<td>Ardizzone, Sebastiano: Development of multi-core magnetic particle imaging</td>
</tr>
<tr>
<td>11:15</td>
<td>Duy, Silvia: A dynamic bolus phantom for the evaluation of the spatio-temporal resolution of MPI scanners</td>
</tr>
<tr>
<td>11:22</td>
<td>Oberg, Samuel: Iron Oxide Nanoparticles as T1 Agents for Low-Field MRI</td>
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<tr>
<td>11:30</td>
<td>Schirle-Finke, Simon: Engineering Magnetic Nanorobots for Medicine</td>
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<tr>
<th>Time</th>
<th>Session 5: Magnetic Drug Delivery</th>
<th>Chair: Quentin Pankhurst</th>
<th>Location</th>
<th>Speaker</th>
<th>Talk #</th>
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<tr>
<td>12:15</td>
<td>Lunch</td>
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<tr>
<td>13:15</td>
<td>Bizeau, Joelle</td>
<td>Innovative nanocomposites for protein release through magnetic hyperthermia</td>
<td>Strasbourg, France</td>
<td>Talk 17</td>
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<tr>
<td>13:30</td>
<td>Guidelli, Ezra</td>
<td>Superparamagnetic Nanodevices as Single Oxygen Carriers for Cancer Therapy</td>
<td>Zarin, Brazil</td>
<td>Talk 18</td>
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<tr>
<td>13:45</td>
<td>Bodziak, Pawel</td>
<td>Novel drug delivery system: Bacterial derived magnetosomes and their implications in MBH therapy</td>
<td>UK</td>
<td>Talk 19</td>
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<tr>
<td>14:00</td>
<td>Wagner, David</td>
<td>Magnetic Nanoparticles for Safe and Steady Delivery of Peroxidase in Diabetic Mice</td>
<td>Zaragoza, Spain</td>
<td>Talk 20</td>
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<tr>
<td>14:15</td>
<td>Sarti, Enrico</td>
<td>Towards drug targeting to the eye with magnetic micromotors</td>
<td>Germany</td>
<td>Talk 21</td>
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<tr>
<td>14:30</td>
<td>Coffee break/Change posters to session II</td>
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<tr>
<th>Time</th>
<th>Session 6A: Magnetic Hyperthermia</th>
<th>Chair: Silvio Dutz</th>
<th>Location</th>
<th>Speaker</th>
<th>Talk #</th>
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<tr>
<td>15:15</td>
<td>Gutierrez, Maru, Lucía</td>
<td>Beyond Classical Magnetic Hyperthermia: From Innovative Characterization Approaches to New Therapeutic Alternatives</td>
<td>Zaragoza, Spain</td>
<td>Invited Talk 2</td>
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<tr>
<td>16:00</td>
<td>Fraillat, Raulica</td>
<td>Critical Parameters to Improve Pancreatic Cancer Treatment Using Magnetic Hyperthermia: Field Conditions, Immune Response, and Particle Biodistribution</td>
<td>Zaragoza, Spain</td>
<td>Talk 22</td>
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<td>16:15</td>
<td>Watersh, Piers</td>
<td>In vivo safety analysis of different magnetic nanoparticles in more extensive hyperthermia experiments</td>
<td>Zaragoza, Spain</td>
<td>Talk 23</td>
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<tr>
<td>16:30</td>
<td>Mueller, Stefan</td>
<td>Hyperthermia and Imaging Performance of Hybrid Spheres with Incorporated Magnetic Nanoparticles for Tumor Ablation</td>
<td>Aachen, Germany</td>
<td>Talk 24</td>
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<tr>
<td>16:45</td>
<td>Stokzukh, Ludmyla</td>
<td>Iron Oxide Nanoparticles as Excellent Heating Agents for Magnetic Hyperthermia Cancer Therapy</td>
<td>London, UK</td>
<td>Talk 25</td>
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<tr>
<td>17:00</td>
<td>Telling, Neil</td>
<td>A magneto-optical microscope for investigating magnetization dynamics of intracellular nanoparticles under hyperthermia conditions</td>
<td>Stoke-on-Trent, UK</td>
<td>Talk 26</td>
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<tr>
<td>17:15</td>
<td>Bussolati, Francesca</td>
<td>Magnetic heating to trigger entrapped enzymes activity</td>
<td>Zaragoza, Spain</td>
<td>Talk 27</td>
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<tr>
<td>17:30</td>
<td>Bussolati, Francesca</td>
<td>Magnetic Hyperthermia as an adjuvant cancer therapy in combination with carbon ions, proteins and photodynamic therapy on pancreatic tumour cell cultures</td>
<td>Paris, Italy</td>
<td>Talk 28</td>
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<tr>
<td>17:37</td>
<td>Castro, Jorge</td>
<td>Development of Handheld Induction Heaters for Magnetic Fluid Hyperthermia Applications and In-vitro Evaluation on Ovarian and Prostate Cancer Cells</td>
<td>Mayaguez, Puerto Rico</td>
<td>Talk 29</td>
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<tr>
<td>17:45</td>
<td>Milette, Angel</td>
<td>Local temperature gradients in intracellular magnetic hyperthermia</td>
<td>Zaragoza, Spain</td>
<td>Talk 30</td>
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<tr>
<td>17:52</td>
<td>Del Sol Fernández, Susana</td>
<td>Composition impacts the structural, magnetic and thermal efficiency of MnFe2O3-NH MNPs. An in vitro and in vivo study</td>
<td>Zaragoza, Spain</td>
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<tr>
<td>18:00</td>
<td>Poster Session II (Posters 53-104)</td>
<td>Free evening - go and get collaborations going!</td>
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**Thursday, June 16, 2022**

**9:30** Registration desk opens in the Wilkins Building, North Cloisters

**9:45** Livesey, Karen Tutorial about the basics of magnetic particles - Part II | Newcastle, Australia | Tutorial 2

**9:15** Scagnoli, Valerio Mapping the Structure and Behaviour of 3D Nanomagnetic Systems | Zurich, Switzerland | Invited Talk 3

**10:00** Radon, Patricia Harmonizing of static magnetization measurements using two commercial SQUID devices of the same type | Berlin, Germany | Talk 35

**10:15** Coffee break

**11:00** Agarwal, Gunjan Multimodal Magnetic Force Microscopy | Columbus, USA | Talk 34

**11:15** Radon, Patricia Mapping the Structure and Behaviour of 3D Nanomagnetic Systems | Berlin, Germany | Talk 35

**11:30** Van Durme, Rikke Magnetic Force Optimization for Improved Magnetic Particle Targeting | Ghent, Belgium | Talk 36

**11:45** Willerueve-Alvaro, Darin Navigation control of Magnetoelastic Bacteria by magnetic fields | Bilbao, Spain | Talk 37

**12:00** Libke-Lupice, Werner Nanomagnetics for diagnostic imaging: Combined magnetic and thermal effects for signal transduction | Zaragoza, Spain | Talk 38

**12:15** Lunch - BBQ generously sponsored by nanoScale Biomagnetics


**14:00** Wang, Yang Characterization of DNA-Chamber Magnetic Nanofibres | Zaragoza, Spain | Talk 39

**14:15** Mostarac, Deniz Characterization of DNA-Chamber Magnetic Nanofibres | Wien, Austria | Talk 40

**14:30** Saugue, Jean-Michel Strain promoted aldehyde alkyne click chemistry, an efficient surface functionalization strategy for microRNA magnetic separation | Paris, France | Talk 41

**14:45** Proulx, Robert Magnetic Nanoparticles for Diagnostic Imaging: Getting into the Clinic | San Diego, USA | Talk 42

**15:00** Coffee break

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<th>Biosensors</th>
<th>Chair: Wolfgang Schütt</th>
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<td>15:45</td>
<td>Deroo, Maikane</td>
<td>Innovative dynamic detection for early diagnosis with a lab-on-a-chip based on two-stage giant magnetoresistance sensors Gif-sur-Yvette, France Talk 43</td>
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<tr>
<td>16:00</td>
<td>Roach, Enja</td>
<td>Sensitive DNA detection via strand displacement mediated disassembly of magnetic nanoparticles Braunschweig, Germany Talk 44</td>
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<tr>
<td>16:15</td>
<td>Christiansen, Michael</td>
<td>Development of Inductively Detectable Probes for Proteolytic Activity Zürich, Switzerland Talk 45</td>
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<tr>
<td>16:30</td>
<td>Wang, Jian-Ping</td>
<td>Handheld Magnetic Particle Spectroscopy (MPS) for Rapid, One-step, Wash-free Detection of SARS-CoV-2 Spike and Nucleocapsid Proteins in Liquid Phase Minneapolis, MN, USA Talk 46</td>
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<tr>
<td>16:45</td>
<td>Oh, Seungjun</td>
<td>Development of Magnetic Particle Spectroscopy That Integrates Both Conventional and Mixing Methods for Virus Detection Gwangju, South Korea Talk 47</td>
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</table>

Talks will stop punctually at 17:00. Then transfer to the boat by Double Decker Bus.

18:30 Boat tour with dinner from the Butler's Wharf Pier generously sponsored by Imagion Biosystems! And the New Orleans type band "Blind Tigers" is sponsored by Chemicell!

22:30 Return to the Tower Millennium Pier (different pier!), travel back to UCL by Double Decker Bus.

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**Friday, June 17, 2022**

8:30 Registration desk opens in the Wilkins Building, North Cloisters

8:45 Livesey, Karen Tutorial about the basics of magnetic particles - Part III Newcastle, Australia Tutorial 3

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Session 12

**Biocompatibility Studies**

Chair: Maciej Zborowski

11:00 Boelens, Peter Use of peptide functionalized Dynabeads for the magnetic carrier separation of Rare Earth phosphors in low and high magnetic field gradients Dresden, Germany Talk 53

11:15 Makridis, Antonios 3D Printing of Polymer-Bonded Magnets Thessaloniki, Greece Talk 54

11:30 Goldfarb, Ron Problems in Magnetic Characterization of Nanoparticles Boulder, CO, USA Invited Talk 5

12:15 Lunch

Session 13

**Biological Applications I**

Chair: Anna Roig

13:15 Block, Findan Magnetic bucket brigade networks as rails for single cell transportation Kiel, Germany Talk 55

13:30 Clement, Joachim Passage of magnetic nanoparticles through a differentiating blood-placenta barrier Jena, Germany Talk 56

13:45 Fernández-Castañed, Alfred Biomanufacturing magnetosomes: nanocarriers with versatile functionalisation for imaging and drug delivery applications Birmingham, UK Talk 57

14:00 Freis, Barbara Active Targeting of Head and Neck Cancer Cells with Dendronized Iron Oxide Nanoparticles and Effect of the Size and Shape of Nanoparticles for Promoting Multimodal Therapy Strasbourg, France Talk 58

14:15 Coffee break

Session 14

**Biological Applications II**

Chair: Lucia Gutierrez

15:00 Romero Urribe, Gabriela Nanomagnetic Actuators for Neural Modulation San Antonio, TX, USA Invited Talk 6

15:45 García, Victor Heterobimetallic probiotic bacteria as new oral magnet-thermal hyperthermia agents Granada, Spain Talk 59

16:00 Horák, Daniel Antioxidant and Antibacterial Magnetic Nanoparticles: Design, Synthesis and Biological Effects Prague, Czechia Talk 60

16:15 Pátek-Aller, Jacqueline Advancing Rewarming for Cryopreservation through Scalable Polymer Coating of Iron Oxide Nanoparticles Minneapolis, MN, USA Talk 61

16:30 Brückner, Wilfried Biocompatibility Studies and Cellular Interactions of Biogenic Magnetic Nanoparticles München, Germany Talk 62

16:45 Closing Comments: Nguyen Thanh & Urs Hafeli

17:00 Meeting ends
Map of London
UCL Map

Map of the Meeting Rooms at UCL
Engineering magnetic micro- and nanorobots for medicine

Sinone Schürle1
1Responsive Biomedical Systems Laboratory, Department for Health Sciences and Technology, ETH Zurich, Switzerland
e-mail: sinone.schuerle@hest.ethz.ch

Engineering robots at the cellular scale could allow us to gain new insights into disease development and provide more targeted means for diagnostic and therapeutic interventions. Magnetic fields have proven to serve as a safe strategy to wirelessly power magnetic microrobots for remote control in physiological environments. In this talk I will give an overview of three distinct examples of magnetic micro- and nanorobots for medical applications and describe their respective design and control schemes (Fig. 1).

First, I will present a method for 3D spatiotemporal probing of tissue models from a single cell perspective using microrobots. We fabricated rod-shaped magnetic microrobots and leveraged 3D magnetic field generation, physical modeling, and image analysis to reveal local shear moduli and remotely apply mechanical stimuli [1]. The heterogeneous mechanical landscape of a tumor’s extracellular matrix (ECM) is in part a result of increased local release of enzymes, in particular certain proteases, which degrades the ECM and is associated with tumor invasion. In a next example, I will describe nanorobots that are either activated or detected via magnetic fields and designed to report a tumor’s proteolytic activity as novel diagnostic [2].

Last, I will show how an individual, synthetic and swarms of living magnetic microbots can help to locally enhance transport of nanoparticles (NPs) mimicking drug carriers in a tissue model [3]. We employed two distinct micropropeller designs powered by rotating magnetic fields to increase diffusion-limited transport of NPs by enhancing local fluid convection. In the first approach, we use a single synthetic magnetic microrobot called an artificial bacterial flagellum, and in the second approach, we control swarms of magnetotactic bacteria to create a directive “living ferrofluid” by exploiting ferrohydrodynamics. With both strategies, we demonstrated the ability to locally and wirelessly drive convective transport in tissue models. The latter strategy has also shown to outperform synthetic ferrofluids in terms of ferrohydrodynamic coupling to drive NP transport (Fig. 1) [4]. Lastly, I will share insights into how these living microrobots can be further engineered to function as therapeutic vectors themselves that can be magnetically controlled [5].

References
[1] Asgerinsson et al., Lab Chip, 21, 3850-3862, 2021

Acknowledgements: Many people contributed to the work that will be presented in the talk. I am especially grateful to Yi-Flan Fernández-A Coron, Laura Asín, Liliame Becla, Susel del Sol, Javier Idiggo, Somil Corea, Lorena Betancor, Yadilen Portilla, Luis Porta, Miguel Castro, Victor Garcia, José María Dominguez-Vera, Sergio Ruta, David Savantes, Roy Chantrell, Domingo Barber, Puerto Morales, Sabino Veintemillas-Verdaguer, Jesús M. de la Fuente, María Moros, Valeria Grana and Raluca Fratila.
INVITED TALK

X-ray three-dimensional magnetic imaging

Valerio Scagnoli1,2
1Laboratory for Mesoscopic Systems, Department of Materials, ETH Zürich, Zürich, Switzerland.
2Laboratory for Multiscale Materials Experiments Paul Scherrer Institute, Villigen PSI 5232, Switzerland.
email: valerio.scagnoli@psi.ch

Three dimensional magnetic systems hold the promise to provide new functionality associated with greater degrees of freedom. For example, predictions suggest that the introduction of curvature into magnetic thin films could lead to unique properties such as curvature-induced anisotropy, magnetocrystallinity, and domain wall automotive effects.

Over the last years, we have worked towards developing methods to fabricate and characterise three-dimensional magnetic structures. Specifically, we have combined X-ray magnetic imaging with new iterative reconstruction algorithms to achieve X-ray magnetic tomography and lamography [1-4]. In a first demonstration, we have determined the three-dimensional magnetic nanostructure with in the bulk of a soft GdCo magnetic micropillar with 100 nm spatial resolution and we have identified the presence of peculiar local magnetic configuration known as "Bloch points" [1, 3]. Subsequently, we have been able to perform imaging of magnetic configurations in a time-resolved fashion determining the magnetization dynamics in a micrometre size GdCo disk. Therefore, X-ray magnetic three-dimensional imaging, with its recent extension to the soft X-ray regime [5], has now reached sufficient maturity that will enable to unravel complex three-dimensional magnetic structures for a range of magnetic systems, possibly including magnetic nanoparticles.

In this contribution, I will first give an overview of our recent results and review the current shortcomings of the magnetic tomography technique. Finally, I will discuss how diffraction-limited storage ring source, together with state of the art instrumentation, will allow three-dimensional magnetic nanotomography to thrive.

Figure: Non-invasive determination of the magnetic configuration of a GdCo disk. The scale bar corresponds to a length of 1 μm. Several cross sections at different heights are presented. The magnetic moment orientation in the plane is represented by an arrow, whilst the component out of plane is illustrated with a colorbar. The magnetic material was grown such that there was no significant magnetic anisotropy at the bottom of the disk (panel a) and b) leading to the formation of magnetic domains. In contrast the top part of the disk has a significant anisotropy leading to the formation of a configuration with magnetic moments almost completely in-plane (panels c) with parallel magnetization alignment (panel d) on the topmost part of the disk.

References:

INVITED TALK

CRISPR/Cas9 Correction of a Mutation in CFTR as a Potential Therapy for Cystic Fibrosis

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Gene editing by CRISPR/Cas9 is a rapidly developing area of gene therapy technologies. It offers opportunities to correct disease causing mutations for a wide range of diseases. Essentially, an RNA guided nuclease, CRISPR, can be used to knockout genes, to repair them with a high degree of specificity, or to replace regions of DNA including complete cDNA coding sequences. We are focused on developing CRISPR strategies to developing novel therapies for cystic fibrosis. Cystic Fibrosis is an autosomal recessive disorder caused by mutations in the CFTR gene. It mainly affects the lung causing production of thick sticky mucus leading to infection and inflammation and loss of lung function. CF-causing mutations of CFTR have been well characterised of which there are approximately 300. The 10th most common mutation, 3849+10kb C>T, generates a cryptic splice site within an intron, leading to a faulty mRNA producing a truncated CFTR protein. We are developing CRISPR to delete this mutation in the intron. This therapy would need to be delivered to the lung by inhalation of an aerosolised formulation of nanoparticles carrying the CRISPR repair molecules.

We have developed a non-viral, receptor-targeted nanocomplex (RTN) formulation to deliver the CRISPR formulation. CF cells with the splice site mutation were transfected with the nanoparticle leading to more than 60% correction efficiency. Normal processing of the CFTR mRNA was restored, leading to normal CFTR protein production. We then showed that the repaired protein behaved correctly as a chloride channel in treated CF cells. Finally, we showed that the nanoparticle can deliver CRISPR to the lungs of mice.
In 1955, Bean first applied the term “super-paramagnetic” to ensembles of small, single-domain, ferromagnetic particles that reach thermal equilibrium through thermal activation, noting that “the particles . . . act as paramagnetic particles of very large moment.” The following year, Bean and Jacobs showed how the magnetization followed a Langevin function of magnetic field and temperature, and that curves measured at different temperatures should be approximately superposable when plotted with respect to \( H/T \).

\[ \chi \propto \frac{1}{T} \]

This scaling is characteristic of superparamagnetism and distinguishes it from simple anhysteretic ferromagnetism.

An exponential dependence of magnetization relaxation time on single-domain particle size and temperature and the concept of blocking were originally developed by Néel. An Arhenius or Vogel-Fulcher relationship between \( T \) and \( T_B \), where \( T_B \) is the frequency in alternating-field susceptibility measurements and \( T_B \) is the blocking temperature, is indicative of superparamagnetism.

Like a ferromagnet above its Curie temperature \( T_C \) and an antiferromagnet above its Néel temperature \( T_N \), the low-field susceptibility \( \chi \) of a superparamagnet follows a Curie-Weiss law, \( \chi = C/(T - T_0) \), between \( T_C \) and \( T_N \). This gives rise to the well-known linear dependence of reciprocal susceptibility, \( 1/\chi \), on temperature. The slope of the linear fit gives the reciprocal of the Curie constant, \( 1/C \), from which the average magnetic moment per particle can be calculated. The temperature-\( x \)-intercept of the linear extrapolation, the superparamagnetic Curie temperature \( T_C \), is an indication of the interaction among superparamagnetic particles, spins in spin glasses, or superparamagnetic clusters in alloys. Additionally, \( \theta \) may depend on packing fraction, particle diameter, applied field, and distribution of particle sizes and \( T_B \).

Many articles hastily invoke superparamagnetism based on a single magnetization-vs.-field curve or a pair of zero-field-cooled and field-cooled magnetization-vs.-temperature curves, without verifying scaling of magnetization at different \( H \) and \( T \), Néel relaxation, or Curie-Weiss behavior above \( T_B \). Virtually always ignored in Curie-Weiss plots is the fact that the modulus of the specimen under test. The effect may be significant for samples of particles such as iron, magnetite, and maghemite that have large magnetization at low fields and, therefore, small reciprocal susceptibilities, \( \chi^{-1} \propto N^{-1} \), where \( N \) is the internal volume susceptibility characteristic of the material.\( \chi \) is the magnetic susceptibility characteristic of the sample, and \( 0 \leq N \leq 5 \) is the demagnetizing factor of the sample (in SI units). An impendiment to correction for demagnetizing factor is that, as functions of temperature, most published data are of magnetic moment, mass or molar susceptibility, or susceptibility in arbitrary units instead of susceptibility referenced to particle volume.

For magnetic characterization, superparamagnetic particles are often packed in capsules or dispersed in films. The effective demagnetizing factor \( N_eff \) for specimens that consist of exchange-decoupled particles may be estimated from classical effective-medium theories, one of which yields a simple interpolation formula. The correction for demagnetizing factor will increase \( \theta \) and, if \( N_eff \) is large enough relative to \( \chi \), even result in a change in sign of \( \theta \) from apparently negative (indicative of superparamagnetic interparticle interactions) to positive (indicative of ferromagnetic interactions).

References
Due to their unique physico-chemical properties, multi-core iron oxide nanoparticles (NPs) also called nanoflowers (NFs), are used as functional materials in many applications, including for diagnosis and therapy in the biomedical field. NFs are efficient magnetic resonance imaging (MRI) contrast agents and performant nano-heaters in magnetic hyperthermia (MHT), with specific loss powers (SLP) values amongst the highest reported ones for magnetic materials. More recently, magnetic NFs have been proved to be promising materials for photothermal therapy (PTT) thanks to their absorption in the first (around 808 nm for maghemite) and second (around 1064 nm for magnetite) infra-red biological windows. However, how the fine structure features of NFs at the nanoscale govern their properties and their collective function in MHT and PTT still needs to be elucidated.

In the present work, we investigate in a multi-scale approach the role of many parameters of the polyol synthesis on the final NFs size, shape, chemical composition, number of cores and crystallinity. These nanofeatures are later correlated to the magnetic, optical and electronic properties of the NFs as well as their collective macroscopic thermal role of iron(III) and heating ramps on the elaboration of well-defined NFs with high number of cores. While MHT responses of the NFs and their collective photothermal properties depend directly on the mean volume of the NFs (as supported by optical cross sections numerical simulations) and strongly on the structural disorder in the NFs, rather than the stoichiometry. The concentration of defects in the nanostructures, evaluated by time-resolved photoluminescence and Urbach energy (EU) measurements, evidences a switch in the optical behavior for a limit value of EU = 0.4 eV where a discontinuous transition from high to poor PT efficiency is also observed.
Novel Reactor Concepts for the Reproducible and Scalable Synthesis of Fine-Tuned Magnetic Nanoparticles

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Despite the wide usage of magnetic nanoparticles, their reproducible synthesis with the desired properties remains challenging at all scales. Hence, the (re-)development and fine-tuning of synthesis protocols remains an unfortunate burden for each project involving magnetic nanoparticles. Scale-up is commonly considered as the logical step following the proof of principle, but up-scaling lab scale syntheses is everything but trivial. This is why scalability and pilot production (at throughput below full-scale production) are crucial to bring research across the so-called “Valley of Death” (the gap between research and commercialisation) in high-cost, and high-risk areas such as nanotechnology. Novel reactor concepts, such as flow reactors are known for their potential to improve mass transfer, reagent mixing, heating and cooling rates, and facilitate precisely timed reagent addition (especially for rapid reactions). In addition, their inherently continuous operation facilitates large scale production via longer operation times, i.e., the same or similar reactors can be used for development and pilot production.

The continuous synthesis of magnetic nanoparticles, however, is not trivial as particle formation mechanisms are complex with limited knowledge of reaction kinetics, and rapid mixing and/or high temperatures are required. Therefore, we have developed a new family of flow reactors, specifically designed for the synthesis of iron oxide nanoparticles (IONP) via i) co-precipitation, ii) partial oxidation, and iii) thermal decomposition. These novel reactors overcome the engineering challenges for each synthetic procedure and allowed not only for robust and reproducible IONP syntheses, but also to gain new insights into the particle formation mechanisms by “freezing” transient reaction locally. This made it possible to characterise the intermediate oxide phases formed during co-precipitation and study particle morphology at early reaction stages. Furthermore, flow reactors facilitated the synthesis of IONPs with no batch equivalent, synthesis (without any growth promoting or inhibiting additives) IONPs ≤ 5 nm showing excellent T1 contrast via co-precipitation, co-oxidability stable 20-30 nm particles with good heating characteristics for magnetic hyperthermia via partial oxidation, and all particle sizes between 2 and 20 nm via a high temperature polyol synthesis using the same precursor solution. To further extend the application range of flow-chemistry for magnetic nanoparticle synthesis, a highly sensitive flow magnetometer was developed to characterise magnetic nanoparticles in solution, in situ and in real-time using alternating current susceptometry.

This holistic engineering approach resulted not only to new ways for magnetic nanoparticle synthesis, large scale production, synthesis monitoring and control, but also paves the way towards high-throughput screening and self-optimised reactors using artificial intelligence to produce magnetic nanoparticles with properties tuned specifically for each application.

Micromixer synthesis for optimized manufacturing of single-core magnetic nanoparticles with tailored properties for versatile biomedical and clinical applications

For every biomedical application of magnetic nanoparticles (MNP), their structural and magnetic characteristics have to be adjusted specifically to the requirements of the envisaged use [1]. For instance, for magnetic particle imaging (MPI), single core MNP with core sizes between 25-30 nm are postulated to achieve optimal performance, whereas ultra small iron oxide MNP with core sizes below 5 nm are aimed for to be used as positive contrast agent in MRI. Thus, tailoring core size of MNP while sustaining colloidal stability even in physiological environment with high ionic strength using a reliable and reproducibly synthesis route still remains a challenging task. Microfluidic nanoparticle production has experienced a remarkably boom during the actual pandemic for synthesis of lipid nanoparticles as a vaccine carrier. However, even the existing technologies often suffer from non-reliable production and lack from direct scale up capability without the need of parallelization. As compared to lipid nanoparticles, the production of MNP in a continuous microfluidic system is even more challenging due the high risk of clogging of the devices.

We established a micromixer process based on an aqueous synthesis route without using any organic solvents or high temperatures. Single-core MNP with a core size of about 25 nm are produced at a synthesis temperature of max. Tsyn=55 °C already within a few minutes reaction time [2]. Optionally, the resulting single-core MNP can subsequently be coated with serum albumin to enhance colloidal stability in physiological environment [3] or be further functionalized to change surface coating to desired ligands [4]. Evaluation of the produced nanoparticles reveal their high potential in different biomedical applications such as MPI, MRI, and magnetic fluid hyperthermia [5]. Combining the high imaging capability (MRI or MPI) with the excellent heat delivery properties tunable magnetic nanoparticles will advance thermosensitive applications of MNP.
Simulated clustering dynamics of magnetic nanoparticles

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Magnetic nanoparticles (MNPs) in liquid suspension may spontanously aggregate, forming a plethora of complex structures. This clustering affects system properties like average magnetisation and hysteresis, which are crucial for applications, e.g. in magnetic hyperthermia [1]. Also, understanding clustering enables control over bottom-up self-assembly of desired structures.

In a recent study [2], we used Langevin dynamics simulations to study the clustering of single-domain spherical MNPs, free to move and rotate in 3D. The model contains magnetic dipole interaction, van der Waals forces, Brownian motion, viscous drag and steric repulsion. We have shown how the relative importance of all these effects can be tuned through the radius of the magnetic core, $R_m$, and of the surfactant layer, $R_s$.

We find that dipole interaction favours linear structures like rings and chains, while van der Waals forces favour compact clusters and Brownian motion may induce dissociation into single particles. In this talk, we will illustrate how these competing dynamics play out for MNP ensembles through snapshots and 3D animations of the time-evolution. Then we present a systematic study of which cluster types form under different combinations of $R_m$ and $R_s$. The results are in general agreement with cryo-TEM experimental work [3]. Besides helping interpret experiments, the generated clusters form a useful basis for further theoretical studies linking cluster structures to their magnetic properties.

Fe3O4 Nanocubes as Multifunctional Theranostic Agents
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The value of magnetic nano and microparticles for in-vitro and in-vivo applications derives from their ability to be remotely controlled, including remotely directed translation, rotation, and magnetization. These functionalities are directly determined by the particle size, shape, and composition. Spherical magnetic particles are most commonly used because they are easiest to synthesize but their high symmetry can limit their functionality. Considerable work is therefore now also directed towards less symmetric / more anisotropic particles. These include different shaped particles such as cubes, rods, and ellipsoids, which offer different rotational and magnetization options beyond those of spherical particles; helical particles and asymmetric particle clusters, which may function as rotational micromotors / microswimmers; and hemispherically coated particles, such as Janus particles with novel bi-directional properties.

Here we present a rational designed synthesis route based on thermal decomposition of iron (III) acetylacetonate which leads to high quality nanocubes over a wide size range (10-80 nm).[2] This synthesis route can be extended to other spinel ferrites (Co, Mn and Zn). In the past it has been reported the synthesis of magnetite nanocubes over 20 nm but below, these synthesis routes fail leading to non-regular nanoparticles.[1] We have shown that 17nm nanocubes still show a great colloidal stability, excellent magnetic hyperthermia, and better NMR performance (much better than their spherical counterparts). Moreover, Fe3O4 nanocubes are outstanding heat mediators for photothermia in the near infrared biological windows (680-1350 nm). In addition, the magnetic and optic anisotropies of the nanocubes have been exploited for a relatively new approach for in situ local temperature sensing.

Fig. 1. TEM images of magnetite nanocubes with different average sizes (left 10 nm, centre 17 nm and right 30 nm).

References
Interaction of Ferritin Derivatives with Lysozyme Amyloid Fibrils

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Transformed ferritin particles and disrupted iron homeostasis are believed to be associated with various pathological processes, including neurodegenerative disorders. We used ferritin derivatives such as reconstructed ferritin (RF) and magnetoferritin (MF) to study the interaction with lysozyme amyloid fibrils (LAF). Firstly, we characterized the physicochemical properties of prepared samples by different methods: UV-VIS, DLS, and SQUID magnetometry. Subsequently, the interaction of ferritin derivatives with LAF was analyzed. For both ferritin derivatives, the incubation with LAF caused a significant increase in the release of toxic ferrous ions.

Free iron is at physiological conditions occurring in two oxidation states. The first one is a relatively soluble but highly toxic ferrous (Fe2+) form, and the second one is a very insoluble but non-toxic ferric (Fe3+) state. Magnetic mineral core in magnetoferritin (as a model system of pathological ferritin) produce more toxic ferrous ions in the presence of reducing agents (vitamin B2 and C) than ferrhydrate mineral core in native ferritin [1]. Neurodegenerative processes are also associated with the presence of abnormal protein aggregates, forming very organized fibrils known as plaques. To simulate the formation of amyloid plaques or fibrils, we used lysozyme amyloid fibrils. We used ferritin derivatives as model systems to study their interaction with lysozyme amyloid fibrils (LAF). To accomplish that, we have successively synthesized magnetoferritin and reconstructed ferritin as well as lysozyme amyloid fibrils, using controlled in vitro synthesis. To reveal the potential adverse effect of ferritin derivatives with LAF interaction, we determined the time dependence of ferrous ions release from the ferritin envelopes. Ferrous ions are highly toxic to the cell. Therefore, any excess iron currently not needed for the metabolic processes must be eliminated by transformation to ferric state and stored, e.g. in ferritin. From the comparison of the average and median values (Figure 1), it is clear that the release of toxic ferrous ions occurs to a greater extent during the interaction of ferritin derivatives with LAF. From this point of view, the LAF behaves like a mineral core reducing agent, similar to vitamins B2 and C [1].

Induction of increased ferrous ions release from the ferritin envelope during interaction with LAF can cause increased oxidative stress and more significant damage for the cells. On the other hand, we found destructive effect of ferritin derivatives on the LAF.

These findings can help better understand the biochemistry behind the pathological processes associated with the iron accumulation and magnetic mineralization, e.g. in neurodegenerative disorders.

Quantitative Imaging of Magnetic Nanoparticles in Large Body Regions using Nonlinear Magnetorelaxometry

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Magnetorelaxometry (MRX) imaging enables the noninvasive detection and quantification of magnetic nanoparticles (MNP). An MRX measurement process consists of (i) an excitation phase, where a set of external coils produces inhomogeneous magnetic fields, aligning the MNPs along the resulting field and (ii) a relaxation phase, measuring the decay of magnetic moment of the particles with a highly sensitive sensor system and rapidly demagnetizing the excitation coils. The state-of-the-art imaging process itself involves the solution of the inverse problem of the linear MRX forward model. This linear model is valid within the (approximately) linear magnetization regime of the MNP, for weak magnetic excitation fields and holds for small fields of view (FOV) (roughly 10 cm in diameter, depending on the MRX setup). In this case, it is typically possible to magnetize particles in the center of the FOV still strong enough such that they produce a measurable relaxation signal at nearby sensor locations, without leaving the linear magnetization regime in any part of the FOV. However, when aiming for larger FOVs (e.g. torso size), larger excitation fields need to be employed to produce measurable relaxation signals in all areas of the FOV that inevitably drive areas close to the coils into the nonlinear magnetization regime, thereby invalidating the linear MRX forward model and preventing accurate reconstructions of the MNP ensembles.

In this contribution, we not only extend the linear MRX forward model by a nonlinear, excitation field dependent magnetization factor that enables simulating realistic relaxation responses for large magnetic fields, but we also present a novel MRX spatial encoding scheme that exploits this nonlinearity by employing different driving coil currents which allows for more accurate MNP imaging results than obtainable by the standard imaging approach. The nonlinear magnetization factor is empirically tuned using real measurement data from MNPs magnetized with different magnetic field strengths. The proposed approach is tested in simulations on a 40 × 20 × 30 cm³ torso-shaped volume, using four large excitation coils and eight sensors with two sensitive axes, respectively, inspired by dual axis optically pumped magnetometers (OPMs) (see Figure 1a). The FOV is discretized into cubic voxels with a side length of 2.5 cm for imaging. Several different MNP phantoms with clinically relevant MNP concentrations are reconstructed using both the linear MRX model and the nonlinear approach applying multiple different coil currents. Realistic model errors (differing voxel sizes for measurement simulation and reconstruction, as well as positioning and orientation deviations of coils and sensors in the range of few millimeters and degrees, respectively) and measurement noise (1 pT/√Hz) were added in the simulations, resulting in an adequate signal-to-noise ratio for MRX imaging of approximately 20 dB. It is evident throughout all reconstructions that the nonlinear approach yields more accurate reconstructions by introducing additional information to the inverse problem through the nonlinear spatial encoding scheme (see Figure 1b for reconstruction examples). Specifically, this is used full since large coil sizes are necessary to generate strong magnetic excitation fields for large FOVs. However, large coil sizes hamper good spatial encoding of the FOV due to their more homogeneous magnetic fields compared to smaller coils. Thus, the proposed approach counteracts this loss of spatial information to some degree. These theoretical findings will be validated in experiments in the near future.

Figure 1. The MRX simulation setup with voxels (grey), coils (red) and sensors (blue) is shown in (a). Subfigure (b) depicts an MNP phantom (left) and its reconstructions using the linear (middle) and the nonlinear (right) approach. CC indicates the Pearson correlation coefficient between reconstructions and ground truth in percent, where 100% is a perfect reconstruction. "Quant. Error" is the quantification error of the reconstructions relative to the true particle mass.

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Labeling T cells with a new tracer tailored for sensitive tracking using magnetic particle imaging (MPI)

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Magnetic Particle Imaging (MPI) is a new molecular imaging technology capable of unambiguous and quantitative tomographic imaging of the distribution of superparamagnetic iron oxide nanoparticle (SPION) tracers in vivo. One exciting application of MPI is in tracking adoptive cell transfer (ACT) therapies. The modification and use of patient's T cells to attack cancer is of great interest due to the potential of eradicating not only primary tumors but also metastases. However, T cell cancer immunotherapy suffers many challenges in treating solid tumors, including achieving accumulation and persistence of ACT T cells at the site of the tumor. Development and evaluation of ACT T cell therapies would benefit tremendously from non-invasive and quantitative imaging of T cell biodistribution. We previously demonstrated tracking of T cells labeled with the commercially available SPION ferucarbotran in mice using MPI, with an estimated cell sensitivity of ~50,000 T cells. Here we report labeling T cells with an optimized MPI tracer, RL-1, coated with the anionic polymer poly(maleic anhydride-alt-1-octadecene) (PMAO). Various labeling strategies were studied, resulting in varying degrees (~5-15 pg Fe/cell) of T cell labeling with the MPI tracer, without affecting T cell viability, phenotype, or cytotoxic function, and resulting in T cell sensitivity of 5,000 T cells labeled with RL-1 PMAO tracer, a 10x improvement relative to labeling with ferucarbotran. MPI was further used to evaluate the extent of SPION eocytosis, degradation, and dilution in T cells, and to monitor long-term clearance of nanoparticles after systemic administration, alone or inside T cells. Furthermore, the therapeutic efficacy of RL-1 PMAO labeled T cells in vivo was not hampered by nanoparticle labeling, thus enabling non-invasive quantitative tracking of T cells without affecting their intended function. These results illustrate the value of optimizing tracers for high signal and efficient T cell labeling and illustrate the potential of MPI for unambiguous, sensitive, and quantitative tracking of T cell cancer immunotherapy.

Figure: Hyperthermia simulation model and magnetic particle imaging. (a) Temperature prediction model of magnetic hyperthermia. (b) Linear relation of acquired MPI signal intensity and mass of nanoparticle inside target position. (c) Initial MPI image of nanoparticle inside tumor and nanoparticle image after 1 week.

Establishment of metabolic tracer based magnetic particle imaging

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Radiation-free imaging techniques are beneficial for the development of brown adipose tissue (BAT)-centered therapies. Magnetic Particle Imaging (MPI) is a non-invasive quantitative 3D imaging technique for detecting magnetic nanoparticles (MNP) in biological systems. Here, we present quantitative MPI imaging of BAT metabolic activity using MNP-loaded lipoproteins. Artificial lipoprotein particles (metabolic MPI-tracer) were synthesized by mixing phosphatidylcholine, triglycerides, and cholesterol and then loaded with Zn-doped iron oxide MNP. Initial suitability testing of the new MPI-tracer for imaging was performed using a commercial MPS device, a zero-dimensional variant of MPI. MPS-based quantification on organ samples was also supported in vivo studies to optimize the pharmacokinetics of the new MPI-tracer. Subsequent quantitative imaging of the new MPI tracer was carried out using a preclinical MPI system (Bruker). Complementary anatomic scans were acquired using a preclinical 1T MRI system (Bruker). MPS evaluation of the metabolic MPI tracer revealed excellent stability, good MPI performance, and that the nanoparticle properties were nearly independent of the surrounding physiological environment. Although lipoprotein encapsulation of MNP resulted in slightly reduced spatial resolution, the measured MPI-signal intensity scaled linearily with tracer amount, indicating their suitability for quantitative MPI. We used BAT activation by acute cold exposure of mice as a model for induced tissue-specific lipoprotein (metabolic MPI-tracer) uptake. Using MPS quantification, we demonstrated that the amount of metabolic MPI-tracer in BAT was significantly increased when mice were kept at 4°C for 20 h (see Figure 1). Moreover, metabolic tracer allowed clear MPI-visualization of the uptake of lipoproteins in active BAT. In contrast, no accumulation in the BAT region was detected in mice treated with the MPI gold standard Resovist®.

We showed for the first time that lipoproteins loaded with MNP facilitate in vivo MPI tracking of lipid uptake and metabolic activity of BAT. Human-sized MPI scanners become available, this opens the possibility of studying lipid uptake and metabolic activity of BAT in humans without radiation exposure.

Figure: Metabolic imaging procedure using MPI

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Talk #13

Developing Magnetorelaxometry Imaging for Human Applications

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Magnetic nanoparticles (MNP) due to their unique magnetic properties, exhibit an excellent potential in biomedical applications such as cancer therapy and diagnosis. For therapy applications such as hyperthermia and drug delivery, it is necessary to quantify the distribution of MNPs in the body before, during and after treatment to improve therapy efficiency and reduce unwanted side effects. Several techniques such as magnetorelaxometry imaging (MRI), magnetic particle imaging (MPI), and AC susceptibility biosusceptometry (ACB) exist that are capable to provide this information. However, none of these imaging modalities has been established yet for quantitative imaging of MNPs over a human body in a clinical environment.

We aim to improve our MRXI setup, which originally was developed for in vivo investigations of animal models (see Figure 1), to provide the technology and infrastructure required to establish MRXI for monitoring of MNPs in human cancer therapies. This requires on the development of a novel imaging infrastructure and measurement procedures to detect MNPs in specific human body regions (e.g., brain, prostate, breast, etc.). MRXI shall be applied in personalized therapy for online monitoring of MNP distributions focusing on fast and direct feedback to the clinicians. Additionally, we explore the MRXI capability for molecular imaging by mapping of MRXI signal features to local viscosity, mobility and MNP density within body regions to investigate physiological and biological processes. We present novel hardware and equipment developments addressing phantom and excitation coil arrangement, the potential of optically pumped magnetometers (OPM) as alternative magnetic sensors for MRXI, and the workflow for online data analysis of MRXI measurements in humans.

As a first realistic model for MRXI in humans, we deploy a head phantom simulating a glioblastoma multiforme (GBM) tumor. For this setup, we developed a reference hollow head phantom and measured MRXI using the PTB 304 channel SQUID system with 55 excitation coils for inducing the relaxation of the MNP moments mimicking a GBM tumor of 4 cm volume (composed of 1 cm cubes of EMG 700 MNPs, Ferrotec, embedded in silicone, iron concentration 20 mg/mL).
A dynamic bolus phantom for the evaluation of the spatio-temporal resolution of MPI scanners

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Magnetic Particle Imaging (MPI) is an imaging modality providing good spatial and high temporal resolution, allowing the 3D visualization of time-critical phenomena such as arterial bolus tracking under realistic conditions. Several different types of MPI scanners have been presented, which use the non-linear magnetization response of magnetic nanoparticles (MNP) exposed to a time varying external magnetic field for the determination of the MNP distribution. To facilitate a consistent assessment of results obtained from different MPI scanners, reference objects with well-defined imaging properties are mandatory. Mostly, static phantoms realized by a defined volume filled with a liquid tracer of known MNP concentration are used. Beside this, MNP embedded into a stiff matrix or 3D-printed magnetic materials are also used for the preparation of such static phantoms. But these phantoms do not offer the possibility to assess time-dependent properties of MPI signal acquisition and data analysis. Therefore, we developed a dynamic bolus phantom, which provides movable liquid objects of different size, tracer concentration, and velocity.

This dynamic phantom is based on segmented flow of a cylindrically shaped bolus (perimag®, MNP dispersion) within a liquid carrier material (silicon oil). A hydrophobic liquid (carrier) is filled into a flexible tube system with different diameters, into which a bolus of an aqueous MNP dispersion (tracer) is added. Due to the high surface tension between both liquid phases, the tracer bolus is stabilized within the carrier and can be moved accurately through the tube system by flowing the hydrophobic carrier liquid. Different geometries (trajectories) of the moving boluses were realized by mounting the tube into two different 3D-printed tube holders. The velocity of moving boluses was adjusted to be 1 cm/s, 5 cm/s, 10 cm/s, 20 cm/s, and 40 cm/s, which represent realistic blood flow velocities within the body. The moving boluses were imaged by two different MPI scanner types (MPI 25/20FF, Bruker BioSpin operated at Charité University Medicine and TWMPI prototype V1, operated at Würzburg). Both scanners successfully imaged all moving boluses, showing an increasing blurring with increasing bolus velocity, see figure. We conclude that the obtained temporal imaging resolution is determined by the bolus dimensions as well as the achievable spatial resolution. Thus, our phantom is capable to assess the correlation of spatial and temporal resolution for moving objects of different size and velocity and is suited to evaluate and compare the performance of different MPI scanner architectures under different imaging parameters such as field modulation frequencies and acquisition times.

Acknowledgments
This work was supported by Deutsche Forschungsgemeinschaft (DFG) in the frame of the projects "quantMPI" (DU1359/1-1 and TR 406/1-1) and "Development of a relaxation based technique for highly sensitive spectroscopy and imaging of magnetic nanoparticles and corresponding measurement sequenence" (BE 5253/1-1).

Iron Oxide Nanoparticles as T1 Agents for Low-Field MRI

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Low-field magnetic resonance imaging (MRI) has the potential to revolutionize accessibility of MRI for patient diagnosis and care. The magnetic fields used in these scanners can be a fraction of the field ∼100 mT compared to 3 T for clinical MRI scanners. Magnetic Particle Imaging (MPI) is an imaging modality providing good spatial and high temporal resolution, allowing the 3D visualization of time-critical phenomena such as arterial bolus tracking under realistic conditions. Several different types of MPI scanners have been presented, which use the non-linear magnetization response of magnetic nanoparticles (MNP) exposed to a time varying external magnetic field for the determination of the MNP distribution. To facilitate a consistent assessment of results obtained from different MPI scanners, reference objects with well-defined imaging properties are mandatory. Mostly, static phantoms realized by a defined volume filled with a liquid tracer of known MNP concentration are used. Beside this, MNP embedded into a stiff matrix or 3D-printed magnetic materials are also used for the preparation of such static phantoms. But these phantoms do not offer the possibility to assess time-dependent properties of MPI signal acquisition and data analysis. Therefore, we developed a dynamic bolus phantom, which provides movable liquid objects of different size, tracer concentration, and velocity.

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Innovative nanocomposites for protein release through magnetic hyperthermia
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A well-known interest of using nanoparticles to deliver drugs is the controlled delivery of the contained therapeutic agents activated by external fields such as magnetic field or light. But these nanosystems are even more interesting if they combine several modalities. In our group, such combination has been used to obtain imaging and magnetic hyperthermia. The system consisted in an iron oxide nanoparticle encapsulated in a Stellate mesoporous silica shell (IO@STMS) and was already reported to be a promising bimodal imaging probe when functionalized with quantum dots and coated with human Serum A Albumin (HSA) [1]. Herein, the aim of our work was to optimize the surface of such IO@STMS NPs in order to make them promising agents for the loading and controlled delivery of proteins for tissue engineering through magnetic hyperthermia.

For this purpose, in a first study, the ability of isobutyramide (IBAM)-grafted STMS was assessed, as this IBAM group has been shown to act as a “glue” able to load a wide range of biomolecules [proteins, nucleic acid, polysaccharide and polypeptide [2]] in a large amount. Thus, the stability of protein coating through the IBAM strategy has been studied using four different proteins and several detection techniques. Then, the stability of this protein loading over scaling-up and washings was assessed prior to investigate the thermo-induced release ability of such system. AFM – force spectroscopy was finally used in order to decipher the interactions at play between the particles and the proteins [3].

In a second study, it was hypothesised that the combination of the IO@STMS with thermo-responsive (bio)polymers will allow the release of the protein through magnetic hyperthermia-induced conformational change, as represented in Figure 1. Several thermo-responsive polymers were then studied, as well as several anchoring strategies on the particles, such as covalent grafting or polymer adsorption through the IBAM strategy [4].

![Figure 1: Schematic representation of the release of protein through magnetic hyperthermia by thermo-responsive polymer-functionalized IO@STMS](image)


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Superparamagnetic Nanodevices as Singlet Oxygen Carriers for Cancer Therapy
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Considering the treatments available for cancer, radiotherapy is one of the most used. Magnetic hyperthermia, which heats up the cancer cells with alternating magnetic fields and superparamagnetic nanoparticles, can also be employed as cancer treatment. Photodynamic therapy can also be used. In this case, a photosensitizer is responsible to produce reactive oxygen species, such as singlet oxygen ($\text{O}_2^*$), that causes cell damage.

The purpose of this work is to sensitize iron oxide nanoparticles covered with a shell of aromatic compounds that can be guided through the body until the tumor to deliver $\text{O}_2^*$. In this context, aromatic compounds can be employed, once they are able to trap $\text{O}_2^*$ and subsequently release it upon heating. Considering the presence of a superparamagnetic core, the heating could be achieved by magnetic hyperthermia. Therefore, $\text{O}_2^*$ release is expected only when the nanoparticles achieve the target tumor cells and are heated by alternating magnetic fields.

Iron oxide nanoparticles, doped with zinc or not, were synthesized and covered with anthracene or naphthalene. The nanoparticles doped with zinc presented smaller sizes compared to the undoped ones. Dynamic light scattering results indicated the growth of an anthracene or naphthalene shell around the magnetic core. The hybrid nanoparticles were then mixed with methylene blue (MB) and exposed to light of appropriate wavelengths so that the nanoparticles could trap the $\text{O}_2^*$ produced by the photosensitizer. The $\text{O}_2^*$ trapping was monitored by fluorescence spectroscopy, as evidenced by the characteristic fluorescence quenching of the aromatic emission after trapping the $\text{O}_2^*$, thereby demonstrating the potential use of these hybrid nanoparticles as $\text{O}_2^*$ carriers. More interesting, the magnetic core increased the $\text{O}_2^*$ loading rate and capacity. The posterior $\text{O}_2^*$ release was stimulated by heating the sample on a vacuum oven and monitored by fluorescence spectroscopy. Also, an evaluation of the toxicity of the samples was performed by adding the magnetic nanoparticles covered with naphthalene to a bacterial culture and analyzing the difference in the bacterial growth curves after the samples were heated to mild temperatures (37 – 46 °C). Decreased bacterial growth rate was observed only for samples containing hybrid nanoparticles loaded with $\text{O}_2^*$, further suggesting that iron oxide nanoparticles covered with naphthalene can be used as biocompatible nanodevices to increase efficiency in cancer treatments combining, in an unexplored way in the literature, photodynamic therapy and magnetic hyperthermia.
Graphene-Encapsulated Magnetic Nanoparticles for Safe and Steady Delivery of Ferulic Acid in Diabetic Mice

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New therapies demand drug delivery systems with added functionalities and proven safety, stability, and biocompatibility to achieve effective drug delivery and uptake. Herein, a magnetic nanovector (Fe@C) was designed by encapsulating iron nanoparticles within a shell of 3-10 concentric graphene layers, structure that was exhaustively characterized through a wide range of techniques. The shell serves as an impervious barrier, mitigating toxicity and enhancing the biocompatibility of Fe@C. Its internalization, subcellular behavior, biocompatibility, and influence on cell viability and proliferation were investigated. Studies on human lung (adenocarcinoma human alveolar basal epithelial) and skin (epidermoid carcinoma) cells indicate Fe@C is less toxic and more biocompatible than the magnetic nanoparticles coated by an amorphous carbon (Fe3O4@C), a popular drug carrier. As advanced HR-TEM and Raman spectroscopy suggest, Fe3O4@C exhibited more signs of degradation than Fe@C when exposed to murine macrophages (mouse monocyte-macrophages J774). Unlike Fe3O4@C, Fe@C has a higher drug loading capacity (0.18 g/g) for ferulic acid, an active pharmaceutical ingredient found in the traditional Chinese herb Angelica sinensis and releases the drug at a constant dosing rate of 8.75 mg/g/day over 30 days. Ferulic acid released by Fe@C injected subcutaneously in diabetic BALB/c mice is effective in lowering the blood glucose level [1].

Towards drug targeting to the eye using magnetic multicore nanoparticles

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If a pharmaceutical agent is needed inside a patient’s eye, an injection directly into the vitreous body is a common and effective strategy, but comes with severe risks and discomfort for the patient, so that an alternative strategy to target the drug would be beneficial. Therefore, we are evaluating the possibility of magnetic drug targeting into the eye by using magnetic nanoparticles (MNP) as vehicles. For this approach, magnetic multicore iron oxide nanoparticles were synthesized by a wet co-precipitation method under slow addition of a alkaline medium to enable the formation of a multicore structure. These optimized particles were coated with several adsorptive coatings, namely starch (S), carboxymethyl Dextran (CMD), dextrane (DEX), citric acid (CA), polyethylene glycol (PEG), and trisodium citrate (NaZ). Magnetic and structural properties of the particles were characterized using VSM, DLS and TEM. The stability of the coated particles was evaluated in different biological media (water for injections, NaCl solution and artificial tears) by means of turbidimetry using an UV/Vis spectrophotometer, showing superior stability of starch coated particles. Numerical simulations performed in a previous study revealed a maximum possible magnetic field gradient of 20 T/m at the side of the eye, resulting from superconducting magnets placed aside/behind the head. This gradient was resembled by a simple permanent magnet setup for ex-vivo laboratory targeting experiments using a 3D printed two-chamber setup (fig. a). By placing the permanent magnet behind the target chamber, particles can be pulled through the tissue sample from the reservoir into the target chamber. The amount of particles that had passed the tissue after 24 h was measured with quantitative magnetic particle spectroscopy relating the amplitude of the measured third harmonic (A3) to the amount of iron in calibration samples. Measurements revealed that only starch coated particles where able to penetrate sclera tissue samples (fig. b) with a mean rate of 5.4 ng/mm² within 24 h, while no particles passed cornea samples. Despite the rather small amounts of targeted particles, the results are a promising proof of principle open the door for future magnetic drug targeting to the eye.

![Image](a)

**Fig (a) scheme of the two-chamber setup (b) amount of particles in the target chamber, quantified by the amplitude of third harmonic A3 in MPS measurements, for four different coating materials and sclera as the tissue sample.**

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Talk #21

Critical Parameters to Improve Pancreatic Cancer Treatment Using Magnetic Hyperthermia: Field Conditions, Immune Response, and Particle Biodistribution

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Magnetic hyperthermia (MH) has been proposed as a promising therapy for the localized treatment of cancer. Under the exposure to an alternating magnetic field (AMF), magnetic nanoparticles (MNPs) act as heating agents inducing cell death and/or sensitizing the cells against other conventional treatments. Despite the advantages of this experimental treatment, researchers working in the field of MH still face several challenges and practical problems such as the difficulty in achieving enough magnetic material in the tumors or the heterogeneous distribution of the particles in the whole tumor volume even after intratumoral injection. In addition, there are still many knowledge gaps in the frame of in vivo MH applications, such as the cytotoxicity mechanisms triggered directly by the heat or the immune response activation stimulated by the treatment. In this work, several AMF conditions were evaluated using three-dimensional (3D) cell culture models of a pancreatic tumor cell line (MiaPaCa), loaded with MNPs, to determine which of them produced the strongest effect on the cell viability. Then, the MH treatment was tested in a heterotopic xenograft mouse model using the optimal AMF conditions. MNP biodistribution, cell death and immune response triggered by MH were evaluated through different techniques: magnetic measurements, flow cytometry, confocal microscopy and histochemical staining. Our results point out several factors that should be considered to improve the treatment effectiveness of pancreatic cancer by magnetic hyperthermia, like the great importance the MNPs biodistribution after intratumoral injection in the treatment effectiveness (Figure).

![Image](b)

**Figure**: (A) Tumor evolution represented as minimum and maximum volume reached during the experiment (B) MNP detection by AC magnetic susceptibility 30 days after intratumoral injection. Significance differences with respect to the control were performed using a two-way ANOVA, GraphPad Prism v7.

**Talk #22**
In silico safety analysis of different metallic implants in magnetic hyperthermia treatments

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In this work, we studied the actual risks of potential MH patients carrying different metallic prostheses using computer simulations. We also analysed the influence of the presence of these objects in the effective magnetic field during the therapy. We have considered different treatment setups varying target sites, implant types and materials to evaluate the temperature increase and the dosimetric values in the major tissue groups. Finally, using these safety parameters, a multi-criteria decision analysis has been performed to assess a risk index for each tissue group in every clinical situation analysed [4, 5].

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[2] www.nocanther-project.eu

Magnetic nanoparticles (MNP) are used as additives for the development of hybrid stents in order to enable local hyperthermia treatment e. g. for endoluminal tumor therapy (esophagus adenocarcinoma or bile duct Klatskin tumors) [1]. In this way, tumor cells can be destroyed in close vicinity to the stent preventing a re-closure of the endoluminal site by tumor tissue ingrowth. Additionally, the MNP can also be used as contrast agents in magnetic resonance imaging (MRI) or as tracers in magnetic particle imaging (MPI) which makes the visualization of the whole stent and a monitoring of its function in vivo possible.

Because of the manufacturing process of the hybrid stents, MNP agglomerations occur influencing the magnetic relaxation properties of the MNP. Since the performance of medical technologies like hyperthermia and imaging depends on Neel and Brownian relaxations, it is expected that the MNP agglomerations will have a significant impact. To characterize this impact, we performed parameter studies with the above-mentioned technologies not only for hybrid stents but also for ferrohydrogels. The latter are model systems consisting of immobilized but non-agglomerated MNP in hydrogels. The hybrid stents had two different sizes (corresponding to the size of the oesophagus and bile duct) and were made of hybrid melt-spin polypyrrole (PP) fibers incorporated with different MNP types (core diameter of 10 nm, 100 nm and 300 nm). Six different MNP concentrations up to 12 wt% were investigated. The MNP concentrations inside the hybrid fibers were examined by thermogravimetric analysis. Figure 1 exemplarily shows the hyperthermia and MPI imaging ability of a typical oesophagus stent incorporated with 4.4 wt% MNP of 10 nm core size. Figure 1a displays a photograph of the hybrid stent. Under an alternating magnetic field ($f = 270$ Hz and $H = 13$ kA/m) the stents surface reached a temperature of ca. 43°C (Figure 1b). Using a 3T MRI T1-weighted spin echo sequence, the cross-section of the hybrid stent can be visualized (Figure 1c). Based on the data collected from the parameter studies, it was possible to create a multi-dimensional map displaying the heating power and saturation temperature as a function of the alternating magnetic field parameters (frequency, amplitude), MNP concentration and MNP type. MRI measurements produce accurate images of the hybrid stents, especially at the low MNP concentrations. The MPI measurements provide high-resolution images for all hybrid fibers, even for those with high MNP concentration. However, MPI imaging succeeds so far only for hybrid fibers and not for braded hybrid stents.

The hybrid stents represent the basis of a new technology providing the necessary local heating for tumor therapy in a controlled, localized and reproducible manner. The possibility of postoperative visualization of the hybrid stent via MRI and MPI increases the patient safety for future clinical use.

Figure 1: (a) Photograph of exemplary hybrid stent. (b) Temperature profile ΔT of the hybrid stent after 900 s under an AMF ($f = 270$ kHz and $H = 13$ kA/m). (c) MRI image of the stents’ cross-section using a spin echo sequence.

References
Iron Oxide Nanoflowers as Excellent Heating Agents for Magnetic Hyperthermia Cancer Therapy

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In this context, the optimisation of IONP properties for magnetically induced hyperthermia (MIH) for cancer treatment is still a very active research area. The heating ability is considered a critical factor in MIH and is usually prioritised when developing synthesis of IONPs destined for this application. However, there is a bottleneck for wide acceptance of MIH therapy due to the quality limitations of commercial iron oxide nanoparticles (IONPs), which display sub-optimal heating efficiency and are associated with high preparation costs. We recently overcame these limitations with our novel synthetic procedure for iron oxide nanoflowers (IONFs) exhibiting heating rates that are 3 times higher than those of any commercially available nanoparticle alternative. The experimental scheme is shown in the Figure (a) below. Polyol process yielded biocompatible single core nanoparticles and nanoflowers (Figure (b)). The effect of parameters such as the precursor concentration, polyol molecular weight as well as reaction time was studied, aiming to isolate NPs with the highest possible heating efficiency. Adding polyacryl acid (PAA) facilitated the formation of excellent nanohotelling agents IONFs within 30 min.

The progressive increase of the size of the IONFs through applying seeded growth approach resulted in outstanding enhancement of their heating ability with intrinsic loss parameter (ILP) up to 8.49 nH m² kgFe⁻¹. Apart from their exceptional heating efficiency, our IONFs feature excellent colloidal stability (more than 3 months) and can be synthesised reproducibly via simple protocols in short time, hence, they have good potential for production at large-scale at significantly reduced costs.

(a) Schematic of simple one-pot thermal decomposition of Fe(acac)3 polyol synthesis yielding single core IONPs (without PAA) and IONFs (with PAA) in Step 1 and Step 2. (b) TEM images of the IONFs synthesized with PAA via seeded growth: 2nd feeding step.

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A magneto-optical microscope for investigating magnetisation dynamics of intracellular nanoparticles under hyperthermia conditions

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Nanoparticle-mediated magnetic hyperthermia treatment is a promising cancer therapy that enables selective heating of cancerous tissues to slow or stop tumour growth, whilst also increasing tumour sensitivity to chemotherapy and radiotherapy. The importance of magnetic hyperthermia has fuelled interest in the development of biocompatible magnetic nanoparticles. However, previous experiments have suggested that the association of nanoparticles with cells modifies their magnetic response, thus dramatically altering heating efficiency. To explain this behaviour and inform on new design configurations for intracellular hyperthermia, the development of new characterisation tools capable of assessing nanoparticles under relevant biological conditions is required.

Here we present a novel magneto-optical microscope based on the Faraday effect, that enables the study of magnetisation dynamics of nanoparticles in cellular environments under hyperthermia conditions, in combination with fluorescence lifetime measurements (Fig. 1). The developed system is capable of mapping localised AC magnetic susceptibility, magnetometry and fluorescence lifetime, under magnetic fields generated at frequencies up to 1 MHz for AC susceptibility (500 kHz for AC magnetometry), and amplitudes of up to 50 mT (dependent on frequency). The intracellular magnetic properties can be probed in situ with <0.5 μm resolution, and the system can also be used to probe nanoparticles in liquid suspensions.

Using this microscope, we present direct observations revealing the influence of cellular environment on the AC magnetic properties of nanoparticles in both fixed and living cancer cells. Sub-micron measurements of magnetization dynamics are discussed, as well as the first demonstration of AC susceptibility microscopy. Crucially, these experiments reveal huge variability as a function of nanoparticle cellular location and AC field frequency, demonstrating the importance of this new optical approach for understanding the magnetic behavior of intracellular nanoparticles for hyperthermia. The results also show how such methods could be used more generally to probe nanoscale magnetism in biology.

Figure 1: Concept of the combined scanning magneto-optical and fluorescence lifetime microscope. The inset shows AC susceptibility (amplitude) images obtained from nanoparticles localised to the perinuclear region of osteosarcoma cancer cells.
**Magnetic heating to trigger entrapped enzymes activity**

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**Nanoparticle-mediated magnetic hyperthermia enhances the breakdown of human blood clots by tissue plasminogen activator**

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**References**


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Thrombolysis is a front-line treatment for stroke. Intravenous injection of the clot-busting agent, tissue plasminogen activator (tPA), is used to enzymatically breakdown a blood clot and re-establish blood flow through the blocked cranial vessel. However use of thrombolysis is currently limited by its short time window of efficacy. Here, we investigated whether platelet-targeted magnetic hyperthermia (MH) induced by Iron Oxide Nanoparticles (IONPs) could be used to enhance the efficacy of tPA-mediated thrombolysis. Platelet-targeted IONPs were created by conjugation to PAC-1, an antibody that specifically binds to activated platelets. Ex vivo generated human blood clots were exposed to tPA in the presence or absence of MH. MH was found to enhance the clot-dissolving activity of tPA, reducing the weight of tPA + MH treated clots to 75.6 ± 1.5 % of untreated control clots, compared to 81.3 ± 2.2 % clots treated with tPA alone (n = 15, P < 0.05). Platelet-targeted MH was found to increase permeability of blood clots to 70 kDa fluorescent dextran, which has a similar molecular weight to that of tPA (Figure 1). Electron microscopy images revealed that localised MH. Clot-targeted MH could improve the treatment of cardiovascular conditions such as Venous Thromboembolism.
Magnetic Hyperthermia as an adjuvant cancer therapy in combination with carbon ions, protons and photons irradiation on pancreatic tumour cell cultures

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Magnetic fluid hyperthermia (MFH) is used in clinics as an anti-cancer therapy, especially thanks to the reached increment of the magnetic nanoparticles’ (MNPs) thermal efficiency and the promising synergy reached in combination of MNPs assisted hyperthermia and carbon ions irradiation on human pancreatic adenocarcinoma cell cultures (BxPC3 cells). Hyperthermia made use of spherical Fe3O4 core coated with meso-2,3-dimercaptopropanionic acid with Specific absorption rate (SAR) of 110 ± 30 W/gFe3O4 under an alternating magnetic field of frequency f = 109.8 kHz and amplitude μH: 19.5 mT. Cell cultures induction with carbon ions and protons was performed using the synchrotron-based clinical scanning beams at the National Center for Oncological Hadron Therapy (CNAO) in Pavia (Italy), and the photons beam was delivered by using a 6 MV linear accelerator at the Fondazione IRCCS Istituto Nazionale dei Tumori in Milano (Italy). The clonogenic survival assay was used to evaluate the effectiveness of the combined treatment; the BxPC3 cells were treated with 3 different protocols: simple irradiation (carbon ions/photons), (ii) magnetic nanoparticles (MNPs) administration and irradiation and (iii) MNPs administration plus irradiation and subsequent hyperthermia (Hyp). Briefly, our results (see Brero, Francesca, et al. Nanomaterials, 10,10 (2020) : 1919 for experiments with carbon ions irradiation) show a significant effect of MNPs administration and hyperthermia for all irradiation protocols, i.e. an enhancement of the cell death rate induced by the irradiation alone. These encouraging results pave the way to further in vivo investigations for finally testing this new combined therapy (hadron irradiation and MNPs assisted hyperthermia) in view of its translation to clinics.

Figure. Clonogenic survival of BxPC3 cells culture for 3 different protocols (see text): carbon ions/photons irradiation only (orange circles), carbon ions/photons irradiation + MNPs administration (tanya triangles) and carbon ions/photons irradiation + MNPs administration + Hyp (green stars).

Tab. #20

Development of Handheld Induction Heaters for Magnetic Fluid Hyperthermia Applications and In-vitro Evaluation on Ovarian and Prostate Cancer Cells

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Magnetic fluid hyperthermia (MFH) is a cancer treatment that takes advantage of the efficient, clean, and accurate method of delivering heat by induction heating and the intrinsic physicochemical characteristics of magnetic nanoparticles (MNPs). When in the presence of an external alternating magnetic field (AMF), MNPs elevate the temperature of the desired target (tumor) site to around 41-45°C, inducing various mechanisms of cell death depending on thermoeffect conditions. Applying these magnetic fields with high spatial resolution is still a challenge in the field. Large magnetic fields will heat unwanted parts of the body if there are metallic implants, pacemakers, or other magnetically susceptible materials, as well as MNPs outside the target area. One solution is to miniaturize induction heating systems down to the level of small tumours, potentially limiting the resulting damage to only the tumouric tissue. To our knowledge, such instruments have not yet been reported in the medical setting. Therefore, the purpose of this work was to develop a novel laparoscopic induction heater (LHI) and a transrectal induction heater (TRIH), both capable of applying high-frequency, high-intensity AMFs in hard-to-reach places within the human body.

A 20-turn and a 30-turn miniature multilayer “pancake” coils were wound using Litz wire. These coils, which were aimed at laparoscopic and transrectal applications for cancer, were inserted into 3D printed enclosures. Both enclosures mimic known medical instruments and include water circulation to remove heat, electrical connection for the coil, and a fiber optic sensor to monitor the temperature at the center of the coil. Figure 1 shows a conceptual diagram of the laparoscopic induction heater. Maximum values of magnetic field amplitudes reached by the laparoscopic and transrectal induction heaters were 42 kA/m at 328 kHz and 25 kA/m at 302 kHz, respectively. The first potential application of the LHI was thought to be an interventional pulmonary malignancies which are regarded as silent killers. The TRIH was designed for prostate cancer after feedback from many surgical oncologists. Therefore, ovarian cancer cell lines (SKOV-3, A2780 and prostate cancer cell lines (PC-3, LNCaP)) were used to demonstrate the instruments’ abilities in killing cancer cells. The normal cell line, NBT13, was also used to observe how healthy cells respond to MFH treatment as compared to abnormal cells.

Figure 2 (a-b) displays the results from utilizing the laparoscopic induction heater on NB13T3, SKOV-3 and A2780, whereas Figure 2 (c-d) shows the results of the transrectal induction heater on NBT13, PC-3 and LNCaP. Temperatures reached using our devices were 41°C by the LHI and 43°C by the TRIH. Both instruments successfully accomplished killing cancer cells, with minimal effects on normal cells, by applying a relatively strong, yet localized, magnetic field to magnetic nanoparticles. We successfully designed a laparoscopic induction heater and a transrectal induction heater and evaluated them on ovarian and prostate cancer cell lines, respectively. These innovations could become an enabler for the development of medical treatments that would require non-contact heating approaches inside the body of a patient.

Tab. #10

Figure 1. A. Conceptual diagram of the laparoscopic induction heating instruments. The coated coils, (i) portable induction, and (ii) thermocouples run the length of the instrument. Five epicardial sacs are included for the (i) portable tubing, (ii) thermocouples, (ii) water, (ii) coil terminals. Before the portable pump is turned on, water starts filling the exterior of the instrument through (ii), until it reaches the top, and flows through (ii).

Figure 2. (a-b) displays the results from utilizing the laparoscopic induction heater on NB13T3, SKOV-3 and A2780, while (c-d) shows the results of the transrectal induction heater on NBT13, PC-3 and LNCaP.
Composition impacts the structural, magnetic, and heating efficiency of MnₓFe₃₋ₓO₄ MNPs. An in vitro and in vivo study.

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Manganese-iron oxide (MnₓFe₃₋ₓO₄) systems have unique properties, such as high magnetic moment values of ca. 5 µB per unit cell, excellent chemical stability, and a surface suitable for ligand functionalization and bioconjugation, which make them particularly promising in biomedical applications. In this work, we present a systematic approach for tuning the composition of a set of MnₓFe₃₋ₓO₄ with control over the size and shape through one-step thermal decomposition method. The composition (x) of the MnₓFe₃₋ₓO₄ nanoparticles, ranging from 0.07 to 1.4, has been carefully tailored by adjusting the Fe(acac)₃/Mn(acac)₂ precursor ratio. The effects of the nanoparticles composition and its impact on the magnetic properties were studied from static magnetic measurements, X-ray Diffraction, Transmission Electron Microscopy (TEM) analysis and infrared spectroscopy (FTIR). Moreover, the synthesis method has been refined to obtain NPs with polyhedral morphology and suitable magnetic anisotropy, which significantly improves their magneto-thermal behaviour. The heating performance has been investigated using two different combinations of alternating magnetic fields (AMFs): high amplitude and low frequency (96 kHz, 60 mT) or with low amplitude and high frequency (10 mT, 763 kHz) in water and in glycerol. A linear increase between the Mn²⁺ content and the heating performance was obtained in samples where x < 0.6, while for x > 0.7 a deterioration of the magnetic output was found, leading to a marked reduction of the magnetothermal efficiency. Interestingly, the heating performance does not change when the samples are dispersed in environments of high viscosity, which is an important requirement for a successful intracellular heating. Selected MnₓFe₃₋ₓO₄ nanoparticles with the lowest, medium, and highest Mn²⁺ content (x = 0.07, 0.4 and 0.6) and thus, different magnetic heating performance were studied in two biological models, in vitro and in vivo: pancreatic tumoral cells and the freshwater invertebrate model organism Hydra vulgaris. In both systems the toxicity and the internalization of the different MNPs were assessed. Moreover, the biological effects after applying mild magnetic hyperthermia were studied, both to kill tumoral cells and enhance Hydra regeneration.

Figure 1. Overview of the work. Fine control over composition of MnₓFe₃₋ₓO₄ impacts their heating performance and thus, their biological performance in two different models.

Local temperature gradients in intracellular magnetic hyperthermia

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Exogenous and endogenous heat generation inside cells is a subject of intense debate in recent times. In particular the generation of temperature gradients on nanoparticles heated externally by a magnetic field is of crucial importance in magnetic hyperthermia therapy of cancer. In the absence of reliable direct measurements of local temperatures on cell-internalized nanoparticles, a controversy has been established between those who predict that it is not physically possible to reach substantial temperature increments between the source of heat, and those who adhere to the possibility of large temperature gradients. Here, we have measured the variation of the local temperature on magnetic nanoparticles under an external alternating magnetic field using a luminescence molecular ratiometric thermometer placed on the nanobacter surface. Moreover, we have also measured the temperature at intracellular sites at some distance from the magnetic heater and on the outside of the cell membrane. Even for moderate magnetic fields (H=2.4×10⁴ A m⁻¹ s⁻¹, H=30 mT, f=100 kHz), temperature increments of about 1.1 °C have been found in the nanoparticles. The T(0) curve shows a steep initial increase and then it reaches a plateau. However, at some distance from the nanoparticles, the temperature increases constantly to values of about 4.5 °C. In the meantime, the temperature at the cell membrane does not show any appreciable increment indicating that the generated heat is too small to produce an increase of the overall temperature of the cells. It was found that these local temperature increments are sufficient to produce noticeable cell apoptosis. When we increased the Hf values close to this limit (4.8×10⁴ A m⁻¹ s⁻¹, H=60 mT, f=100 kHz), the specific absorption rate (SAR) increased from 45 to 150 W g⁻¹ (Fe₃O₄) and, thus, the apoptosis ratio increased to 60%, that is already relevant for the final goal of therapeutic performance. In conclusion, our in vitro results are indicating that the approach of local hyperthermia therapy suggested as an improved alternative to actual global heating hyperthermia could be feasible.

Figure. Local temperature variation on the magnetic nanoparticle (T₁) surface, at some distance in the cytoplasm (T₂), and on the exterior of the cell membrane (T₃) during the application of an alternating magnetic field to a cell culture.
On the mechanisms of magnetization reduction in iron oxide nanoparticles
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Iron oxide nanoparticles are presently considered as promising objects for various medical applications including targeted drug delivery and magnetic hyperthermia. The nanoparticle solution in water has to be free of large aggregates to avoid blocking of capillaries and simultaneously the nanoparticles have to possess large enough saturation magnetization to react to an external magnetic field. However, there remain several unsolved questions regarding the effect of size onto the overall magnetic behavior of nanoparticles. One aspect is the reduction of magnetization as compared to bulk samples. A detailed understanding of the underlying mechanisms of this reduction will allow one to improve the particle performance in the applications.

There are several proposed models for the spatial distribution of the magnetization, which include the presence of a magnetic core-shell structure, spin disorder around defects and a reduced magnetization in the core due to reversed moments and frustration. In this work [1] we combine neutron and synchrotron X-ray scattering techniques with magnetochemistry, transmission electron microscopy (TEM), elemental analysis and Mössbauer spectroscopy to study nanoparticles of various sizes and to obtain an as complete as possible picture of their properties. We find that the nanoparticles possess a macroscopically reduced magnetization, mostly due to the presence of antiphase boundaries as observed with high-resolution TEM (HRTEM) and X-ray scattering, and to a lesser extent due to a small magnetically depleted surface layer and cation vacancies.

Figure: (a) HRTEM micrograph of an isolated nanoparticle viewed along [310]. A region with an antiphase boundary is marked with the red square. (b) Marled region of (a) with a schematic of the crystal structure. The lattice plane along which the translation occurs is indicated with the white rectangle. (c) Small-angle neutron scattering of polarized neutrons for 5 different contrasts. The black line represents the best fit of a core-shell model with a sticky hard sphere potential (inset on the lower left).


Multimodal Magnetic Force Microscopy
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Magnetic force microscopy (MFM) is a scanning probe technique that can map nanoscale magnetic domains in a sample. MFM employs a magnetically coated probe to track the sample topography and detect long-range forces due to magnetic stray fields at user defined lift heights above the sample. Although MFM is widely used in solid-state devices, there are several challenges in application of MFM for biological samples. These include, contamination of the MFM probe by sticky biological materials, topological cross-talk in MFM images and incompatibility in a fluid environment.

In this study we developed two methods to overcome the limitations of MFM towards making it amenable to biological samples. In our first approach, we developed a novel indirect-MFM (ID-MFM) technique to detect fluorescently labeled iron-oxide nanoparticles. In ID-MFM an ultrathin silicon-nitride window is used to create a physical barrier between the sample and the probe. The window prevents direct contact between the sample and the probe thereby eliminating probe contamination and topological cross-talk. We show how ID-MFM does not dampen the MFM signal and the samples prepared on silicon-nitride windows are amenable to multi-modal analysis by fluorescence or transmission electron microscopy (TEM).

In our second approach we analyzed rodent spleen tissue sections via conventional MFM. We investigated how scan rate and surface roughness can impact the topological cross-talk in MFM experiments. We elucidate how thin sections with reduced surface roughness (as that used for TEM) can minimize the topographical cross-talk. In addition thin sections can be compatible for multimodal microscopy analysis via both conventional (direct) and ID-MFM.

Taken together our work has advanced the use of MFM for imaging and mapping nanoscale iron-oxide deposits in biological samples. Future work along these directions could enable MFM analysis of physiological and pathological iron deposits in tissues sections in a label-free, multimodal and high throughput manner.

Figure: (a) In conventional (direct) MFM, a first scan is performed to determine the topology of the sample. A second scan is performed at a user-defined lift height (z) to determine long-range magnetic probe-sample interactions. In indirect MFM (ID-MFM), the sample is immobilized under an ultrathin silicon-nitride window and the MFM probe scan the top surface. Long-range magnetic interaction is detected through the membrane. The silicon-nitride windows are transparent to light and electron optics (Sifford et al, Nanoscale Advances, 2019).
Harmonizing of static magnetization measurements using two commercial SQUID devices of the same type

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The characterization of magnetic nanoparticles (MNP) is an important issue, which demands for reliable and sensitive magnetic measurement techniques. Nevertheless, there exists no internationally accepted protocol for reliable and reproducible determination of their magnetic properties. Static magnetization measurements using highly sensitive superconducting quantum interference devices (SQUIDs) are commonly used to characterize MNP. While the continuous verification of the proper operation of SQUID devices within one laboratory is state of the art, interlaboratory comparisons are not common. Here, we conducted a comparison of static magnetization measurements of MNP on two commercial SQUID devices of the same type using the same palladium (Pd) calibration reference sample at IMFM Ljubljana and PTB Berlin.

Initial magnetization curves and hysteresis loops of a Pd reference sample were recorded at 298K using identical SQUID devices (MPMS-XL-5, Quantum Design Inc). The Pd measurement data were used to calibrate the external magnetic field values. With these corrections the static magnetization measurements of an identical MNP sample on both devices were corrected and compared to assess the accuracy of magnetic moment determination.

The analysis of the paramagnetic Pd curves reveal non-linear deviations of the external magnetic field values from the nominal field experienced by the sample leading to implausible effects like inverted hysteretic behaviour as reported by other groups, before [1]. This is found for both devices but to varying degrees. Applying the field correction on MNP measurements resulted in a significant reduction of the total difference between the MNP magnetization curves measured in the two laboratories. In the low field region, the differences in the magnetic moment decreased from about 15% down to about 1.5% after field correction.

The corrections validated by our interlaboratory comparison help to harmonize magnetic measurement techniques for the characterization of magnetic nanoparticles and demonstrate the importance of interlaboratory comparisons between different laboratories working and using the same magnetic measurement devices. This is an important step towards establishing a reference measurement site for static magnetization of MNPs at PTB.

Figure 1: Comparison of the measurement of the initial magnetization curve and the hysteresis loop of the paramagnetic palladium reference sample at 298 K and between ±0.1 mT. Left: Without correction. The inset shows the whole hysteresis loops over ±5 T. The branches of the hysteresis loop are inverted. The descending hysteresis branches cut the field axis in the positive and the ascending branches in the negative field range. Right: After correction. The descending and the ascending hysteresis branches overlay.

Navigation control of Magnetotactic Bacteria by magnetic fields

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Magnetotactic bacteria (MTB) are biological microorganisms with the ability to align and navigate along geomagnetic field lines to reach hypoxic regions. To develop this ability, MTB biomineralize magnetic nanoparticles, called magnetosomes, that organize forming a chain to respond optimally to an external magnetic field. The intrinsic properties of MTB, such as self-propulsion, aerotaxis, and their capability to grow and proliferate in regions with low oxygen concentrations, make them suitable as biocarriers for potential anticancer applications. In addition, the presence of the magnetic chain allows control in their navigation. All these characteristics explain why MTB are considered a promising nanorobot for biological applications [1,2]. The latter indicates that MTB nanorobots could be employed as localized drug transport, tumor monitoring agent, and even in cancer treatments (magnetic hyperthermia) [3,4].

However, its activity as a nanorobot is fundamentally limited by its navigation control [5]. To try to shed light on this matter, in order to study their mobility we have developed software algorithms for the automatic detection and tracking of magnetotactic bacteria, applying image sequencing techniques to the analysis of videos acquired by optical microscopy. We have worked with two different species (Magnetospirillum gryphiswaldense and Magnetospirillum magneticum) in different biological media, applying controlled flows to emulate blood streams. In addition, we have precisely controlled the magnitude and direction of the external magnetic field applied to regulate navigation and evaluate their swimming capacity. Preliminary results are shown in Fig.1.

![Image](image1.png)

**Figure 1:** (a) Frequency histograms (%) of the swimming velocity of *Magnetospirillum gryphiswaldense* under a magnetic field of 0.5 mT. Two distributions of bacteria are distinguished, those that are self-propulsed (blue) and those that move with the flow (yellow). (b) Normalized polar graph (%) of the *Magnetospirillum gryphiswaldense* navigation direction under a magnetic field of 0.5 mT (left) and 11.2 mT (right).

References


Magetically navigating superparamagnetic particles using MRI in phantom and swine chemosembolization model

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Superparamagnetic nanoparticles (SPIONs) can be combined with tumor chemoembolization agents to form magnetic drug-eluting beads (MDEBs), which can be navigated magnetically in the MRI scanner through the vascular system.

Magnetic resonance navigation (MRN) uses the outstanding imaging properties of MRI to detect liver tumors, the Bs-magnetic field to magnetize MDEBs, and the imaging gradient generated by imaging gradient coils to steer them in the targeted vessels. In this paper, the MDEBs (200 ± 12 μm) were fabricated using Fe3O4 SPIONs (12 ± 3.6 nm) coated with C12-bisphosphonate and poly(lactic-co-glycolidic) acid (PLGA), and then we demonstrated the feasibility of MDEBs in vivo and in vitro.

The experimental setup is shown in Figure (a). Before MRN, the swine was rotated (the target lobar and segmental vessel in a decline position) to combine magnetic and gravitational forces. The MDEBs were injected using a partially inflated balloon catheter. After balloon inflation, the blood flow rate in the proper hepatic artery was measured at 2.5 ± 0.7 mL/s using the 2D cine phase-contrast sequence. The steering gradient durations were 8 ms in the left (+X) and down (-Y) direction for amplitudes of 26.5 mT/m and 18 mT/m, yielding a 32 mT/m nominal amplitude for 29.5% duty cycle given TR = 14 ms and Gmax = 43 mT/m. In each MRN cycle, an MDEB aggregate (20 MDEBs) was released from our injector and followed by the opening of the pre-set MRN sequence. The sequence would last 30 s for each MRN cycle. A volumetric interpolated breath-hold examination (VIBE) sequence (radio-frequency-spoiled 3D gradient-echo sequence) was used to locate the MDEBs in vivo using their MRI artifacts. The experimental results reveal that the combination of the magnetic and gravitational forces can navigate the MDEBs into the targeted vessel branches shown in Figure (c).

![Image](image2.png)

**Figure:** (a) Setup of the MRN of the MDEBs in the pig liver. The MDEB aggregates are formed in a particle injection system. The catheter, inserted into the hepatic artery of a living swine, is connected to the MRI-compatible injection system to allow the injection of the MDEB aggregates into the proximal proper hepatic artery. MRN was conducted using the VIBE sequence and the 2D cine phase-contrast sequence. In the red box, projection of a 3D angiography in supine (orange) and left decubitus (green) showing the optimization of gravitational forces.
Combining bioorthogonal click chemistry and magnetic hyperthermia for siRNA transfection

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The fast generation by magnetic nanoparticles (MNPs) in the presence of an alternating magnetic field (AMF) has traditionally been studied for cancer treatment applications upon the accumulation of MNPs inside target cells. Herein, we developed an innovative approach to apply localized heating onto living cell membranes for inducing changes in membrane biophysics. Our approach is based on the covalent immobilization of MNPs on the cell membrane via bioorthogonal click chemistry, more specifically the strain-promoted [3+2] azide-alkyne cycloaddition (SPAAC) between azide-labelled cell membranes and strained alkyne-functionalized MNPs.

First, the expression of azide reporters on human breast adenocarcinoma cells (MCF7) was optimized through metabolic glycomeering. Then, 15 nm iron oxide MNPs were decorated with two different strained alkynes with different reactivity towards azides, namely cyclooctyne (CO) and dibenzocyclooctyne (DBCO). Their bioorthogonal reactivity was assessed in suspension, onto artificial azide substrates and their attachment to the cell membrane was confirmed with electron microscopy, flow cytometry and elemental mass analysis.

Finally, upon the application of an AMF, these MNPs acted as “hotspots” to generate a very localized heating of the cell membrane, leading to changes in cell membrane fluidity that promoted the intracellular delivery of a siRNA to silence the expression of a Green Fluorescent Protein. Our transfection approach led to a silencing effect comparable to the one observed using a commercially available siRNA transfection reagent; however, it resulted notably less toxic for the cells. Therefore, our approach overcomes one of the most limiting aspects of existing transfection strategies, i.e. impact on cell viability.

Characterisation of DNA Nano-Chamber Magnetic Filaments

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DNA nano-objects are one of the most prominent building blocks for engineering self-assembled morphologies that can broadly be classified as supra-molecular polymers. These polymers can carry nanoscopic cargos, can serve for changing optical and rheological properties. We previously reported on the directional assembly of DNA nanocuboids (DNCs) with tailorable multi-linking bonds into long polymer-like chains.[1,2] In this contribution we treat directional assembly as a platform for synthesis of polymer-like magneto-responsive materials, namely magnetic filaments (MFs).

By comparative analysis of equilibrium properties of DNC filaments functionalised with magnetic nanoparticles (DNC MFs) under compression in constant, homogeneous magnetic fields, we quantify the impact of cubic monomer shape and bonding mechanism of DNC. DNC MFs have a surprisingly smooth, and controllable response to compression. Furthermore, combining MD and Lattice-Boltzmann method we study the effects of monomer shape and magnetic nature of colloids on the behaviour of MFs subjected to the simultaneous action of shear flow and a stationary external magnetic field perpendicular to the flow. External magnetic field strongly inhibits tumbling only for filaments with ferromagnetic monomers, with an orientation angle independent of monomer shape. Reorientational dynamics of MFs with super-paramagnetic monomers, are not inhibited by applied magnetic fields, but enhanced, particularly for cubic monomer shape. The latter finding suggests the DNC filaments might be ideal candidates to create magnetically responsive polymers.


Strain promoted azide alkyne click chemistry, an efficient surface functionalization strategy for microRNAs magnetic separation

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Magnetic nanoparticles, used in biological and biomedical assays, like magnetic particle spectroscopy-based applications [1], are made of a superparamagnetic iron oxide core capped with an organic or inorganic layer, to prevent aggregation and to improve their physicochemical stability. Precise surface bio-functionalization is also mandatory to allow highly selective chemical interactions with the biological target to quantify.

In this work, γ-Fe2O3@SiO2 core-shell nanoparticles [2] were used to anchor single strand nucleic acid (ssDNA) using two surface functionalization strategies. A comparison of two grafting protocols (figure 1), one based on maleimide chemistry and the other on strain promoted azide alkyne click chemistry (SPAAC) reveals that the SPAAC strategy allows for a higher grafting yield and a more accurate control of the amount of the grafted ssDNA.

Figure 1: surface functionalization strategies.

Optimized SPAAC grafting protocol enables the grafting of six different ssDNA, complementary of miRNA sequences specific of liver (miR 122), skeletal (miR 133b, 206) and/or cardiac (miR 208a, 133a, 1) muscles, as they are promising biomarkers.

Magnetic separation of the complementary miRNA sequences in model buffer solution results in the rapid capture of miRNAs, corresponding to 50-60% of ssDNA’s hybridization. Furthermore, capture experiments carried out in complex biological media (fetal bovine serum or rat plasma) reveal only a slight decrease in the amount of miRNA extracted. Finally mismatch experiments using miR 133a and 133b sequences, which differ only by one nucleic acid, indicate a fairly good selectivity.

Dehybridization of captured miRNAs is now being studied in a lab-on-a-chip format using mild magnetic hyperthermia conditions [3] to quantify miRNAs on the surface of microelectrodes, as part of the DIMELEC and e-miRGency projects, funded by the French National Research Agency, and the Labex NanoSaclay, respectively.

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Magnetic Nanoparticles for Diagnostic Imaging: Getting Into the Clinic

Proulx, R., Zhang, M., Jayalakshmi, Y. – Imagon Biosystems

Iron oxide nanoparticles have been used in preclinical and clinical research as imaging agents for decades because of their magnetic properties and their known safety profile. Few, however, have made it through clinical development and regulatory approval to be made commercially available. We have developed iron oxide nanoparticles for both non-targeted and targeted uses, including an anti-HER2 conjugated nanoparticle currently being investigated in a Phase I study for lymph nodal staging. We propose reviewing some of the challenges associated with developing iron oxide nanoparticles for clinical diagnostic imaging, and provide examples of their use in three forms of imaging, magnetic resonance imaging (MRI), Magnetic Particle Imaging (MPI), and Magnetic Relaxometry (MRX).
Innovative dynamic detection for early diagnosis with a lab-on-a-chip based on “two-stage” giant magnetoresistance sensors

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The development of early diagnosis techniques, that are fast, sensitive, inexpensive and point of care, is a challenge in the field of health but also in the field of defense or the environment. Currently, among the easy-to-use early diagnostic devices, there are strip tests in which the targets migrate in the cellulose. Other methods used routinely in biology laboratories, such as ELISA or PCR tests, have better sensitivities but require a qualified staff. Optical detection is still not suitable for some opaque matrices and electrochemical or static magnetic detection have too many non-specific interactions. In this context, we propose a patented biochip, based on Giant Magnetoresistance (GMR), to detect biological objects in very small quantities, in complex matrices without a prior washing step. This approach is based on the use of magnetic nanoparticles functionalized by monoclonal antibodies, directed against target biological objects. Their dynamic detection, after interaction with the magnetic nanoparticles, is carried out using GMR sensors which allow to count the magnetically targeted biological objects one by one.

Very promising results were obtained with a first GMR biochip [1] based on GMR sensors placed under the microfluidic channel, developed on a eukaryotic cell model, allowing reaching sensitivities and specificities equivalent to those obtained on the same biological model in ELISA tests, with a greater ease of use and a slight time gain. Until now, the main limitation has been the bead aggregates that lead to false positives.

The new patented biochip [2] (Figure 1A) has sensor arranged face to face on either side of the microfluidic channel, which allow each magnetic object to be detected simultaneously (Figure 1B). For the first time, thanks to this technique, it is possible to determine the magnetic moment of the objects flowing in the channel and thus to discriminate the aggregates of beads from the targeted biological objects.

This detection technique allows to obtain a sensitivity 30 times higher than that obtained with the Elisa test or with the first prototype making this biochip very competitive.


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Development of Inductively Detectable Probes for Proteolytic Activity

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Inductive detection of magnetic nanoparticles (MNPs) via time-changing magnetization in response to applied fields is the basis of technologies including magnetic particle imaging and magnetic particle spectrosopy. Because inductive readouts may be advantageous for the development of low cost, point-of-care devices, they have also been considered for diagnostic sensing of biomolecules. Most often, this has involved the selective binding of an analyte to the surface of the MNPs, resulting in a subtle shift in frequency-dependent susceptibility. Additionally, modulation of aggregation behavior by chemical linkers and sensing saturation characteristics with high amplitude alternating magnetic fields has been shown to produce robust changes in inductive signal. Nevertheless, these approaches have not yet become competitive methodologies for commonplace analyte detection. Alternative methods, including sensing paradigms that lower the cost and required power of associated electronics, should be explored.

Here, we develop and evaluate an inductive sensing concept for detecting proteolytic cleavage. In addition to acting as a highly informative class of biomarkers with early and underlying roles in disease, proteases are inherently catalytically amplified and offer a combinatorial space of peptide substrates that can be tailored for selective response. In our scheme (Fig. a), MNPs are covalently bound to larger nonmagnetic scaffold nanoparticles via cleavable peptide linkers. With transmission electron microscopy, we show that these structures are indeed formed (Fig. b) and that they undergo disassembly in response to nonspecific proteolytic cleavage by a blend of Proteinase K and Chymotrypsin (Fig. c-d). To detect whether MNPs are in a bound or free state, we developed a prototype pulsed field magnetometer with adjustable pulse width and magnitude (Fig. e). The design directly incorporates the drive coil, sense coil, and compensation coil into a printed circuit board (Fig. f). A proof-of-concept test with samples containing MNPs in a solid or liquid matrix to mimic the free and bound states show that during the rising and falling edges of the pulse, the MNPs produce signals that depend on whether they are bound or freely suspended in solution (Fig. g). Parameters such as the magnitude of the pulse can be selected to maximize the change in voltage signal distinguishing the free and bound states (Fig. h).

Figure. (a) The concept for inductively detectable protease responsive magnetic nano assemblies (PRIMAs) is shown. Under conditions of enzymatic cleavage, MNPs dissociate from a central nonmagnetic scaffold particle. (b) Representative TEM of PRIMAs incubated overnight without proteases. (c) Representative TEM of PRIMAs incubated overnight with 1.8 μM active Proteinase K and 1.8 μM Chymotrypsin. Scale bar: 200 nm. (d) The number of MNPs visible on the perimeter of a 25 nm randomly selected PRIMA was found with and without exposure to cleavage conditions. Error bars show standard deviation and ** indicates p < 0.0001 in an unpaired t-test. (e) Pulses resulting from a 100 μs trigger and various discharge capacitor charging voltages are shown. (f) The schematic of a printed circuit board incorporating the pulse, sense, and compensation coils is shown. (g) The inductive signals from a 100 μL solid and liquid sample of Ocean Nanotech 25 nm MNPs at 500 μg/mL is shown for a 15 V, 100 μs pulse. (h) A figure of merit defined to maximize the change in signal observed between bound and free states is evaluated over a range of pulse amplitudes.

Handheld Magnetic Particle Spectroscopy (MPS) for Rapid, One-step, Wash-free Detection of SARS-CoV-2 Spike and Nucleocapsid Proteins in Liquid Phase

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With the ongoing global pandemic of coronavirus disease 2019 (COVID-19), there is an increasing quest for more accessible, easy-to-use, rapid, inexpensive, and high accuracy diagnostic tools. Traditional disease diagnostic methods such as qRT-PCR (quantitative reverse transcription-PCR) and ELISA (enzyme-linked immunosorbent assay) require multiple steps, trained technicians, and long turnaround time that may worsen the disease surveillance and pandemic control. In sight of this situation, a rapid, one-step, easy-to-use, and high accuracy diagnostic platform will be valuable for future epidemic control especially for regions with scarce medical resources. Herein, we report a magnetic particle spectroscopy (MPS, see Fig. 1) platform for detection of SARS-CoV-2 biomarkers: spike and nucleocapsid proteins. This technique monitors the dynamic magnetic responses of magnetic nanoparticles (MNPs) and uses their higher harmonics as a measure of the nanoparticles’ binding states. By anchoring polyclonal antibodies (pAbs) onto MNP surfaces, these nanoparticles function as nanoprobes to specifically bind to target analytes and form nanoparticle clusters. This binding event causes detectable changes in higher harmonies and allows for quantitative and qualitative detection of target analytes in liquid phase. We have achieved detection limits of 0.156 nM (equivalent to 125 fmoles) and 3.13 mM (equivalent to 250 fmoles) for detecting SARS-CoV-2 spike and nucleocapsid proteins, respectively. This MPS platform combined with one-step, wash-free, nanoparticle clustering-based assay method is intrinsically versatile and allows for the detection of a variety of other disease biomarkers by simply changing the surface functional groups on MNPs.

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Development of Magnetic Particle Spectroscopy That Integrates Both Conventional and Mixing Methods for Virus Detection

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Infectious diseases spread by viruses can be quite lethal. Viruses usually have a high rate of spread, which has been made obvious by the Covid-19 pandemic. Early detection of disease causing viruses using sensitive, rapid and accurate methods is very important for efficient reaction. In this regard, various technologies for detecting viruses are being researched, but there are still many aspects of this work that need to be improved, such as the long time requirement, high cost and poor accuracy. Compared to other techniques for virus detection, Magnetic Particle Spectroscopy (MPS) is a novel magnetic detection technique that has many advantages, such as portability, high-sensitivity, ease of use, low-cost, non-invasiveness and avoidance of radiation exposure. Through the use of superparamagnetic iron oxide nanoparticles (SPIONs) and a sinusoidal magnetic field at high frequency, harmonic components can be obtained, which can be used to indicate the bound states of the SPIONs. Coupling the virus receptors at the surface of the SPIONs by using conjugation methods can make magnetic nanoparticles (MNPs) for virus detection. In this case, the functionalized SPIONs can form clusters with the virus and lead to changes in the hydrodynamic volume of the SPIONs. This technology can be used for virus detection as it causes a phase delay to be detected in the MPS. There are two kinds of MPS; the conventional MPS that uses one sinusoidal magnetic field to excite the SPIONs and the mixing method that uses two sinusoidal magnetic fields with distinct frequencies. Each type of MPS has different strengths and weaknesses. In this paper, we present a MPS that can handle both conventional and mixing methods for virus detection, and provide guidelines for choosing the appropriate method. Our integrated MPS system and its connection diagram are shown in Figure 1. The excitation coil used in the proposed system has 2 layers of 18 turns each and the drive coil has 4 layers of 18 turns each. The excitation and drive coils can generate magnetic fields of 20mT and 9.6mT, respectively. In future works, the developed model will be tested and verified through experiment.

Figure 1. (a) Cross-section view and (b) photograph of the integrated MPS system. A copper plate is sandwiched between the excitation and drive coils to remove external noise. (c) Connection diagram of the integrated MPS system. We can control the driving mode through a switch and a software running in LabVIEW® controls the system operation.

PEGylated Magnetic Nanoparticle-Induced Acute Hypersensitivity Reaction: Role of Bioactive Corona

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Polyethylene glycol (PEG) is a common surface modulator that increases the half-life of nano-drugs in circulation; however, intravenous administration of PEGylated pharmaceuticals often induces acute hypersensitivity reactions (HSR) with symptoms including systemic hypotension, followed by tachyphylaxis with unknown mechanism. We hypothesize that the formation of protein corona with a composition specific to PEGylated nanoparticles induces transient microvascular occlusion that entrains hemodynamic effects. In anesthetized rats, administration of PEGylated magnetic nanoparticles (PEG-MNPs), but not the pristine MNPs, induced a transient decrease in arterial pressure and cardiac output, which was associated with a reduction in blood flow of the kidney and cremaster muscle, as demonstrated by ultrasound flowmetry and laser speckle contrast imaging, respectively, which were subjected to tachyphylaxis in response to the 2nd dose. Calculated renal vascular resistance was significantly increased with a reduction in cross-sectional area of the renal vasculature, suggesting PEG-MNPs-induced hypotension is unlikely due to dilation of resistant vessels. Nevertheless, histological analysis reveals no iron retention in the kidney. Proteomic analysis of the hard corona demonstrated much more complement proteins on PEG-MNPs vs. MNPs, suggesting a more vigorous complement activation occurred on the surface of PEG-MNPs in circulation. After i.v. administration of PEG-MNPs, the remaining plasma proteins with high affinity to PEG-MNPs were greatly reduced, suggesting consumption of the corona proteins with repeated exposure. In conclusion, bioactive corona of nano-drugs may directly or indirectly participate in the hemodynamic responses associated with HSRs; such information may be amendable to prediction and/or prevention of the adverse effects of, especially PEGylated nanomedicines.
Biomimetic capturing of pathogens using SPIONs functionalized with salivary agglutinin (GP-340)-derived peptides

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Biocompatibility and cellular interactions of biogenic magnetic nanoparticles

Biogenic nanoparticles are an intriguing example for a biomineralization process. Magnetotactic bacteria like the model organism Magnetospirillum gryphiswaldense are capable of synthesizing so-called magnetosomes, single-domain nanocrystals of chemically pure magnetite that are enveloped by a biological membrane. Magnetosome biosynthesis is genetically highly controlled, thereby generating nanoparticles with extraordinary properties (such as high crystallinity, strong magnetization and uniform shape and size). Moreover, the magnetosome membrane is accessible to genetic engineering, which enables the selective and controlled functionalization of the particle surface with reactive moieties. Due to these unique characteristics, bacterial magnetosomes have the potential to yield promising agents for biomedical applications in diagnosis as well as magnetic imaging techniques or as drug carriers. In order to comprehensively evaluate the biocompatibility of isolated magnetosomes when administered to mammalian cell lines (cancer cells and primary cells), different cytotoxicity assays were performed. For the magnetosome-treated cell lines FaDu, BeWo, HCC78, and iP-CPL, concentration-dependent effects on cell viability were observed, however, even increased particle concentrations of up to 400 μg mL⁻¹ were considered to be biocompatible. Using different microscopy techniques, we could demonstrate that the particles are internalized and accumulate in endolysosomal vesicles in the vicinity of the nucleus. Remarkably, even upon short-term incubation magnetosomes – cell interactions were strong enough to allow for magnetic cell sorting, with ~80% of the treated FaDu cells being magnetically separated.

In order to enhance these interactions and to address distinct cancer cell types, genetic engineering techniques will be used for the display of specific anticancer peptides on the magnetosome surface. Thereby we will generate a set of multifunctional magnetic nanoparticles that provide a flexible “tool” with potential in e.g. the targeting of circulating tumour cells.

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References:

Figure 1: Principle of SPION-APTES-Pep enhanced diagnostic time and potential treatment.

Talk #50

Biomimetic capturing of pathogens using SPIONs functionalized with salivary agglutinin (GP-340)-derived peptides

Talk #50
NP-cellular hitchhiking system for targeted combination therapy and diagnosis of glioblastoma
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Glioblastoma (GBM) remains an incurable tumor and there is a paramount need for more effective therapeutic approaches, taking into consideration the Blood Brain Barrier impediment. In this project, we propose a novel nanoparticle (NP) cellular hitchhiking system (NPCHS) for GBM treatment. Here, monocytes were conjugated with PLGA NPs packed with the drug paclitaxel (PTX) and Super Paramagnetic Iron Oxide nanocrystals (SPIONs) which will bestow the system with MRI contrast, magnetic targeting and hyperthermia treatment while monocytes will provide a direct targeting to GBM by natural chemotaxis. For this end, fluorocarbon labelled plain and PTX-loaded PLGA NPs were synthesised using the nanoprecipitation method, and fully characterised for their physicochemical properties and drug loading efficiency using DLS, Zeta potential, TEM, HPLC and ICP-MS. The NPs were screened for toxic effects in relevant human and mouse cell lines, namely: monocytes, endothelial cells and glioma cells, using high content screening and image based flow cytometry systems. The optimal ratio of NP-cell conjugation was determined. Next, SPION nanocrystals, approximately 20 nm in size were loaded into the PLGA NPs. MRI measurements of SPION loaded PLGA NPs or U87 cells incubated with SPION-based NPs revealed the increase of T2 relaxation rates with increasing Fe concentrations. In vivo chemotaxis was investigated using optical imaging with the IVIS Spectrum and via intravital microscopy, in subcutaneous and orthotopic glioma tumors following intravenous injection of NP conjugated monocytes. Tissue slices from tumors and major organs were investigated for targetting and therapeutics using H&E staining and immunohistochemistry. In general, formulation showed homing ability towards GBM tumors, in vivo, promising a potential for targeted GBM treatment.

Figure 1. A) A representative sketch of the proposed NP-cell formulation. B) In vivo homing of NPCHS in subcutaneous glioma tumors. C) In vivo homing of NPCHS in orthotopic glioma tumors.

References
Use of peptide functionalized Dynabeads for the magnetic carrier separation of Rare Earth phosphors in low and high magnetic field gradients

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ABSTRACT

Superparamagnetic composite beads are widely used as magnetic carriers in biotechnological processes, including the purification of biomolecules, organelles and cells [1,2]. Their wide range of applications include diagnostic, as well as industrial purposes. Furthermore, the immobilization of surface-binding peptides can render highly specific surface properties to composite beads and facilitate their selective interaction with target particles. In this context, peptide functionalized composite beads have been shown to be promising tools for environmental applications, including biominning and wastewater treatment [3-5]. Nevertheless, to the best of our knowledge, their use has so far only been investigated in low magnetic field gradients, on a milliliter scale.

The waste of fluorescent lamps contains several valuable Rare Earth phosphors in the form of fine particles that are hard to separate and therefore lack efficient recycling schemes [6]. Our junior researchgroup, BoxKoLab, has previously identified selectively surface-binding peptides that interact with the Rare Earth phosphor LaPO₄·Ce₂O₃ [7]. Recently, we have chemically immobilized the identified peptides and have tested their interaction with several target phosphors [8]. We have thoroughly characterized a range of Rare Earth phosphors and we have shown their compatibility with an upscalable High-Gradient Magnetic Separator [9], which was specifically designed for biotechnological separations with superparamagnetic carriers [10].

In this work, we investigate the use of Dynabeads® M-270, functionalized with previously identified peptides, for the separation of Rare Earth phosphors. First, we characterize the physical properties of functionalized and unfunctionalized beads. Subsequently, we examine the beads’ selectivities towards various Rare Earth phosphors in an LGMAS setup. Finally, we compare the carrier behaviour of the beads in low and high magnetic field gradients by the use of an optical microscopic setup. A special focus is placed on the magnetically induced chain formation by sets of beads. Finally, this work can shine a light on the future perspectives of peptide functionalized superparamagnetic composite beads for a selective and upscalable separation process of fine particles.

REFERENCES


3D Printing of Polymer-Bonded Magnets

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Three-dimensional printing technology has emerged as a promising tool for meticulously fabricated scaffolds with high precision and accuracy, resulting in intricately detailed biomimetic 3D structures. Producing magnetic scaffolds with the aid of additive processes, such as 3D printing, opens up a multitude of state-of-the-art areas of application like tissue engineering, bone repair and regeneration, drug delivery and magnetic hyperthermia. A crucial first step for this is to develop innovative polymeric composite materials. The current work presents a protocol to fabricate (Fig. 1) and 3D print polymer-bonded magnets using the Fused Deposition Modeling (FDM) method. Polymer-bonded magnets are defined as composites with permanent-magnet powder embedded in a polymer binder matrix. By using a low-cost mixing extruder (Fig. 1c), commercial magnetite magnetic nanoparticles are mixed with PLA (PolyLactic Acid) powder (Fig. 1b), a typical thermoplastic material used as 3D printing filament. The powder mixture is compounded, extruded to fabricate the 3D printing filament (Fig. 1d) which is subsequently characterized structurally (Fig. 1a) and magnetically (Fig. 1f) before the printing process. Finally, magnetic scaffolds are successfully printed and evaluated in magnetic hyperthermia.

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Magnetic bucket brigade networks as rails for single cell transportation

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The application of nanomaterials in a medical context is rapidly progressing within the past years. However, there is still the necessity to understand the interaction between nanomaterials and the human body in more detail, especially at cellular barriers. Since clinical trials on pregnant women are difficult to perform, physiologically appropriate models of the human placenta to study nanoparticle-placenta interactions in vitro are needed. The placenta delivers nutrients from the maternal blood to the foetus and clears metabolites in reverse direction. This organ is furthermore responsible for the protection of the foetus from harmful substances. Various cell types form the blood-placenta barrier (BPB), e.g. cytotrophoblasts, endothelial cells, placental macrophages (Hofbauer cells), and pericytes. During pregnancy, the placenta is highly dynamic in its morphology and composition, e.g. the cytotrophoblasts fuse and form the syncytiotrophoblast. The aim of our investigations is to gain a better understanding of the interactions of nanomaterials, especially magnetic nanoparticles (MNP), with the blood-placenta barrier. Recently, we studied the interaction of different magnetic nanoparticles under fluidic conditions in a microfluidic biochip with special focus on extended incubation times and passing abilities of the MNPs [1,2]. In the present study, we investigated whether the fusion of cytotrophoblasts to syncytiotrophoblasts affects MNP passage through the barrier. The in vitro BPB was established in a microfluidic chip by using the cytotrophoblast cell line BeWo and human primary placental pericytes. After 6 days the integrity of the barrier was confirmed by sodium fluorescein permeability (permeability coefficient: empty chip > 3.0E-5 cm/s; BeWo/pericyte barrier < 6.0E-6 cm/s). The fusion of the cytotrophoblasts was induced with 20 μM forskolin for 24h. The morphological changes were confirmed by fluorescence microscopy and qPCR. The fused BeWo cell layer was incubated with citrate-coated MNP for 24h. Magnetic Particle Spectroscopy was used to determine the MNP distribution in the apical and basolateral compartment as well as in the cell layer. The penetration rate of MNP was not affected by the formation of syncytiotrophoblasts. In the basolateral compartment, no significant difference in MNP content was measured between the untreated setting (2.3% ± 2.0%) and after cytotrophoblast fusion induced by forskolin (2.4% ± 1.6%). We demonstrate that MNPs pass a cytotrophoblastic cell layer as well as a syncytiotrophoblast.

Figure. Transport of fibroblast cells carried by magnetic beads (MB) along arrays of ferromagnetic elements.
(a) Cell trajectories around collecting (C) and switching (S) elements for a clockwise or a counterclockwise rotating magnetic fields are shown. (b) Transport of a fibroblast cell along a network of multiple elements using a combination of magnetic field rotation directions is performed.

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Passage of magnetic nanoparticles through a differentiating blood-placenta barrier

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The application of nanomaterials in a medical context is rapidly progressing within the past years. However, there is still the necessity to understand the interaction between nanomaterials and the human body in more detail, especially at cellular barriers. Since clinical trials on pregnant women are difficult to perform, physiologically appropriate models of the human placenta to study nanoparticle-placenta interactions in vitro are needed. The placenta delivers nutrients from the maternal blood to the foetus and clears metabolites in reverse direction. This organ is furthermore responsible for the protection of the foetus from harmful substances. Various cell types form the blood-placenta barrier (BPB), e.g. cytotrophoblasts, endothelial cells, placental macrophages (Hofbauer cells), and pericytes. During pregnancy, the placenta is highly dynamic in its morphology and composition, e.g. the cytotrophoblasts fuse and form the syncytiotrophoblast. The aim of our investigations is to gain a better understanding of the interactions of nanomaterials, especially magnetic nanoparticles (MNP), with the blood-placenta barrier. Recently, we studied the interaction of different magnetic nanoparticles under fluidic conditions in a microfluidic biochip with special focus on extended incubation times and passing abilities of the MNPs [1,2]. In the present study, we investigated whether the fusion of cytotrophoblasts to syncytiotrophoblasts affects MNP passage through the barrier. The in vitro BPB was established in a microfluidic chip by using the cytotrophoblast cell line BeWo and human primary placental pericytes. After 6 days the integrity of the barrier was confirmed by sodium fluorescein permeability (permeability coefficient: empty chip > 3.0E-5 cm/s; BeWo/pericyte barrier < 6.0E-6 cm/s). The fusion of the cytotrophoblasts was induced with 20 μM forskolin for 24h. The morphological changes were confirmed by fluorescence microscopy and qPCR. The fused BeWo cell layer was incubated with citrate-coated MNP for 24h. Magnetic Particle Spectroscopy was used to determine the MNP distribution in the apical and basolateral compartment as well as in the cell layer. The penetration rate of MNP was not affected by the formation of syncytiotrophoblasts. In the basolateral compartment, no significant difference in MNP content was measured between the untreated setting (2.3% ± 2.0%) and after cytotrophoblast fusion induced by forskolin (2.4% ± 1.6%). We demonstrate that MNPs pass a cytotrophoblastic cell layer as well as a syncytiotrophoblast.
Biomanufacturing magnetosomes: nanocarriers with versatile functionalisation for imaging and drug delivery applications

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Magnetosomes are functional magnetic nanoparticles (MNPs) generated by magnetotactic bacteria (MTB) and are arranged as single-domain magnetic crystals individually wrapped in a phospholipid membrane. Magnetosomes have advantageous properties when compared to chemical synthetic MNPs: they are ferromagnetic; have narrow size distribution; are coated in organic material, preventing aggregation; and can be functionalized in vivo using genetic engineering tools, allowing one-step manufacture of functionalized particles. In addition, the presence of different chemistries on the surface of magnetosomes such as amino and carboxyl groups makes them amenable for different functionalisation strategies. Therefore, magnetosomes can be used as versatile magnetic nanocarriers.

On the other hand, biosynthesis of magnetosomes is a clean process carried out at mild temperatures and generates safe waste. Magnetosomes therefore have highly attractive properties as “smart materials” for biotechnology and nanomedicine uses. However, their true potential to become the next generation nanomaterials hangs the ability to develop high-yield and robust bioprocesses. Here, we address the challenges and opportunities in magnetosome biomanufacturing and present our strategy to biomimic magnetosome in bench-top bioreactors. Our findings demonstrate that the employment of process analytical technologies (PAT) during the production, purification and formulation stages are key to not only to understand the influence of external stimuli on the process yield but also to ensure the magnetosome quality attributes (e.g., size, chain length, membrane integrity, stability and residual impurities). As examples of the numerous potential applications of magnetosomes, we present how (i) genetic engineering approaches can be used to express functional peptides on the surface of magnetosomes capable of binding fluorescent molecules and (ii) electrostatic interactions can be useful in the application of magnetosomes for the delivery of macromolecular payloads.

![Diagram of a single magnetosome with Briquet and transmembrane proteins.](image)

Figure. (A) Circular approach to the development of high-yield and robust magnetosome biomanufacturing. (B) Schematic representation of a single magnetosome composed by a magnetic iron oxide core encapsulated by a phospholipid bilayer. Magnetosome membrane contains magnetosome-associated transmembrane proteins. Variation of shape and colour denote the diversity of proteins.

**Active Targeting of Head and Neck Cancer Cells with Dendronized Iron Oxide Nanoparticles and Effect of the Size and Shape of Nanoparticles for Promoting Multimodal Therapy**

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Head and neck cancers (HNC) represent 4% of all cancer worldwide and are hard to treat due to their location especially for children. Developing multimodal theranostic nanoparticles (NPs) to speed up targeted diagnosis and increase its sensitivity, reliability and specificity is a promising tool for a better management of the disease. Besides being excellent T2 contrast agents for MRI, iron oxide NPs are promising as therapeutic agents by magnetic hyperthermia when correctly designed (high magnetocrystalline anisotropy) and they also have an interest for photothermal treatment and ultrasound therapy thanks to ROS activation. Another challenge is to specifically target cancer cells by coupling targeting ligand at the surface of NPs to enhance the NPs accumulation in tumoral cells.

In that context, we develop dendronized iron oxide NPs with a mean size of 10 nm, which have been proved along several in vivo studies to present a very good biodistribution with no captation by the RES [1]. Recently, we have developed a strategy to biomanufacture magnetosomes in bench-top bioreactors. Our findings demonstrate that the decomposition method by tuning synthesis parameters such as the reaction temperature, the heating rate and the nature of surfactant. These dendronized NPs were found biocompatible without cytotoxicity up to 150 μg/mL and generates safe waste. Magnetosomes therefore have highly attractive properties as “smart materials” for biotechnology and nanomedicine uses. However, their true potential to become the next generation nanomaterials hangs the ability to develop high-yield and robust bioprocesses.

1- Confocal images of FaDu cell lines (top) and 93-VU cell lines (bottom) with and without targeting ligand (respectively left and right). 2- Magnetic resonance images of CD45 mice taken at 9.4T A) pre-injection, B) 3min after IV injection with 12nm dendronized NPs at a dose of 45μg/kg body weight. White arrows point the liver.

**References**

**Talk #57**

**Talk #58**

**Figure.** (B) Circular approach to the development of high-yield and robust magnetosome biomanufacturing. (C) Schematic representation of a single magnetosome composed by a magnetic iron oxide core encapsulated by a phospholipid bilayer. Magnetosome membrane contains magnetosome-associated transmembrane proteins. Variation of shape and colour denote the diversity of proteins.
Heterobimetallic probiotic bacteria as new oral magneto-optical hyperthermia agents

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Probiotic bacteria were used as carriers of gold nanoprisms (AuNPR) and superparamagnetic maghemite nanoparticles (MNP) to develop innovative oral agents for hyperthermia cancer therapy. The adsorption of metallic nanoparticles takes place in the biofilm, an extra-bacterial conglomeration of products, composed mainly of extrapoly saccharides (EPS), that surrounds the bacterial wall of the probiotic bacterium. Two synthetic strategies were used to produce the different therapeutic agents. First, the probiotic bacterium Lactobacillus fermentum was simultaneously loaded with MNP and AuNPR to produce AuNPR-MNP-bacteria systems with both types of nanoparticles arranged in the same layer of bacterial EPS. In the second approach, the probiotic was first loaded with AuNPR to form AuNPR-bacteria and subsequently loaded with MNP-EPS to yield AuNPR-bacteria-EPS-MNP with the MNP and AuNPR arranged in two different EPS layers. This second strategy has never been reported and exploits the specific EPS-EPS recognition, which allows the layer-by-layer formation of structures on the bacteria external wall. The potential of AuNPR+MNP-bacteria and AuNPR-bacteria-EPS-MNP as magnetic hyperthermia or photothermal therapy agents was assessed, validating their capacity to produce heat either during exposure to alternating magnetic fields or near-infrared light. Interestingly, Lactobacillus fermentum is marketed as an oral supplement to reinforce the gut microbiota and has already been proposed as an oral drug carrier, able to overcome the stomach medium and deliver drugs to the intestines. Therefore, our results open the way for the development of novel therapeutic strategies using these new heterobimetallic AuNPR/MNP-bacteria systems in the frame of gastric diseases, using them as oral agents for magnetic hyperthermia and photothermal therapy [1].

Figure 1. A) HAADF-STEM/EDX image of the AuNPR+MNP-bacteria (Au, pink; Fe, green). B) HAADF-STEM/EDX image of the AuNPR-bacteria-EPS-MNP bacteria (Au, pink; Fe, green). C) Heating curves obtained after laser irradiation of 2 mg/ml of AuNPR-MNP-bacteria and AuNPR-bacteria-EPS-MNP plus water as a control sample. D) Temperature variation over time for MNP, MNP-bacteria, AuNPR+MNP-bacteria and AuNPR-bacteria-EPS-MNP at 0.5 mg Fe/mL after exposing during 5 min the samples to a high-frequency alternating magnetic field.

Advancing Rewarming for Cryopreservation through Scalable Polymer Coating of Iron Oxide Nanoparticles

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Donated organs have a short time limit for preservation after collection leading to shortages, morbidity, and mortality of transplant recipients. We have successfully rewarmed vitrified, cryopreserved (-140 °C – indefinite storage) organs using radiofrequency (RF) excited iron oxide nanoparticles (IONPs) in cryoprotective agents (CPAs).1 CPAs are aqueous solutions containing high concentrations of salts, sugars, and organics such as dimethylsulfoxide (DMSO), formamide, and propylene glycol. We previously demonstrated that although scalable silica-coated IONPs form stable colloidal suspensions in CPAs, these suspensions were limited in iron concentration to 15-20 mg Fe/mL, depending on the silica shell thickness.2 Herein, we present biocompatible polymers (i.e. polyethylene glycols, PEG) coated IONPs via a phosphonate linker (PLink) that is stable in CPAs, increases saturation concentration, and is inexpensive for scale-up (> 1g per batch).3

PLink displaces the initial coating on commercial IONPs (Ferrotec Inc.) such as EMG-1200 (hydrophobic) and EMG-308 (hydrophilic) and allows attachment of the polymers of interest, in a simple ligand exchange step. PLinked-PEG increases colloidal stability and decreases aggregation of EMG-1200 in water and CPAs from minutes (uncoated) to up to 2 weeks. PLink has high affinity for iron oxide due to the phosphonate anchoring moiety and a carboxyl chemical handle for ligand attachment. The heating of coated EMG-1200 was enhanced significantly comparing to uncoated hydrophobic EMG-1200 (20 to 150 W/g Fe in H2O) due to better dispersion and colloidal stability in the solution, while the heating of coated EMG-308 was the same as the hydrophilic EMG-308 indicating the polymer coating did not affect IONP core’s heating capability. The concentrations of IONP in VSS (a common CPA) reached 25 mg Fe/mL of 308-PEG5000 and 60 mg Fe/mL of 1200-PEG5000, which is significantly above our previous published capabilities of sIONP at 30 mg Fe/mL. Further, at these concentrations cryopreserved human dermal fibroblast cells were successfully nanowarmed at an applied field of 360 kA/m and 20 kA/m, with higher viability as compared to convective rewarming in a water bath and a heating rate close to 200 °C/min, 2.5 times faster than our previous tests with sIONPs. PLink coated IONPs have since been scaled to over 30 g synthesis and used to nanowarm rat kidneys at and above these rates.

The PLink coating allows for facile, inexpensive, and scalable synthesis of PEG-functionalized IONPs for, as needed for human scale organ cryopreservation. In future experiments, PLink IONPs will be tested at higher Fe concentration in various CPAs, maximizing the heating rates with EMG308 IONPs and translating nanowarming to transplantation.


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Hybrid Magnetic Nanoparticles as Molecular Agents in Magneto-motive Ultrasound Imaging

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Magnetic nanoparticles (MNPs) can work as a source of heat in response to the alternating magnetic field which is practically used in magnetic hyperthermia treatment. Additionally, MNPs can be affected by the application of the static magnetic field which is important for magnetic separation process.

Studies of nanostructures have been established as promising approaches in the diagnosis and therapy of cancer through the last decades. Magnetic nanoparticles (MNPs) and gold nanorods (GNRs) are known as the most widely used nanomaterials due to their considerable physicochemical properties. Herein, using simultaneously a combination of magneto-optical NPs provides new prospects in various medical fields.

In this study, we used negatively charged citrate-coated manganese ferrite and synthesized positively charged GNRs coated by CTAB to produce hybrid NPs of GNRs and CiMnFe2O4. These hybrid NPs were developed as contrast agents in magneto-motive ultrasound imaging (MMUS). In this regard, two different samples were made: the first one contained just CiMnFe2O4 (0.8 wt. %), and the second one was made of hybrid NPs of GNRs (0.4 wt. %) and CiMnFe2O4 (0.8 wt. %). Moreover, several characterizations were performed including UV-Visible spectrometry, transmission electron microscopy (TEM), and magnetic separation (SEPMAG) to examine the interaction of GNRs and CiMnFe2O4. The MMUS setup is depicted in Figure 1a which consisted of a magnetic coil with a steel core, and a capacitor bank that is charged by a half-drive inverter. After the charging of this capacitor, the magnetic field pulse is generated by an electronic switching device.

The results showed the hybrid NPs interacted electrostatically and small nanoclusters were generated with an average size of 55 nm. These NPs homogeneously embedded in a tissue-mimicking phantom reported a larger displacement of 19.42 μm rather than using just CiMnFe2O4 (8 μm) in MMUS when exposed to an external oscillating magnetic field of 740 mT. The MMUS image for the sample containing just CiMnFe2O4 is illustrated in Figure 1b, and the regions presenting higher displacements indicate where the NPs are located. Thus, based on the achieved results, GNRs and CiMnFe2O4 hybrid NPs can be considered as potential contrast agents in MMUS.

![Image](https://via.placeholder.com/150)

Figure 1: Experimental setup of MMUS (a) and MMUS image of the phantom containing CiMnFe2O4(b).

Partial Financial Support: CAPES, FAPESP, and CNPq.

Reference


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Gold nanoshells with magnetic cores for multimodal imaging and sensing

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Complex nanoparticles combining multimodal imaging with local sensing can provide a breakthrough in biomedical research, but reports demonstrating the contrast effect of a single nanosized probe in several imaging modalities together with its sensing performance are scarce. Gold nanoshells with magnetic cores and specific organic functionalization enable the development of such smart contrast agents. The present contribution describes complex gold nanoshells, whose surface functionalization is designed for pH sensing by means of surface-enhanced Raman spectroscopy (SERS) and which, at the same time, can be used as a multimodal contrast agent for MRI, fluorescence techniques and photoacoustic imaging (PAI). In addition, the potential of gold nanoshells as a platform for analytical applications is demonstrated in a case study on the functionalization of the gold surface with a urea-based receptor for sensing of fluoride anions.

Gold nanoshells with silica-coated Mn-Zn ferrite cores were obtained by a multistep procedure: (1) hydrothermal synthesis of Mn0.6Zn0.4Fe2O4 nanoparticles with the mean crystal size of 12 nm, (2) encapsulation into silica by the Stöber process, (3) electrostatic self-assembly of polyelectrolyte multilayer that alters the negative zeta potential of silica to positive values, (4) adsorption of negatively charged 30 nm gold seeds, (5) growth of the gold seeds to coalescence by reduction of a soluble Au(III) precursor. For the construction of a multimodal contrast agent capable of pH sensing, the gold surface was co-functionalized with 4-mercaptopentanoic acid (MBA) as a SERS-active pH sensor and 7-mercapto-4-methylcoumarin (MMC) as a fluorescent tag. 

In the case study on the use of gold nanoshells for sensing of fluoride anions, the nanoshells were co-functionalized with the molecular sensor N-(4-thiophenyl)-N’-(4-nitrophenyl)urea, synthesized directly on the gold surface, and the internal standard 4-nitrophenylthionaphthphenol (NTP). The SERS study in aqueous solutions of tetrabutylammonium fluoride (NBu4F) showed that the spectral response of the urea sensor was dependent on the concentration of the fluoride in the range of 10⁻⁶–10⁻⁳ mol L⁻¹.

Development of multimodal phantoms for Magnetic Resonance Imaging and Magnetic Particle Imaging

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Magnetic particle imaging (MPI) is an emerging quantitative imaging technology visualizing the 3D distribution of MNP used as tracers, in vivo. However, since the signal is generated only by the MNP, the surrounding biological tissue cannot be imaged directly. Therefore, another imaging technique, such as magnetic resonance imaging (MRI), is usually needed to provide anatomical information. For experiment planning, quality assurance, as well as validation, multimodal phantoms are required that serve both imaging modalities simultaneously. MPI phantoms are usually solid bodies with cavities of different sizes and geometries filled with different concentrations of MPI tracer. Biomimetic phantoms with cavities corresponding to anatomical geometries are used to simulate the uptake of MPI tracer in a given organ. Whereas MRI phantoms mostly consist of a gel (e.g., agar) to achieve the imaging properties of human tissue. These types of phantoms are usually produced by conventional processing techniques, such as molding and casting. In these existing forms, neither MPI nor MRI phantoms are compatible for imaging with the other modality. Due to the constraints of conventional manufacturing techniques, geometric freedom in the production of phantoms is limited.

In this work, we present the development of a multimodal phantom using additive manufacturing (AM) and address the challenge of selecting appropriate materials for the fabrication of MPI/MRI phantoms. Physical parameters of five commercially available materials for AM were evaluated, including absorption of MPI tracer, shore hardness, aging, and printing accuracy. Time-domain Nuclear Magnetic Resonance (TD-NMR) was used to analyse the MRI performance of these materials. The materials were checked for potential magnetic contaminations and unwanted MPI tracer absorption by magnetic particle spectroscopy (MPS, i.e., 0-dimensional PM). Of all investigated materials, silicone (Dreve, Biocite) exhibited the best properties (see Fig. 1) with a sufficient MR-signal performance ($T_2=26$ ms, $T_1=397$ ms) and the lowest absorption of MPI-tracer at the interface of AM materials ($900 \text{ ng(Fe)} / \text{cm}^2$).

From this, a phantom consisting of MR-visible silicon material (BioTec, Dreve) was designed and fabricated by AM (3D+) using photopolymerization (Syracem, Micromed Partikeltechnologie GmbH). The multimodal phantom was successfully imaged by MPI (preclinical MPI scanner, Bruker) and MRI (1T ICON, Bruker). Additive manufacturing of silicone components that are MRI visible and compatible with MPI tracers enable fabrication of functionalized commercial particles by exhibiting high catalytic activities and stable substrate conversion.

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Generation of reusable nano-biocatalysts by genetic engineering and functionalization of bacterial magnetic nanoparticles

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Magnetosomes are biogenic magnetic nanoparticles biosynthesized by magnetotactic bacteria. In the alphaproteobacterium Magnetospirillum gyroids, they consist of a mono-crystalline core of chemically pure magnetite ($\text{Fe}_3\text{O}_4$) that is surrounded by a biological membrane. Subtle control on each step of biomineralization generates nanoparticles with unique characteristics such as high crystallinity, strong magnetization and a narrow particle size distribution. In addition, the enveloping membrane is accessible to genetic engineering and provides sites for covalent attachment of foreign protein "cargo."[1]

Using optimized expression cassettes that enable the highly selective and controllable magnetosome display of functional moieties at distinct stoichiometries, a "set" of model particles was generated that feature one or several catalytically active enzyme proteins on the surface. Using the examples of the reporter enzyme glucuronidase (GusA) and the biotechnologically more relevant glucose oxidase (GOx), we could demonstrate that even multimeric and cofactor-dependent enzymes can be stably expressed on the magnetosome surface. Kinetic parameters suggest the successful oligomerization of single monomers into functional units, which might be facilitated and stabilized by immobilization on the magnetic carrier "material."[2]

In order to further enhance the flexibility of the magnetosome display system, we investigated the expression of versatile coupling groups, thereby turning the particle surface into a multimodal platform for the immobilization of complementary-tagged protein cargo. Utilizing the SpyTag-SpyCatcher biocompatible system, we coupled a SpyTag-equipped version of a phenolic acid decarboxylase (PAD) to SpyCatcher-displaying magnetosomes.[3] The functionalized magnetosomes outperformed similarly functionalized commercial particles by exhibiting high catalytic activities and stable substrate conversion. Moreover, they could be efficiently utilized as reusable bio-nanocatalysts in flow processes, thereby significantly expanding the genetic toolbox for particle surface functionalization.

Acknowledgement:
Structural and magnetic characterization of citrate-coated superparamagnetic iron oxide nanoparticles for magnetically controlled immune therapy

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Superparamagnetic iron oxide nanoparticles (SPIONs) are promising for biomedical applications such as drug delivery, imaging, and magnetic hyperthermia. In our work, we used water-based SPIONs coated with citrate molecules (SPION Citrate) to obtain highly cyto-compatible and stable particles in blood. In the magnetically controlled immune therapy, the T cells, which are part of the immune system, are loaded with such SPIONs and are guided into a certain region of the body using a magnetic field gradient. The aggregation behavior of SPIONs is crucial for proper utilization and this is determined by their interface properties. Thus, a detailed knowledge of the inter-particle structural organization and the resulting magnetic properties is of great importance to avoid thromboembolic effects caused by agglomeration of released particles during future in vivo application and optimize the nanoparticle response to the applied magnetic field.

SPION Citrate was synthesized and stored in dry form. To obtain the properties of interest described above, the dry particles were dissolved in water and immobilized in an amorphous matrix of poly(ethylene glycol) crosslinked with DMPA (2,2-Dimethoxy-2-phenylacetophenone). The morphology of the particles in water and in solid matrix was determined by small angle x-ray scattering (SAXS) and transmission electron cryomicroscopy (Cryo-TEM). The TEM and SAXS results indicated a formation of large particle aggregates with an average size of 60 nm. However, the magnetometry data on the immobilized SPION Citrate, crosslinked in polymer matrix, points to the classical superparamagnetic behavior of single particles with a small size distribution. The obtained blocking temperature of 154 K corresponds rather to a particle diameter of 10-15 nm.

As a future plan, small-angle neutron scattering (SANS) experiment combined with contrast variation will be performed to obtain information about the internal structure of the particle aggregation. Additionally, SANS in magnetic field will be performed to directly determine the ensemble’s magnetic size and clarify this surprising magnetic behavior.

This work was supported by OP RDE project ‘Strengthening interdisciplinary cooperation in research of nanomaterials and their effects on living organisms’ [CZ.02.1.01/0.0/0.0/17_048/0007421].


Commonly used methods for RNA isolation from biological samples are based on liquid-liquid extraction or solid-phase extraction. Very often, the commercial kits and methods for RNA isolation use chemicals such as phenol and chloroform, which are hazardous to work with and can also cause contamination of the final product. We wanted to develop a new method of RNA isolation from cells or from biological fluids that would be safer to perform and possibly more affordable as well.

It was previously described, that materials based on TiO2 have an affinity to nucleic acids thanks to their strong interactions with phosphate backbone. Nucleic acids are negatively charged and the charge of TiO2 under acidic conditions is strongly positive. In addition, it was suggested that the adsorption of DNA on TiO2 is caused by interaction between DNA and hydroxy groups on the surface of TiO2 [1]. Similar principles apply for TiO2 interactions with RNA.

In our work, we tested different materials based on TiO2 to determine their applicability for RNA isolation. Among other materials, we used newly developed TiO2 nanotubes coated with Fe3O4 (TiO2NTs@Fe3O4NPs, CEMNAT). Magnetic properties of this material offered advantage in higher affinity towards RNA as well as an easier and faster performance of the protocol. This material was also successfully used for SARS-CoV-2 viral RNA isolation.

Figure 1: Structure of TiO2 magnetic nanotubes, captured by SEM.
Combining iron oxide nanoparticles and fluorescent protein for selective magnetic nanoeating studies
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The heating properties of the magnetic nanoparticles (MNPs) have been extensively applied in medicine for thermal treatments of tumors, by taking advantage of the capability of the MNPs to absorb magnetic energy and dissipate it as heat when exposed to an alternating magnetic field (AMF). Only recently, this property has been explored for the regulation of enzymatic processes, where an extreme control of the local temperature is needed to obtain a fine tuning of the enzyme activity. This tuning can be reached by modulating the properties of the magnetic nanoparticles, such as composition, size, shape and aggregation state, or the frequency and field intensity of the AMF. A crucial point in finding the best activation conditions is the correct measurement of the local temperature reached during AMF activation at the active position of the enzyme. Commonly used systems, such as fluorophores or lanthanides, are not suitable for simulating the behaviour of a protein due to their small size and low complexity of their structure. Here, we report the use of fluorescent proteins, the Green Fluorescent Protein (GFP) or the Red Fluorescent Protein (RFP), as molecular thermometers immobilized to the magnetic nanoparticles, to simulate the one-pot activation of two proteins under AMF. These proteins possess, indeed, a temperature dependence decay of their fluorescence that can be easily monitored, furthermore, their emission spectra are compatible for a one-pot detection. We demonstrate the possibility to selectively activate the MNPs by adjusting the AMF conditions. Moreover, the differences in local heating observed among the different MNP systems under the same or different AMF settings support the feasibility to achieve simultaneously or sequentially different local temperatures in a one-pot scheme, paving the way for the implementation of a selective regulation of multi-enzymatic reactions.

Figure 1. A) TEM images and particle size distribution of the nanoparticles used. B) Photos of the nanoparticle suspensions at different times during the degradation process. C) Magnetic Hyperthermia and Photothermal measurements of PMAO-NPs at different AMF settings compared to PMAO-NPs. D) Temperature dependence of the AC magnetic susceptibility profiles of tumor tissues collected at different time points and iron concentration in the form of particles in the tumor calculated from the out-of-phase susceptibility data.
Reversible chain formation during magnetic hyperthermia experiments

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In addition to the AC field conditions or the particle average size, others factors, often neglected, may play a fundamental role on the heating capacity of magnetic nanoparticles during magnetic hyperthermia treatments. In particular, the organization of particles into assemblies, such as chains, as a consequence of the AC field exposure has been poorly studied. Previous theoretical works had shown the impact of chaining on the heating properties of magnetic nanoparticles [1] and very recently the formation of chains or columns along the magnetic field direction during hyperthermia experiments has been demonstrated experimentally [2].

In this work, we have used two types of particles (≈13 nm spherical and ≈26 nm octahedral) (Figure 1A) and several experimental set-ups to evaluate the chain formation over time during magnetic hyperthermia experiments. First, the particles were dispersed in a resin and this suspension was placed in a magnetic hyperthermia device with a closed coil. The alternating magnetic field was applied during 30 min. After, the sample exposed to the AC field and the control suspension was placed to a thermomixer at 60°C so that the resin fully polymerized. For small particles, long chains were observed by TEM in the sample exposed to the AC field but not in the sample not exposed to the AC field (Figure. 1B). In contrast, for bigger particles, macroscopic chains were observed in the sample exposed to the AC field only. The effect of chain formation is investigating using computation model. The dynamics of chain formation at different applied field times were studied using the 26 nm octahedral nanoparticles. An increase of the chain length over time under the exposure to the AC magnetic field was observed (Figure. 1C). Once the magnetic field was removed, chains started to break down. This chain formation during the magnetic hyperthermia measurements may be a critical parameter to consider in the study of the heating properties of magnetic nanoparticles in the frame of magnetic hyperthermia.

Figure 1: A) TEM images and particle size distribution of the nanoparticles used. B) TEM images of the magnetic nanoparticles (≈13 nm) in resin before and after AC magnetic field exposure C) Images of magnetic nanoparticles in resin when magnetic field is applied at different times.

A Pickering emulsion is an emulsion stabilized by solid particles that accumulate at the surface of droplets. Depending on the application, different types of particles can be utilized as stabilizers including magnetic particles that become a heat source when exposed to alternating magnetic fields.

The magnetic field-induced temperature increase of the emulsion system was recently shown, among others, to form colloidal capsules from Pickering droplets precursors [1]. While most researchers use an oscillating magnetic field because it is relatively easy to generate, there has been another approach, namely the use of rotating magnetic fields (RMF) which could yield a higher heat output. Our study presents the results of the calorimetric measurements in oil-in-oil emulsion stabilized by magnetic nano- and microparticles under the influence of RMF. In our system, such a field is produced by four separate magnetic fluxes shifted in phase and space by $90^\circ$ (Fig. 1a). The promising results show that RMF can be used for efficient heating of Pickering emulsion stabilized by magnetite particles (Fig. 1b).

**Fig. 1.** a) Experimental setup used for generating a rotating magnetic field. b) Temperature increase measured in magnetic Pickering emulsions under the rotating magnetic field (RMF).

Iron oxide nanoparticles (IONPs) are one of the most employed nanomaterials for biomedical purposes such as hyperthermia due to their high biocompatibility and their ability to release heat in response to different stimuli. Nanoparticle-mediated hyperthermia can be classified as magnetic hyperthermia (MHT) or photothermal therapy (PTT) depending on the activation mechanism: alternating magnetic fields (AMF) or near infrared radiation (NIR), respectively. Recent studies have shown that, in contrast to magnetic losses, optical losses remain invariant inside live cells. This PTT efficiency preservation represents a major advantage with respect to MHT. At the same time, heating mediated by IONPs is of particular interest to address therapeutics in some types of cancer requiring minimally invasive and efficient approaches. This is the case of peritoneal carcinomatosis, an aggressive spread of a primary tumour in the peritoneal cavity.

In this work, we have assessed the in vitro efficacy of combining PTT and mitomycin C (MMC) on peritoneal carcinomatosis in HCT-116 cell line. Initially, we have determined the average heat dose per cell released in order to perform dose ranging study. We have also studied the effects of the combination of PTT with MMC, a widely used chemotherapeutic agent. PTT was performed irradiating IONP-loaded cells with an 808 nm laser at 1-2 W/cm² for 30 minutes. Cell viability and cell morphology were evaluated 24 hours after treatment. The multimodal treatment was performed in cells loaded with both IONPs and MMC at different experimental conditions, varying the MMC concentration and the irradiation power. The intracellular average heat dose per cell was estimated by calorimetry under non-adiabatic conditions in IONP suspensions at the same irradiation conditions and iron concentration than the ones in IONP loaded cells. Cytotoxicity assays and cell morphology analysis indicates that PTT is able to reduce cell viability to 80% when temperature reaches 42ºC. Similarly, MMC by itself is able to reduce cell viability from 80% to 10% depending on MMC concentration and incubation time. However, multimodal treatment shows a stronger cytotoxic effect even using moderate heat and MMC doses. When we analyze the type of cell death produced by these treatments with Hoechst-33342, both apoptotic and necrotic cell death are found. The origin of the synergy between PTT and MMC is studied in deep. However, the combinational treatment using both approaches shows an appealing potential for cancer therapy which could allow for reducing chemotherapy dose and consequently, its undesired side effects.
The Impact of Alternating and Rotating Regimes on the Heating Characteristics of Magnetic Colloids and Dense Cellulose Structures.

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Magnetic hyperthermia is a well-established scientific field in nanomedicine. Thanks to the huge number of possibilities how to influence the hyperthermic indicators, this area always offers new and interesting research stimuli.

The hyperthermia efficiency itself and the heating effect is determined not only by the material properties but also by the technical-application factors. For this reason, we subjected our experimental materials to experiments in an alternating magnetic field (AMF) as well as in a rotating magnetic field (RMF). In general, according to known numerical models as well as comparative experiments, a higher efficiency is assumed in the case of the applied RMF.

As is shown in Figure 1, for the experimental Dextran FF sample, the d\(T/dt\) values are significantly different when compared in RMF and AMF. Such tendency can be changed in the systems of higher density. This affects the particles’ freedom of movement during field application, and thus there is a block of rotation. To research this, bacterial cellulose was magnetized in contact with magnetic fluid. By magnetic modification of bacterial cellulose, another range of potential applications is opened up including hyperthermia. Preliminary temperature evolution data of magnetized cellulose sample in RMF and AMF indicate a different behavior than in the case of a magnetic fluid.

Bacterial cellulose can be modified with a well-controlled amount of magnetic nanoparticles and can be potentially surgically located at the treated site. Such a system is promising for the synthesis of potential implants for multiple applications of an external magnetic field and repeated heating of cancer tissues. However, in the case of bacterial cellulose, it is necessary to consider the significant fixation of the particles in the cellulose structure.

The main goal of this study is to provide an analysis of various magnetic systems in the form of colloids and dense structures in conditions of rotating and oscillating magnetic fields.
Magnetic heating of superparamagnetic KFeO$_2$ nanoparticles for treatment of cancer

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ABSTRACT

Hyperthermia is a therapeutic treatment in which malignant cancer cells are destroyed by increasing the temperature to a range of 42–46 °C under applied alternating field. Superparamagnetic nanoparticles have attracted huge attention in cancer treatment due to their selective heating of cancer cells via targeting cancer cells under the application of alternating magnetic field. The hysteresis loss generation from single domain superparamagnetic KFeO$_2$ nanoparticles is zero due to its zero coercive and remanence field. In early theoretical approaches Neel and Brown calculated the switching probability under the assumption of coherent rotation, i.e., at any time — even during the reversal — the magnetic moments of the entire particle remain magnetized in the same direction, behaving like a single giant spin (superparamagnet). Under these requirements, the switching rate is described by the so-called Neel-Brown law. In addition to above, it has been reported so far that superparamagnetic nanoparticles may lose their heat energy due to Brownian and Neel’s relaxation mechanisms.

Keywords: KFeO$_2$, Superparamagnetic, Neel relaxation, Brownian, magnetic susceptibility.

Reference:
Magnetic properties of iron oxide FeO/Fe3O4 core-shell nanocubes tuned by the preparation method

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Superparamagnetic cubic iron oxide nanoparticles (IONPs) have shown great promise in cancer diagnosis and treatment due to their superior properties compared to the spherical ones of the similar size, such as higher magnetization, higher specific absorption rate (SAR) values1, better T1 relaxivity2 and higher cellular uptake3. Our aim was to synthesize functionalized superparamagnetic cubic IONPs with impressive magnetic and magnetic-thermal properties and low cytotoxicity as a potential agent for cancer treatment. In this study, monodisperse cubic IONPs with a high value of saturation magnetization were synthesized by thermal decomposition method and functionalized with 2,3-dimercaptosuccinic acid (DMSA) via ligand exchange reaction, and their cytotoxic effects on HeLa cells were investigated. DMSA functionalized cubic IONPs with an edge length of 24.5 ± 1.9 nm had a specific absorption rate value of 197.4 W/g Fe (15.95 kA/m and 488 kHz) and showed slight cytotoxicity on HeLa cells when incubated with 3.3 × 1010, 6.6 × 1010 and 9.9 × 1010 NPs/mL for 24, 48 and 72 h. The results show a promising potential on the use of the cubic IONPs functionalized with DMSA for biomedical applications. To the best of our knowledge, this is the first study to investigate both the cytotoxic effects of DMSA-coated cubic IONPs on HeLa cells and hyperthermia performance of these nanoparticles4.

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References

Synergistic effect of the doxorubicin loaded thermal and pH-sensitive nanocarriers on the different cell lines

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Hyperthermia has been considered as a promising therapy for cancer since the last century. However, currently, only a few of them are translated into the clinical stage indicating a ‘medically underexplored nanoparticles’ situation, which encourages their comprehensive biomedical exploration.

The magnetic iron oxide cores were synthesized by the microwave method and conjugated with DOX via pH-cleavable imine bonds by a thermo-responsive copolymer. This study presents, for the first time, (i) a comprehensive biological evaluation of our previously well-developed dual pH and thermo-responsive polymer-coated magnetic doxorubicin nanocarrier (MNC–DOX) and (ii) multidirectional assessments on the thermally induced synergistic effects of intracellular/ extracellular hyperthermia with the same type of DOX loaded magnetic nanocarrier in different cancer cell lines.

More specifically, this dual response system limited the cellular and systemic cytotoxicity compared to free DOX without AMF stimulation, enabling the lower side-effect when the therapy is applied in vivo. The thermo-chemotherapy treatment implemented with our system presented a much more potent and synergistic effect than either chemotherapy or magnetic hyperthermia alone, for multi-modal cancer therapy in nearly every studied condition.

Cell viabilities of RM1-CMV-LucF cells 24 h following either (A) direct treatment or (B) treatment after internalization. The asterisks refer to significant levels compared to the corresponding control experiment or the combined therapy; p < 0.05 (*), p < 0.01 (**) and p < 0.001 (***).

Reference:

Reacting elements in nanomaterials for multi-modal cancer therapy

Determining the key parameters to reach synergistic effects between magnetic hyperthermia and ROS production in ZnFe2O4 magnetic Nanoparticles.

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Current challenges in the field of cancer research have gradually shifted their focus from monotherapy to combination therapy for enhanced treatment effectiveness [1]. In this way, the fast evolution in the field of nanomolecules has led to the promising combination between nanocatalytic or chemodynamic therapy (CDT) with other kinds of therapies such as photothermal therapy (PTT) [2], photodynamic therapy (PDT) [3] and Magnetic Fluid Hyperthermia (MFH) [4] to improve their therapeutic results.

When talking about nanocatalytic therapies, the main idea is to use of the hydroxyl radical (·OH), the most toxic of the reactive oxygen species (ROS), to induce initial oxidative damage to the cell membrane, improving the permeability of the cell membrane and making it more sensitive to heat. This radical is produced by the disintegration of hydrogen peroxide (H2O2) through a Fenton reaction with a metal ion. In this way, great therapeutic effects have been reported to threaten breast cancer and osteosarcoma cell lines [4, 5]. However, it is imperative to study how the intrinsic parameters of magnetic nanoparticle (MNP) used as nanzymes affect the ROS production and heat release, to find the best relationship between them and improve the synergy between the therapies. In this work, a series of ZnFe2O4 MNPs with mean diameters <d> between 11-32 nm were studied. A detailed characterization study, including Proton-Induced X-ray emission (PIXE), Transmission Electron Microscopy (TEM), SQUID Magnetometry, Ferromagnetic Resonance (FMR), Electron Paramagnetic Resonance (EPR) and Specific Loss Power (SLP) was performed, unravelling a compromise between the heating efficiency of the MNPs and their ROS production. Values of SLP up to 1440 w/g and concentration up to 1000 nM of hydroxyl radical (<OH>) were obtained. (see Figure). The optimal size of the MNPs for the combination therapy is in the range of 20-25 nm.

Figure. a) SLP in function of <d> for samples dispersed in toluene b) Angular dependence of HR for sample with <d> 25 nm. c) EPR spectrum and the corresponding fitting obtained. A) Sample AM12. B) Sample AM28, measurement 10 min after addition of H2O2 at room temperature in pH = 5. (+) indicate the characteristic peaks of <OH>

Reference:
Investigation of AC hysteresis from magnetic nanoparticle suspensions using magneto-optical methods

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Magnetic nanoparticles (MNPs) exposed to high frequency alternating magnetic fields, can generate localized heat and induce death of cancer cells; an effect termed magnetic hyperthermia (MH). AC magnetometry measurements of MNPs can quantify the heating effect, eliminating multiple systematic errors confronted by conventional calorimetric methods [1]. A new microscope was used here based on magneto-optical methods using Faraday rotation to determine the AC magnetisation of samples instead of conventional inductive pick-up coils. This increased the highest frequency at which measurements can be performed compared to coil-based magnetometry. The microscope could also measure AC magnetisation with spatial resolution of <0.5 μm, and simultaneously probe the fluorescent lifetime, which is advantageous for simultaneous biological structural and functional imaging.

In this work, AC hysteresis loops of magnetite and maghemite nanoparticle suspensions with different sizes were measured at different frequencies using the microscope (Figure 1). For all samples, with increased field amplitudes, AC hysteresis evolves from minor to major loops. Nanoparticle size has a dominant effect on the uniaxial effective anisotropy, we simulated systems with different particle-intrinsic parameters (size, anisotropy) and experimental conditions (frequency, interactions). We determined four regions (I-IV) of magnetic behaviour as a function of relative anisotropy (anisotropy field with respect to the amplitude of the ac field), that dictate the SPA in MFH experiments through the area enclosed by hysteresis loops (see Figure) [4].

The boundaries between regions change with all of these parameters. We analyzed linear MNP arrangements and found out that, for the low relative anisotropy range, dipolar interactions increase the SPA while they are detrimental for the range of high relative anisotropy. This resolves the seemingly contradictory results of interaction effects in this kind of aggregates reported in the literature [1,2]. For low relative anisotropy regions, we also explained how the enhancement of the SPA by dipolar interactions (reflected by an increase in coercivity) is actually caused by the shift between the local and the applied magnetic field [5]. We also provide a simple, analytical tool aimed at the design of MNPs and the choice of the experimental conditions for optimal heating. Through the thermal interpretation of its validity range, we conclude that systems with low-thermal-fluctuation influence are the best candidates for MFH due to their high SPA values.

Figure 1. AC hysteresis loops measured with magneto-optical methods. (a) magnetite nanoparticles with core size of 8.5nm under 129 kHz field. (b) magnetite nanoparticles with core size of 10.5nm under 129kHz. (c) maghemite nanoparticles with core size of 17.4nm under 129kHz. (d) the same as (a) but under 508 kHz field. Different loops on each plot show four different AC magnetic field amplitudes used.

Multifrequency hyperthermia characterisation by calorimetry and dynamic magnetisation

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Magnetic field hyperthermia (MFH) is a promising, novel approach to cancer treatment. First, magnetic nanoparticles (MNP) are injected into the patient so that they accumulate within the tumour tissue. High frequency-time-varying magnetic fields are then applied. The magnetic field causes the MNP to dissipate heat into their immediate surroundings. This localised heating is used to inflict thermal damage to the cancer cells, leaving the surrounding healthy tissues intact. MFH therapy has already shown great promise in clinical trials. The synthesis of new MNP types engineered to maximise their heating performance and biocompatibility has been the subject of many recent studies. Measurements of the MFH heating performance of nanoparticles are often reported in the literature. A major interlaboratory study recently highlighted the lack of consistency between MFH characterisation measurements conducted at different laboratories using different calorimetric apparatus and analysis2. In addition to differences in the sophistication of the measurement and analysis methods, this study also highlighted that the limited range of frequencies employed in many laboratories contributed to an incomplete picture of the overall MFH behaviour of MNP. The study highlighted the need for improved accuracy and standardisation in MFH characterisation measurements to support MFH therapy in reaching higher technology readiness levels.

To address this need, we present a comparative study between MFH characterisation measurements performed using two distinct methodologies. An AC magnetometer (Nanotech Solutions, Spain) measures the dynamic hysteresis of MNP (Drive fields: 10-100 kHz, 8 kA/m - 32 kA/m), with the specific loss power (SLP) heating characteristic calculated via the area enclosed by this loop. A homemade calorimetry system (Drive fields: 23 kHz, 177 kHz, 2 kA/m - 10 kA/m) was used to measure specific loss power for the same MNP samples, with the SLP calculated via the corrected slope technique3. Data sets spanning a broad range of drive-field frequencies and amplitudes were measured using both techniques for commercial nanoparticle systems (Ferucarbotran (Meito Sangyo, Japan), RCL-01 (Resentum Creatis, UK) and Synomag (Micromod, Germany)). The SLP datasets spanning multiple drive-field parameters were analysed and used to calculate the intrinsic loss power (ILP) for each MNP system4. A detailed analysis of the measurement results indicates significant agreement between the multifrequency characteristics measured using the two techniques demonstrating the benefits of multifrequency characterisation methods using multiple complementary techniques.

Theoretical three-dimensional predictions for spatial focusing of magnetic hyperthermia using field-free point-line concept

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Magnetic hyperthermia is a promising, non-invasive approach that has the potential for tumor treatment at deep tissue [1]. This method is based on using an alternating magnetic field at radiofrequencies with amplitudes in the range of 10–30 kA/m to generate heat through magnetic nanoparticles (MNPs), which have been delivered to the tumor site [1]. Precisely, studies have shown that conventional hyperthermia has many advantages, namely, no depth limitations, high heating performance, remote and temporal controllability, and is biocompatible since benefiting from non-ionising radiation [2]. At present, due to the limitations of drug-targeting methods, only a small amount of the injected MNPs can be delivered to the desired area and the rest are distributed throughout the body, specially accumulated in the exocrine organs (liver, spleen, or kidneys). Thus, the application of conventional hyperthermia can lead to damage to healthy tissues, wherein MNPs exist in the region of the magnetic field [3]. To minimize the damage to the non-targeted areas, the spatial focusing heating control using field-free point (FFP) or field-free line (FFL) at the targeted area has been proposed and developed [4, 5]. The spatial-thermal resolution and specific loss power (SLP) of nanoparticles have mainly been investigated through experiments [4, 5]. To optimise the treatment protocols as well as invasive temperature monitoring during the treatment, a model to predict the spatial-thermal resolution and SLP of MNPs is required. Although a one-dimensional model for spatial focusing using FFP and without considering the magnetic field direction to predict the spatial-thermal resolution and SLP was introduced [6], the model may not provide enough information for the prediction necessary before applying it in practical use. In addition, as far as we know a model for the spatial focusing using FFL (two-dimensional) has not yet been considered. Thus, a multi-dimensional model to predict the spatial-thermal distribution and SLP using FFP/FFL should be considered. In this paper, by using the Shliomis (MRES) equation, the temperature/SLP distribution in three dimensions for nanoparticles is investigated. As an example for the SLP spatial focusing using FFP is shown in Fig. 1. From the distribution of the SLP in three-dimensions, the bio-heat equation, and COMSOL Multiphysics software, the temperatures distributions of nanoparticles in a human brain are also investigated. This model will be tested through experiment in future works.

References


Poster #27

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Poster #28

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Capturing magnetic nanoparticles with external magnetic fields in the fluidic flow
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Magnetic nanoparticles (MNPs) have recently attracted a lot of attention in biomedical applications due to their exceptional qualities such as low toxicity, biocompatibility, and large surface to volume ratios. One of the most important applications of MNPs is magnetic field-based bio separation systems, which are gaining popularity due to their vast applications in biomedical research, clinical diagnostics, and biotechnology. Moreover, MNPs can be used as controllable carriers of medical agents and flow through the bloodstream. Targeted application of magnetic field can be applied to capture the MNPs at a target spot.

The effectiveness of magnetic bio separation and/or targeting is determined by the interaction of numerous parameters, including the flow velocity of the fluid containing magnetic nanoparticles, the size of the nanoparticles, and the strength of the external magnetic field. In order to build an efficient micro fluidic bio separation device, it is necessary to understand the particle behaviour in the fluidic flow, as well as the ideal range of velocity, nanoparticle diameter, and magnetic field strength.

In this study, we investigated the capturing behaviour of MNPs in phosphate buffered saline solution upon application of external magnetic field. For this purpose, a modified optical microscope setup is used which is equipped with light polarization options and an AC/DC external magnetic field generator up to 500 mT. The external magnetic field was applied perpendicular to the flow direction to observe capturing phenomena. Effect of three parameters on capturing was studied: i) the velocity of the fluid containing the magnetic nanoparticles, ii) the diameter of the magnetic nanoparticles, and iii) the strength of the magnetic field. The magnetic flux density necessary and sufficient to capture the MNPs for a short time period (blue data in Fig. 1) and to long-term capture the MNPs (red data in Fig. 1) were measured at different constant flow rates and shows linear increase. Furthermore, a mathematical model will be developed to combine these findings and aid in the design and development of innovative micro fluidic bio separation system.

Figure 1: Magnetic field necessary to capture MNPs for a short time period (blue) and to long-term capture (red).

Visible Light-Driven Amide Synthesis from Thioacid and Amine with CdSe QDs-Coated Magnetic PMMA nanocomposites in an Aqueous Solution
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Amide bond formation is one of the most basic important reactions in organic synthesis of numerous organic molecules such as peptides, natural products, synthetic polymer and pharmaceutical agents. To obtain higher yield and produce less organic waste, CdSe semiconductor quantum dots (CdSe QDs) are the one promising photocatalysts for the synthesis of amide from thiocids and simple amines in water at room temperature by visible light irradiation. However, the toxicity of cadmium leads to the requirement of efficient separation and recovery of the QDs out of the reaction mixture for avoidance of Cd contamination in the system. Moreover, the reported separation approaches need intensive labor and high energy consumption and could lead to the loss of the catalysts.

From properties of magnetic nanoparticles (MNPs), the attachment of MNPs to the catalyst could provide superparamagnetic character on the catalyst with colloidal stability and easy removal using magnet. Nonetheless, MNPs are semiconductor with small bandgap. The direct contact of CdSe QDs and MNPs could lead to fast photogenerated electron-hole recombination and photodissolution of MNPs, which could reduce photocatalytic activity of CdSe QDs. To maintain photocatalytic activity, facile insertion of PMMA as insulator to prevent electron-hole transfer between the photocatalyst and MNPs are required. In this work, novel composites of MNPs embedded biocompatible polymer PMMA and CdSe quantum dots were fabricated and investigated as photocatalyst for synthesis of amide bonds from thiocids and simple amines in water solvent at room temperature under visible light irradiation with ease of separation and reusable, high activity, mild and safe conditions.
Highly selective separation of magnetic nanoparticles using dynamic magnetic fields: a novel approach for MPI tracer purification

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Additive manufacturing (AM) is characterized by a high degree of design freedom and individualization and thus, magnetic nanoparticles (MNP) intended for biomedical applications such as site-specific imaging in vivo, cancer detection, or cancer therapy must exhibit a specific magnetic behavior resulting from a combination of crystal structure, shape, size, and size distribution. To exploit the full potential of the applications ensuring their safety and treatment success, the MNP properties must be tuned very precisely. Therefore, it is often challenging to find a synthesis route that provides sufficiently repeatable results, since many synthesis methods vary in both, MNP size and shape. Magnetic separation can be used to remove the low-performing components of a synthesis product and thus recover the valuable materials in high purity. Static magnetic separation is a versatile technique for sample quality enhancement by addressing the magnetic moments of MNP [1].

Here, we will present a novel dynamic magnetic separation approach for sample purification that exploits both, the magnetic moment and the anisotropy of MNP. A sophisticated separation system was modeled, designed, and manufactured for purification to improve the performance of Magnetic Particle Imaging (MPI) tracers. The system uses a special separation column filled with magnetic beads exposed to a high-frequency magnetic field (f = 486 kHz, B = 10 mT).

Our results show that purification of a high-performance MPI tracer using dynamic magnetic separation resulted in a further increase in MPI signal, such that the signal amplitude was 3.2-fold higher compared to the MPI gold standard Resovist®. This indicates the capability of the system to separate MNP according to their magnetic moment and anisotropy. In the future, this new separation approach could be used for purification and quality assurance of MPI tracers.

Figure 1. (a) Dynamic magnetic field generator. (b) Separation column filled with magnetic (orange) and non-magnetic beads (grey).

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References:

Magnetic anisotropy in polymeric magnetic hybrid material induced by vat photopolymerization additive manufacturing

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Additive manufacturing (AM) is characterized by a high degree of design freedom and individualization and thus, ideally suited for the production of specimens for biomedical research. A fast and cost-effective AM variant for producing medical specimens is Digital Light Processing (DLP), in which the specimen is created layer by layer from light-curing photopolymer. This process can be used to fabricate parts from a wide range of materials with high detail and precision. In addition, the mechanical, electrical, magnetic, or optical properties of the photopolymers can be influenced by incorporating additives [1-3], e.g., materials that are dissolved or dispersed in small quantities into the photopolymer to induce and adjust desired material properties.

Different magnetic composites of liquid photopolymer and homogeneously distributed magnetic nanoparticles (MNP) as a magnetic additive were prepared using a special synthesis reactor. From this cylindrical standard specimen (diameter 5.2 mm, height 5.2 mm) were printed. For process and quality control, established magnetic measurement methods were used linear and non-linear dynamic susceptibility together with static magnetization measurements. A homogeneity demonstrator was developed composed of ten standard specimens stacked in building direction. Magnetic analysis of the individual standard hybrid material specimens showed that no sedimentation of the MNP occurred during the manufacturing process (duration 8 h, height 10 cm) for any of the fabricated magnetic composites. However, the investigation of the magnetic properties revealed an unexpected easy-plane (perpendicular to the building z-axis) anisotropy in the standard sample bodies (see Fig. 1). This indicates that the MNP prefer to align their magnetic moments within the printing plane. Results show that the formation of magnetic easy plane anisotropy in the AM process is influenced by the MNP type and concentration used. Due to this special behavior of the manufactured bodies, the orientation of these could be visualized using multicolour magnetic particle imaging (MPI) in a preclinical MPI scanner (Bruker).

The AM of materials with anisotropy magnetic behavior might find broad application in magnetic labelling, such as Magnetic Particle Imaging-guided endovascular devices.

Figure 2. (a) Cylinder made of polymeric magnetic hybrid material additively manufactured in building direction z. (b) Magnetic measurement (magnetic particle spectroscopy) of the cylinder made of magnetic composite at different angles θ with respect to the building direction z.

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References:
Improved Magneto-Microfluidic Separation of Nanoparticles through A Scalable Magnetic Control Strategy to Suppress Off-Target Nanoparticle Transport

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Formation of the β-Cyclodextrin–Curcumin Inclusion Complex

Advances in nanomedicine have enabled delivery of therapeutics with reduced off-target effects. However, passive and active targeting strategies employed thus far fail to meet the expectations for enhanced, selective transport of drugs, particularly in hard-to-access tissues such as deep-seated solid tumors. Two approaches proposed to overcome such limitations are the use of external forces and harnessing biological agents to improve the drug transport. Magnetotactic bacteria (MTB) that biomineralize iron-rich nanocrystals merge the benefits of both strategies [1]. Common techniques for magnetically-assisted delivery of nanoscale drug carriers suffer from lack of scalability and selectivity for deep targets. Recently, we reported on the capability of MTB to act as flow mediators due to their optimal magnetic and hydrodynamic properties under RMF. Here, we augment the scalable magnetic actuation scheme by rendering it selective through addition of a magnetostatic field.

By superimposing a magnetostatic field onto a uniform rotating magnetic field (RMF) and using MTB as a unique flow mediator, we transport nanoparticles (NPs) as model drug carriers in locations far from the source of the magnetic field. A microfluidic chip consisting of a central chamber as the model target tissue, surrounded by four off-target tissue chambers was fabricated. Such a design allows comparing different sizes of magnets placed at varying distances from the center. The magnetostatic field distribution, calculated through finite element modeling using COMSOL Multiphysics, indicates the ability to adjust the resolution of the zero-point in the central chamber (Fig. 1A). PV analysis of the torque-driven translational velocity of MTB in the wells containing only the bacterial suspension demonstrates complete suppression of motion in off-target chambers while MTB still generated flow in the target chamber (Fig. 1B).

Contact pinning lines centrally incorporated inside each well confined collagen in the center of each chamber, while an MTB-NP mixture was added around the tissue-mimicking compartment. RMF was generated by an electromagnetic setup composed of eight electromagnets. Two different actuation schemes were applied for 1 h: i) RMF alone and ii) selection field which is RMF superimposed with magnetostatic field from NdFeB magnets. Compartmentalized collagen and MTB-NP suspension. (D) NP transport under RMF and selection field. Contact pinning lines centrally incorporated inside each well confined collagen in the center of each chamber, while an MTB-NP mixture was added around the tissue-mimicking compartment. RMF was generated by an electromagnetic setup composed of eight electromagnets. Two different actuation schemes were applied for 1 h: i) RMF alone and ii) selection field which is RMF superimposed with magnetostatic field from NdFeB magnets. Patterning was confirmed using labelled collagen type I and fluorescent NPs. (Fig. 1C). NP transport into the collagen was quantified in Fiji where integrated signals were normalized to the zero time point. Transport of NPs was reduced to the diffusion level in off-target areas when exposed to the selection field (Fig. 1D), while more than 40% of the magnetically enhanced transport was maintained in the target area. An even higher percentage is expected to be achieved in larger setups at animal or human scale. Here, a tradeoff between suppression and enhancement is attributed to field gradients acting against the transport to the target due to its proximity to the coils. This actuation scheme has the potential to pave the way for scalable and selective magnetic manipulation for drug delivery applications in combination with MTB or synthetic analogues as locally controlled flow mediators.

Fig. Mechanism of primary agglomeration of βCD-coated IONP through the formation of a 2:1 βCD-CUR inclusion complex. The addition of CUR to the nanoparticle solution is expected to promote both 1:1 and 2:1 βCD-CUR inclusion complexes on the IONP surface with sketch and results of the experimental setup with microfluidic channel (implemented in an enlarged scale) with a micropillar used for the magnetic separation when the field-induced aggregates accumulate around the magnetized micropillar and are separated from the suspending liquid under flow.

Red blood cell magnetophoresis as a function of oxygen partial pressure.

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Red blood cell (RBC) magnetophoresis is the magnetic field-induced cell motion in viscous media such as blood plasma or physiologic saline solutions. We studied it as a function of the concentration of dissolved oxygen in normal RBCs using cell tracking velocimetry (CTV, Fig. 1A) [1]. The hemoglobin (Hb) magnetic susceptibility changes from diamagnetic (when fully oxygenated, oxyHb) to paramagnetic (when fully deoxygenated, deoxyHb) resulting in a small shift in the RBC diamagnetic susceptibility from lower than that of water (-9.05×10⁻⁶) to a higher than that of water, respectively. We systematically measured the resulting changes in the RBC magnetophoresis as a function of incremental changes in the solution O₂ concentration (measured by the O₂ partial pressure, pO₂) and compared them with the O₂ equilibrium curve (OEC, by Hemox Analyzer and Blood Oxygen Binding System, BOBS™).

The de-identified, normal blood samples were procured from the Cleveland Clinic Pathology discarded tissue repository with the approval of the institutional ethics committee. The resulting dependence of the RBC magnetophoretic velocity, \( u_m \) (in \( \mu \text{m/s} \)) on pO₂ (in millimeters) resembled an inverted, sigmoidal shape characteristic of the OEC curve (Fig. 1B) indicating that the intracellular Hb magnetic moment changes according to the kinetics of the cooperative Hb-O₂ binding. Understanding the detailed mechanism of RBC magnetophoresis may provide additional means to diagnose and treat hematological diseases.

Magnetoresponsive nanocomposite aggregation during magnetic targeting

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The polymer, polyethylene glycol (PEG), is a stable, biocompatible, hydrophilic polymer, which has been extensively studied for applications to drug delivery. Moreover, PEG reduces the response of the immune system to nanoparticles. To reduce the clearance of the nanoparticles from the circulation, thereby allowing a longer circulation time and more nanoparticle accumulation at the target site, MNPs are prone to aggregation due to magnetic dipole-dipole interactions or Van der Waals forces which lead to their detection by the mononuclear phagocytic system (MPS) before they can reach their target sites, thus, limiting their biomedical applications. To generate the magnetic field, we used a Neodymium 50 type magnet (NdFeB50) with a maximum energy product (BxH) of 50 MGOe. During magnetic particle targeting, 20 ml of the model suspensions are injected by the syringe pump in the mean flow into the artery model. In the present experiment, the MC_PEG delivery at the targeted site is achieved by flow-mediated particle transport. The evolution of the functionalized magnetoresponsive clusters build-up is acquired at a frame rate of 30 frames/s. The MP’s deposition and the magnetically induced chain length are investigated at the end of the injections (after 30 s).

The effect of SPIONs modified by aluminium nanoparticles on the growth of S. aureus and E. coli

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Understanding the importance of methodology in traditional medicine could provide us with additional knowledge about the development of new drugs for serious diseases. Antibiotic resistance poses a significant threat in the treatment of bacterial infections. Ethnobotany provides us with a lot of information about plants with remarkable antibacterial effects, such as neem (Azadirachta indica). Furthermore, nanomedicine brings additional possibilities, thanks to different types and variations of nanoparticles. In this work, we focused on a new type of aluminum nanoparticles (AlNPs) which were synthesized by the green method from the leaves of (AlNPsN). SPIONs (Fe3O4) were modified with chitosan (300 rpm, 25 °C), then purified on a magnet. SPIONs/Chito were subsequently modified with AlNPsN (300 rpm, 25 °C, 6 h). Afterwards, the particles (SPION/Chito/AlNPsN) were washed with phosphate buffer (pH 7) and their properties were studied on bacterial cultures (S. aureus (MSSA, MRSA) and E. coli), which were grown reproducibly in a pure medium (the areas under the growth curves (AUCs) were considered as a baseline). The antibacterial activity of particles was observed on bacterial growth curves, which were measured at 450 nm/540 nm. Following the addition of AlNPsN, the minimum inhibitory concentrations (MICs) and the minimum bactericidal concentrations (MBCs) were observed to be lower for E. coli (MIC = 310 µg/mL, MBC = 630 µg/mL) than for S. aureus (MIC = 470 µg/mL, MBC = 960 µg/mL). The study provided initial information on the effect of newly synthesized nanoparticles on S. aureus and E. coli.
The effect of SPIONs modified by silver nanoparticles and vancomycin on the growth of S. aureus and E. coli

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Biodegradable PLGA-Based Magnetic Nanocomposites for Magnetic Target Retention and Sustained Release of Triamcinolone Acetonide from Detachable Microneedles

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Triamcinolone acetonide (TA) is a well-known synthetic corticosteroid used as an anti-inflammatory drug to treat some autoimmune diseases such as psoriasis, psoriatic arthritis, and alopecia areata. Furthermore, TA is commonly used to treat allergic rhinitis, acne, and aphthous stomatitis. Although injection. To overcome the problems, intralesional injection of 10 to 40 mg/mL of TA is usually used for the treatment to provide sustained therapeutic level. The use of large drug dose can cause many side effects including skin atrophy, angiotelectasis, women's menstrual disorders, rupture in the injection sites and adrenal suppression. To prolong therapeutic level without use of large drug dose, encapsulation of TA in slow biodegradable polymer or poly(lactic-co-glycolic acid) (PLGA) is necessary.

Dissolving microneedle treatment is one type of transtranscutaneous drug delivery approaches. This treatment uses arrays of biodegradable polymer microneedles to provide controlled drug release into a cutaneous tissue. Compared to hypodermic injection, this route is non-invasive, rapid, pain-free, and possible for self-administration. Moreover, the microneedles may reduce the spread of disease from needle-reuse and needle-based injury.

Dissolving microneedles with detachable design have been extensively studied because of their controlled and sustained drug delivery ability of the polymers. Nonetheless, the polymers generally have very weak mechanical properties. Magnetic nanoparticles (MNP) are interesting materials when forming composites with polymer particles due to their high mechanical properties. Furthermore, existing of magnetic properties from MNPs show good potential to provide high retention and good localization of polymer particles to improve drug release profile and minimize side effect from drug. In this work, the microneedles made from composites of MNPs and TA loaded PLGA particles will be investigated. The microneedles with 50 mg MNPs loaded composites could improve mechanical strength of the needles up to 44% (2.3N at compression displacement 200 µm). Furthermore, the composites with 25 mg MNPs loaded composites show slower in vitro TA release profile when apply magnet about 71% cumulative release on 20 days (compared to 90% cumulative release of without magnet applying condition). The MNPs loading into these composites show good potential to fabricate a new microneedle-drug delivery system with improved mechanical properties, magnetic target retention and sustained drug release.

Figure: SPIONs modified with chitosan followed by AgNPS and vancomycin to monitor their antimicrobial activity with an aim to establish their potential for further targeting of the injection site.

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The magnetic field generated by single or multiple magnets for the magnetic drug targeting process

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Single magnets or multiple magnets configurations can be used to conduct the drug targeting process. A permanent magnet assembly consists of two or more magnets in an integrated magnet system designed to obtain an increased magnetic field. The main challenge for magnetic drug targeting (MDT) is that the magnetic gradients drop off fast when the distance from the magnet's surface increases. Using multiple magnet combinations, we wanted to investigate the differences and advantages of their magnetic fields compared to the ones generated by single magnets. This paper aims to investigate both numerically and experimentally the magnetic fields generated by several single neodymium permanent magnets (NdFeB) and multiple magnet combinations used in magnetic drug targeting. The heights at which the magnetic fields were measured are closely related to the fact that most organs are not at a distance more prominent than 4 centimetres from the skin's surface. The obtained magnetic field values were used to analyse a series of magneto-rheological fluids (MRFs). The model suspension of magnetic carriers used in experiments was obtained, mixing blood analogous carrier fluid (CF) with PEG_CMC (sizes in the range 80–150 nm), dispersed in distilled water, with 0.1% mass concentration, silver particles (size in the range 8–10 μm), and iron particles with two different dimensions (range 4–6 μm and range 8–10 μm), Carl Roth GmbH, Karlsruhe, Germany. Magneto viscous characteristics were measured using a rotational rheometer (MOR 300, Physica, Stuttgart, Germany).

Molecular Insights of the Oxidation Process of Copper-Zinc Ferrites Nanoparticles

Coated by a Polymer Layer

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The clinical use of MRI has been continuously developed since 1973, when Paul C. Lauterbur1 collected the first MRI images, later enhanced in quality upon the introduction of gradient field selectors by Peter Mansfield. Lauterbur and Mansfield were awarded the 2003 Nobel Prize for their work. Meanwhile, two revolutionary ideas were introduced, namely functional MRI and the use of magnetic contrast agents. The first commercial MRI contrast agent, Magnex® (Gd-DTPA) was presented in 1988. Unfortunately, there are several reports on the nephrotoxicity of gadolinium that result as well from concentration-dependent deposition of Gd in the brain revealed as high signal intensities in the globus pallidus and dentate nucleus on enhanced T1-weighted images2. This is why iron oxides and ferrite nanoparticles have been intensively researched as alternative MRI contrast agents. However, the biomedical application of ferrite and iron oxide nanoparticles is limited by the aggregation phenomenon3. The use of polymer coatings can prevent this negative phenomenon3. We showed that the coatings based on ionic derivatives of chitosan4,6 ensured the stability and biocompatibility of iron oxide nanoparticles5. Importantly, the applied derivative can form functional metal-polymer connections by chelating relevant metal ions. Moreover, such coating enables further functionalization of the nanoparticles by applying oppositely charged polymers in the so-called “layer-by-layer” approach6. However, there are reports that the attachment of ligands via anchor groups to nanoparticles may cause changes on the particle surface, such as oxidation or surface degradation8. Oxidation process can reduce the saturation magnetisation of iron nanoparticles11. Although the appropriate ligands can reduce spin-spinning in the surface region, Salkin and coauthors12 showed that a higher surface density of capping molecules improves the magnetic properties of iron oxide nanoparticles.

The main goal of the project was to investigate the influence of the polymer layer (a cationic derivative of chitosan and dextran, PEG) on the magnetic structure of copper-zinc ferrite nanoparticles. For the application of copper-zinc ferrite nanoparticles as contrast agents in magnetic resonance imaging (MRI) or in magnetic hyperthermia, their surface has to be coated by a polymer or surfactant layer. This modification can influence the surface oxidation state and the magnetic properties of the particles. In this project, the effect of the layer of three polymers, cationic chitosan, cationic dextran, and polyethylene glycol on copper-zinc ferrite nanoparticles was evaluated. For this purpose, X-ray absorption spectroscopy (XAS) and X-ray magnetic circular dichroism (XMCD) measurements were used, thanks to which the local magnetic and electronic properties of the particles' surface area were examined with and without surface modification. The local structures around the Cu, Zn, Fe, and O sites were investigated as reflected by X-ray Absorption Spectra. Based on a multivariate analysis supported by 3P/Mo/SAXS and ICP-OES data, the nanoparticles composition was determined. To further explore the structure of all obtained nanoparticle systems, XPS spectra of all polymer layers were analyzed to check the chemical states.

Reference
NP-cellular hitchhiking system for targeted combination therapy and diagnosis of glioblastoma

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Glioblastoma (GBM) remains an incurable tumor and there is a paramount need for more effective therapeutic approaches, taking into consideration the Blood Brain Barrier impediment. In this project, we propose a novel nanoparticle (NP) cellular hitchhiking system (NPCHS) for GBM treatment. Here, monocytes were conjugated with PLGA NPs packed with the drug paclitaxel (PTX) and Super Paramagnetic Iron Oxide nanocubes (SPIOs) which will bestow the system with MRI contrast, magnetic targeting and hyperthermia treatment while monocytes will provide a direct targeting to GBM by natural chemotaxis. For this end, fluorescently labelled plain and PTX-loaded PLGA NPs were synthesised using the nanoprecipitation method, and fully characterised for their physiochemically properties and drug loading efficiency using DLS, Zeta potential, TEM, HPLC and ICP-MS. The NPs were screened for toxic effects in relevant human and mouse cell lines, namely; monocytes, endothelial cells and glioma cells, using high content screening and image based flow cytometry systems. The optimal ratio of NP-cell conjugation was determined. Next, SPIO nanocubes, approximately 20 nm in size were loaded into the PLGA NPs. MRI measurements of SPIO loaded PLGA NPs or U87 cells incubated with SPIO-loaded NPs revealed the increase of r2 relaxation rates with increasing Fe concentrations. In vivo chemotaxis was investigated using optical imaging with the IVIS Spectrum and via intravital microscopy, in subcutaneous and orthotopic glioma tumors following intravenous injection of NP conjugated monocytes. Tissue slices from tumors and major organs were investigated for targeting and therapeutics using H&E staining and immunohistochemistry. In general, formulation showed homing ability towards GBM tumors, in vivo, promising a potential for targeted GBM treatment.

Trifunctional Fluorescent Cobalt Ferrite Nanoparticles for Hyperthermia Therapy, Cell Probing and Drug Delivery

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Here we have reported a new protocol for drug delivery from hollow sphere cobalt ferrite nanoparticles (HCF NPs). The structure and crystalline size of HCF NPs are analysed by XRD measurement and the morphological information is obtained from FESEM & TEM analysis. Here the HCF NPs are properly designed for delivery of dopamine (DA) as anticancer drug to cancer site. The DA polymerizes to its giant molecule polydopamine (PDA) inside hollow HCF in presence of TRIS buffer at higher pH 9 and a composite, HCF-PDA is formed. Being giant molecule polydopamine remain stable inside the hollow particles, but when these HCF-PDA come in contact of low pH i.e. pH 5 (cancer cells pHi), free DA start to be released. The DA release studies are monitored by UV-visible spectroscopy with progress of time at two different pH and temperatures. At hyperthermic temperature (45 °C) release enhances compared to physiological temperature (37 °C). It has been observed that HCF-PDA has a fluorescent property whereas DA has no such effect. So, tagging of HCF-PDA with cancer cells can also be monitored by fluorescence imaging. Hence, we have successfully synthesized trifunctional HCF-PDA composite which can serve three purposes like cancer cell probing, hyperthermia therapy and drug delivery.

Figure 1. A) A representative sketch of the proposed NP-cell formulation. B) In vivo homing of NPCHS in subcutaneous glioma tumors. C) In vivo homing of NPCHS in orthotopic glioma tumors.
Hybrid iron oxide core@mesoporous silica shell nanoparticles for magnetic hyperthermia, photothermia and drug delivery

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Designing hybrid nanoparticle platforms responding to external fields such as radiofrequency magnetic field and light has become a great challenge for the development of new treatments for nanomedicine. Iron oxide nanomaterials appear as suitable remotely wave-responsive materials respectively for magnetic hyperthermia and phototherapy applications while mesoporous silica (MS) are suitable shell coatings given their biocompatibility, easy surface modification and high drug delivery capability. In this talk, we will present various iron oxide@MS core shell controlled nanostructures designed and functionalized as various nanoplatforms that may serve as : multimodal theranostics probes for fluorescence/MRI imaging coupled with magnetic hyperthermia,[1–3] hybrid fluorescent nanoplatforms assessed in vivo models [4] or drug release coupled with NIR light-induced photothermia applications[5].


LC-MS/MS as a Study Method of the Release Kinetics of Remdesivir from Magnetic Nanoparticles

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Originally targeted against Ebola and Marburg viruses, antiviral drug remdesivir (RDV) has shown clinically relevant effects against SARS-CoV-2 virus. RDV is metabolised into its triphosphate form which acts as an inhibitor of viral replication by being an ATP analogue and stalling viral RNA polymerase. In blood, 93% of RDV is bound to proteins and its half-life is around one hour. Because of its concentration declining quite rapidly, it might be beneficial to develop a magnetic nanocarrier with the ability to release RDV over time. Firstly, we aimed to develop a LC-MS/MS method to detect RDV in blood plasma/serum. Secondly, we prepared magnetic nanoparticles (MNPs) to which we bound RDV. Then, the release kinetics of RDV in blood plasma/serum/buffers was studied at different pH. Finally, we compared the stability of free RDV with RDV bound to MNPs in blood plasma/serum in order to determine whether the attachment increases RDV half-life. LC-MS/MS method for the detection of RDV was developed - mobile phase A (100% water + 0.1 % HCOOH), mobile phase B (95% ACN + 5 % water + 0.1 % HCOOH), colon Zorbax C18, RT 1.88 min, 603.2 m/z → 200 m/z. In buffer solution, the RDV signal-concentration relation was linear (r = 0.9996), LOD 0.3 ng/ml, LOQ 5 ng/ml. In plasma/serum, the relation was linear, too (r = 0.9996/0.9996), LOD 1.9 ng/ml, LOQ 6.5 ng/ml. RDV was bound to the prepared MNPs primarily by electrostatic interaction (24 h, 25°C, 400 rpm). Subsequently, the dynamics of RDV release into the media was studied over 24 h. RDV was successfully eluted from the magnetic carrier and detected by LC-MS/MS. For the potential biomedical use of nanoparticles, it is necessary to study the effects of selected molecules that modify the surface in a significant way by the formation of a protein corona. The protein corona can affect the behavior of the nanotransporter, both positively and negatively.

Figure. (a) LC-MS/MS peak of RDV with RT 1.88 min. (b) structure of MNPs with bound RDV (red squares) and protein corona made primarily of albumin.

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Functionalization of primary T cells with magnetic Nanoparticles for guided immunotherapy

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Adoptive T cell therapies are an emerging part of immunotherapies targeting cancer. While these forms of treatment can significantly improve patient survival and reduce disease burden, they can also cause severe adverse side effects. Furthermore, the positive results of T cell therapy against blood cancers cannot yet be reproduced on solid tumors. This might be due to the immunosuppressive microenvironment of solid cancers, limiting T cell functionality and infiltration. Therefore, it is of interest to improve the efficacy of T cell therapies against solid tumors by increasing the number of Tumor infiltrating T cells. However, a systemic escalation of administered T cell numbers is not advisable due to the aforementioned risk of serious side effects. To accumulate T-cells in the tumor region, adoptive T cells will be loaded with superparamagnetic iron oxide nanoparticles (SPIONs) and re-administered administered into the vascular supply of the respective cancer tissue. Due to the magnetic properties of SPIONs, T cells are guidable by an external magnetic field, allowing the local enrichment in the tumor, which should increase anti-tumor activity and a reduction of systemic side effects.

Adaptive T cell therapies are an emerging part of immunotherapies targeting cancer. While these forms of treatment can significantly improve patient survival and reduce disease burden, they can also cause severe adverse side effects. Furthermore, the positive results of T cell therapy against blood cancers cannot yet be reproduced on solid tumors. This might be due to the immunosuppressive microenvironment of solid cancers, limiting T cell functionality and infiltration. Therefore, it is of interest to improve the efficacy of T cell therapies against solid tumors by increasing the number of Tumor infiltrating T cells. However, a systemic escalation of administered T cell numbers is not advisable due to the aforementioned risk of serious side effects. To accumulate T-cells in the tumor region, adoptive T cells will be loaded with superparamagnetic iron oxide nanoparticles (SPIONs) and re-administered administered into the vascular supply of the respective cancer tissue. Due to the magnetic properties of SPIONs, T cells are guidable by an external magnetic field, allowing the local enrichment in the tumor, which should increase anti-tumor activity and a reduction of systemic side effects.

Prior experiments resulted in the development of a suitable particle system with citrate-coated SPIONs, which we improved to enhance SPION stability in the medium, SPION uptake and T cell viability. We were also able to enrich these particle-loaded T cells magnetically in a dynamic flow system. Additionally, we investigated the impact of SPION loading on the immune response of primary human T cells. No difference in the production of cytokines such as IFNγ, TNFα or IL-2 after polyclonal stimulation was detected (Figure A). Additionally, we found that the SPIONs were located either intracellularly or were stably attached to the plasma membranes, without spilling over to non-loaded cells (Figure B). Therefore, we have shown a particle system suited for the local magnetic enrichment of T cells for possible future therapeutic approaches.

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Figure. Activation of SPION-loaded T cells and cellular SPION localization. Primary human CD3+ T cells were isolated from peripheral blood and loaded with SPIONs overnight. A) After loading, T cells were polyclonally stimulated with anti-CD3/CD28/CD2 antibodies and rh IL-2 for 24 h and analyzed for cytokine expression. B) Transmission electron microscopy picture of a T cell after SPION loading. Intracellular SPIONs and SPIONs attached to the plasma membrane are marked via red arrows (from Boosz et al., Cancers 2021).

Magnetic nanoparticles (MNPs) are a core research topic in medical nanotechnology because they are nano-scale particles that can be manipulated in the human body. Targeted drug delivery (TDD) and Magnetic Hyperthermia are the latest medical technologies using MNPs, which are being researched as a representative. What these two technologies need in common is to focus the injected MNPs into a single point. So, we studied how to focus MNPs into the blood vessel into a single point within the blood vessel.

As per Earnshow’s theorem, a static magnetic field cannot focus a magnetic particle to a point in a 3D environment. Therefore, existing studies utilize a coil system to focus particles with a dynamic magnetic field. However, these systems have problems with heat generation due to the operation of the coil, the size and weight of equipment becoming large and heavy, and it is difficult to concentrate particles immediately. This study proposes a method that utilizes an array of permanent magnets to instantly focus magnetic particles on the vessel wall through a compact and lightweight system. Taking advantage of the specificity of blood vessels, we use a static magnetic field to target MNPs to a point on the vessel wall rather than a point in space. This system is simple and small, so it can be used together with TDD and Magnetic Hyperthermia systems.

The permanent magnet arrangement of the system is simulated in Figure (a). In this system, two axes out of three axes in space apply a collecting force based on the center point, and the other axis gives a pushing force. In Figure (b), we experiment with focusing MNPs in a static fluid environment. The size of the MNPs is 1μm (Resovist, 55.85 Fe-mg/ml), and the size of the working space is 3cm. In the figure (c), the MNPs focusing experiment in dynamic flow is conducted by constructing a blood vessel model. The core size of MNPs is 60mm (Resovist, 55.85 Fe-mg/ml) and the fluid is 60% aqueous glycerol solution. The fluid velocity is 5mm/s. The radius of the tube is 3.5mm. Through these experiments, we show that the MNPS focusing system can be implemented using a simple permanent magnet system.

Figure. (a) COMSOL simulation of permanent magnet arrangement. The direction of the arrow indicates the direction of the force received by the MNPs. (b) An experiment in which MNPs were injected in a static flow. Tested in oil environment. (c) A system that tested the focusing performance of MNPs in dynamic flow. After flowing the fluid at a constant rate using a cylinder pump, 10μl of particles are injected through a syringe, and the amount of MNPs collected at the target location is measured.
A Novel Guidance Scheme for Magnetic Particles Inspired by the Artificial Potential Field

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Magnetic nanoparticles (MNPs) can be controlled using a magnetic field for magnetic drug targeting (MDT), and they can also be used as a contrast agent for imaging devices using technologies such as Magnetic Particle Imaging (MPI). Magnetic actuation has the benefits of safety and depth of penetration into organic tissue, however accurate control and monitoring of the MNPs is difficult. To enhance the targeting efficiency of MDT, a MNPs guidance system that integrates actuation and imaging feedback needs to include the application of a path-planning algorithm for the MNPs. Furthermore, an effective actuation method capable of driving the MNPs according to the planned path must also be considered. In this research, we propose a system for guiding the MNPs along a desired path generated using an Artificial Potential Field algorithm. In this system, the attractive and repulsive fields are generated using a permanent magnet and electromagnetic coils, respectively. This method can contribute to the path-planning required to increase the targeting ratio of MNPs by manipulating the magnetic gradient field using a method inspired by the artificial potential field method that is usually used for robot navigation.

The coil configuration used in this experiment is shown in figure (a). The PM shown in this figure is a permanent magnet, while Dx denotes the drive coils for the x-axis. The coil configuration used in this system consists of one Maxwell coil (Selection coil) and two Helmholtz coils (Drive coils for the x- and y-axis). The operation of these coils is controlled using a C-RIO (National Instruments, USA) controller and interface device. Figure (b) shows the experimental model and the result of the experiment carried out with the developed apparatus. The model size is 32 x 32 mm and BNP-Dextran MNPs are used in this experiment. To detect the MNPs, a camera (Logitech Brio UHD PRO, Korea) is used. The result of the experiment, presented on the right side of figure (b), shows that the actuation system was able to move the MNPs to the desired position without any collision with the wall.

Figure: Demonstration of interparticle interactions and predicted MPS measurement data

Figure (a) Coil configuration for the proposed actuation system. (b) Experimental model and results. The red line (APF) is the result of the Artificial Potential Field simulation and the blue line (MGF) is the experimental result with the developed apparatus. The MNPs are injected at the starting point (red dot) and moved to the target point (green dot) by the permanent magnet (PM) shown in (a). If the MNPs come close to the model wall during the experiment, the coil system generates a magnetic field and forces them away from the wall.

Quantitative measurements of the influence of polymer brush length on magnetic nanoparticle interactions and signal enhancement during linear aggregation via magnetic particle spectroscopy

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The design of magnetic nanoparticles for functional polymer nanocomposite materials is an expanding field with recent interest in therapeutic techniques like magnetic hyperthermia for biomedical applications, separation of transuranics for environmental remediation, and functional catalytic materials utilizing inductive heating.

The interest of this study is to measure the influence of magnetic dipole-dipole interactions on hysteresis curves, signal intensity and the corresponding harmonic spectra which elucidates physical and structural properties of the particle and bound analytes valuable to the design and application of magnetic bioassays. A recently proposed solution to controlling cluster formation is the surface modification of the particles with stabilizing hydrophilic polymers which has shown to be a promising method for controlling colloidal arrangement.1 Rinaldi et al. recently demonstrated by theoretical modeling that magnetic dipole-dipole interactions between chains formed by aggregation under an applied field enhances the MPI signal.2 This suggests that the intensity of the signal and the higher odd harmonic frequencies emitted by the particles can be tuned by surface modification. Herein, this study aims to experimentally demonstrate this prediction by evaluating the influence of steric repulsion between stabilizing ligands on chain formation via MPS. In this work, we have synthesized and characterized nitroDOPA terminated poly(ethylene oxide) coated iron oxide nanoparticles of molecular weights 2,000, 5,000, and 10,000 g/mol. MPS measurements of each sample will be conducted to measure the hysteresis curves and relaxation behavior. The postulated results of this study include demonstration of the tunability of particle signal strength under surface modifications and further evaluation of the interactions between chains and clusters of particles under applied field. The implications of this are improved synthesis techniques that can generate higher contrast images for MPI applications and a deepened understanding of the parameters that modulate variations in theoretical particle behavior.

References:
Human-Head-Sized Magnetorelaxometry Imaging of Magnetic Nanoparticles using Optically Pumped Magnetometers

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Magnetic Particle Imaging (MPI) is a very promising imaging modality for disease theranostics. Magnetic nanoparticles (MNP) are used as tracers for imaging by utilizing their non-linear response signal to an alternating magnetic field to image their spatial distribution. Furthermore, magnetic hyperthermia, where the particles are heated by a high frequency external magnetic field, is an application for this method. In this study, we employ our single harmonic MPI approach for temperature imaging with the signal of the 3f0 harmonic of the nanoparticles. After measuring a line phantom with a size of 4 x 1.5 mm filled with the same particles at different temperatures, a reconstruction of the measured images was performed at the 3f0 harmonic signal frequency. The reconstruction results show a temperature difference of ΔT ≤ 1°C, compared between the measured temperature with a fibreoptic sensor and the estimation from the particles.

Fig. 1: Temperature image of the line phantoms at different temperatures, calculated by the calibration function

Fig. 2: Reconstruction based on the 3f0 harmonic of a line phantom (left). Measured temperature with a fibreoptic thermometer (right, blue) and the calculated temperature (right, red).

Fig. 1: Left: Experimental OPM MRXI setup, composed of 3D-printed helmet (red), 25 OPM (black), 64 small magnetization coils (green) and 8 large coils (red, glued to the helmet). The head phantom (blue) is carrying cubes of immobilized magnetic nanoparticles.

Figure 1. Left: experimental OPM MRXI setup, composed of 3D-printed helmet (red), 25 OPM (black), 64 small coils (green) and 8 large coils (red, glued to the helmet). The head phantom (blue) is carrying cubes of immobilized magnetic nanoparticles. Right: Ground truth and reconstructed MNP distribution.

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References
Magnetic particle imaging (MPI) is an emerging tomographic imaging technique capable of quantitatively determining the 3D distribution of a magnetic nanoparticle (MNP) based tracer material. MPI technology is still under development and requires the characterisation of available tracers for imaging performance at a dedicated MPI scanner. For this purpose, we developed an MPI performance quantification called 2-voxel-analysis simulating different arrangements of two MNP accumulations from the measured system function (SF) required in Liisajus scanning MPI. The SF is a calibration measurement acquired for image reconstruction that is recorded with a point-like reference sample for a tracer in a grid-like manner at different selected positions of the field of view.

For our 2-voxel-analysis, we measured the SFs of six commercial and five non-commercial tracer systems as shown in Fig. 1a, the corresponding data are extracted from SF and superimposed including additionally the noise data of a blank scanner measurement. The SF S contains for all voxel positions the individual measurements with the reference, including positions i and j stored in the columns S_i and S_j. To simulate an arrangement of two distinct MNP sources as shown in Fig. 1a, the corresponding data are extracted from SF and superimposed including additionally the noise data of a blank scanner measurement giving the total signal S

\[ S = S_i + S_j + n_{noise} \]

Figure 1: (a) Voxel i and j filled with MNP (grey) separated by one or more voxels without MNP (white); (b) The plane containing voxel i and j of the reconstructed MNP distribution for the case of one separating distance voxel; (c) separation quality Q as a function of distance (number of empty voxels) between i and j exemplified for the two commercial MNP systems Synomag (Micromod, GER) and Resovist (Bayer Healthcare, GER). By inversion of S = S_i + n_{noise}, the resulting image of the MNP distribution is calculated, see Fig. 1b for the case of two voxels separated by one empty voxel. By repeating the stepwise procedure increasing the number of empty (distance) voxels, the quality of the separation Q_i of the voxel arrangement is assessed by the factor Q_i (ratio between reconstructed MNP content and maximum voxel positions i, j) in Fig. 1c. Fig. 1d shows Q_i as a function of the distance between the two voxels for different tracer types resolving the different resolution and performance under real scanner conditions.

Our 2-voxel-analysis is a powerful procedure to quantify the image quality of a tracer directly from a SF measurement, without the need for additional MPI measurements to estimate resolution and detection limit. This allows us to compare the imaging properties of different tracers, incorporating constant scanner and reconstruction parameters. In contrast, this becomes much more difficult when using measurements with real 1-mm cubes as a phantom. With these, for example, only a very small displacement of the cube determines whether this cube is distributed either over one voxel or up to 8 voxels. In addition, there are other parameters that can vary in real phantom measurements, which leads to greater uncertainties when comparing tracers. These uncertainties are significantly reduced by the 2-voxel-analysis.

Tracer comparison including MPI scanner characteristics by 2-voxel-analysis

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Probing Relaxation Characteristics of Magnetic Nanoparticles by a Home-made Magnetic Particle Spectroscopy Setup

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Magnetic particle spectroscopy (MPS), sometimes called zero-dimensional magnetic particle imaging (MPI), represents a versatile method enabling not only assessment of tracers for MPI but also studying of processes that modulate magnetic response of a particle suspension to an AC magnetic field, such as Néel relaxation and Brownian rotation. In MPS, a sinusoidal magnetic field is applied to a suspension of magnetic nanoparticles (MNPs), and the dynamic magnetic response of the suspension, which is in essence non-linear, is collected by pick-up coils. The Fourier transform of the time-dependent signal provides an MPS spectrum that consists of odd higher harmonics of the drive-field frequency.

In our laboratory, we have built a single-drive-field MPS setup with five excitation coils that are impedance-matched to frequencies of ~10, 15, 25, 35, and 50 kHz, with magnetic induction of up to 20 mT. The signal is collected by an oscilloscope and Fourier transformed, see Fig. 1 for an illustrative MPS spectrum of Resovist. The analyzed parameters comprise the amplitudes normalized to the concentration of the suspension and also the amplitude ratio of the 3rd (3f) and 5th (5f) harmonics. The amplitude of the 1st harmonic may not be used, its signal is suppressed by the two pick-up coils and a high-pass filter. The selected drive-field frequencies roughly correspond to the Bruker PreClinical MPI scanner (available at Charles University, Prague) with the drive-field frequency of ~25 kHz and an actual induction of up to 14 mT.

In this contribution, we compare MPS parameters of suspensions of MNPs prepared by two different methods, solvothermal synthesis and thermal decomposition. First, superparamagnetic Zn-doped magnetite/maghemite nanoparticles with Zn:Fe ratio of ~0.1 and size of ~8–12 nm were prepared by a solvothermal method (metal acetylacetonates in benzyl alcohol). The particles were stabilized by citrate, which forms a monomolecular surface layer, or coated with ~4 nm silica by the Stöber process (Fig. 2a), which led to coated clusters. Second, the thermal decomposition in presence of surfactants was employed to prepare doped magnetic nanoparticles of (i) Co0.69Fe2.31O4 with high magnetic anisotropy and size of ~16 nm, and (ii) Zn0.37Fe2.63O4 with size of ~15 nm, which are superparamagnetic at room temperature. The particles were coated with silica of various thicknesses by the reverse microemulsion method, which produced individually coated crystals (Fig. 2b). Apart from the results on these samples with different Néel relaxation times, we will also present data on suspensions in water/glycerol mixtures with modified Brown relaxation.
Core-shell structured MNPs: coating effect on the $^1$H-NMR relaxation properties

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The Magnetic Resonance Imaging (MRI) is a diagnostic technique based on the nuclear relaxation times (spin-lattice T1 and spin-spin T2) of the hydrogen nuclei composing the tissues of the investigated region. The MRI is utilized by the modification of the relaxation rates of the nearby nuclei, carried out by the contrast agents (CAs) that perturb the local magnetic field at the nuclear sites. Thus, the MRI contrast is enhanced according to the distribution of the CA in the biological structures, where the signal can be locally increased or decreased depending on the kind of injected system (paramagnetic/superparamagnetic). The CA efficiency is quantified by the relaxivity $r_i$ ($i = 1, 2$), defined as the change of relaxation rate normalized to 1 mM of CA concentration. In this framework, iron oxide magnetic nanoparticles (MNPs) are widely studied because of their high magnetization that generates sizeable inhomogeneities in the local magnetic field. The organic coatings of the MNPs are of considerable importance for biocompatibility and biodistribution of these systems and have been recently suggested to influence the magnetic properties at a certain extent, depending on the core size. The present work focuses on the effects of the coatings on the longitudinal and transverse relaxivities. In detail, we studied two sets of colloidal solutions of spherical superparamagnetic iron oxide nanoparticles (SPIONs) with different magnetic core sizes. The first set presented with a mean diameter $d_S1 = (8.86 ± 0.90)$ nm, coated with 3-Aminopropylphosphonic acid (APPA) or meso-2,3-Dimercaptosuccinic acid (DMSA). The core diameter of the second set is $d_S2 = (4.4 ± 0.7)$ nm, coated with Polyaspartic acid (PAA) or Benzene-1,3,5-tricarboxylic acid (TMA) or DMSA. The samples were structurally and morpho-dimensionally characterized by means of X-Ray Diffraction (XRD) and Transmission Electron Microscopy (TEM). The magnetic properties of the samples have been investigated by measuring the zero-field cooled/field cooled ZFC/FC curves and the hysteresis curves. The Magnetic Nuclear Relaxation Dispersion (NMRD) profiles of the longitudinal ($r_1$) and transverse ($r_2$) relaxivity have been determined at room temperature, ranging from 10 kHz to 86 MHz. The physical mechanisms that influence the Nuclear Magnetic Resonance (NMR) relaxation rates of SPIONs are often well modeled by a heuristic model, however, the experimental data were fitted with the Roch-Müller-Gillis model, and it emerged that for frequencies approximately below 1 MHz, the nuclear relaxation rate enhancement is led by the Néel correlation time, while at higher frequencies the Curie relaxation mechanism is dominant. Furthermore, as predictable, magnetic cores that differ in size present distinct NMRD profiles (Fig. 2). In the second set of samples, for distinct organic coatings, the different frequency behaviour of the NMRD profiles is singled out (Fig. 2b). This occurrence is tentatively attributed to the effect of the diverse polymeric shells on the surface spins dynamics and topology, with a subsequent influence on the fundamental magnetic properties. We suggest that the polymeric coating could help in finely tuning the relaxometric properties of small dimension systems, i.e., few nanometres.

![Figure](image.png)

**Figure.** (a) Longitudinal NMRD profile ($r_1$) of two samples of MNPs presenting different core size and same polymeric coating (DMSA). (b) Longitudinal NMRD profile ($r_1$) of two samples of MNPs presenting the same core and different polymeric coating (DMSA, PAA).

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**Poster #60**

Magnetic Particle Imaging for cell tracking: Establishing quality and effectiveness in magnetic cell labeling

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Magnetic nanoparticles (MNPs) are of great interest in biomedicine as they offer numerous promising therapeutic and diagnostic applications such as using specific magnetic properties of the MNPs. An emerging method for visualizing the spatial distribution of MNPs in biological objects for preclinical research studies is magnetic particle imaging (MPI). In addition, the capability of MPI cell tracking, e.g., monitoring living cells labeled with MNP by MPI has successfully been shown [1]. Nevertheless, the signal quality of MNPs often decreases due to cell uptake and subsequent degradation processes, which diminishes the effectiveness and quality of MPI cell tracking. Thereby, the cell uptake is impacted by the selection of the MNP system (coating size, zetapotential) and the type of biological medium. Presently, there is no magnetic quality control of cell labeling available including these aspects. Here, we will present a magnetic quality control procedure of MPI cell labeling for the examples of THP-1 cells labeled by two MNP systems Synomag and Perming (Micromod, GER). This consist of three phases (see Fig.).

**magnetic quality control procedure**

1. Unlabeled THP-1 cells  
2. Magnetic cell labeling  
3. Magnetic cell tracking

![Figure](image.png)

**Figure:** Three phases (1-3 inside the arrow) of the magnetic quality control procedure for MPI cell tracking. (a) Unlabeled THP-1 cells and (b) Synomag loaded THP-1 cells (visualized by Prussian Blue staining and Nuclear Fast Red staining).

First, we perform a magnetic and structural characterization of the MNP systems in the presence of different biological media which often directly might change the magnetic behavior. To this end, advanced separation techniques will be used to identify MNP-media interaction [2]. In the second phase, signal changes during and after cell uptake are quantified by magnetic real-time measurements using magnetic particle spectrometry (MPS), i.e., 0D-MPI with much higher sensitivity [3]. Finally, in the third step, the success perspective of MPI cell tracking for the selected MNP and media is estimated by analyzing of signal changes and resolution during and after cell uptake. Applying the presented procedure to magnetically labeled cells will propel the controlled and reproducible development of MPI-active cells.

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Optimising excitation field frequency for handheld detections of magnetic nanoparticles

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Magnetic nanoparticles (MNPs) are used in many biomedical applications, including sentinel lymph node biopsy (SLNB) and magnetic particle imaging (MPI). Recently, several handheld probes (based upon nonlinear detection principles) have been developed for SLNB with MNPs. These methods use an excitation coil to activate the MNPs, and a detection coil to acquire the consequent magnetization of the MNPs. In this paper, we investigate a method to optimize tracer-detector sensing for a nonlinear handheld detection during SLNB procedure.

We use superparamagnetic quantifier (SPaQ) to predict handheld detection by acquiring the consequent magnetization curve of MNPs in a homogeneous magnetic field. SPaQ is oil-cooled, custom-built system (University of Twente), and uses an AC excitation field |HAC| = 1.33 mT and a DC offset field |HDC| ≤ 13.3 mT. The consequent magnetization of the sample induces a voltage in a pair of gradiometric detection coils. A digital phase-sensitive detection algorithm is applied to sense the amplitude of the acquired signal.

The handheld detections are acquired using in-house build DiffMag system based upon a patented nonlinear principle (differential magnetometry). The DMH system is (at the same time) sensitive to small amounts of MNP and oblivious to strong first-order responses (e.g. like the human body would generate). The system consists of a DMH probe, a base unit, an isolation transformer, and a laptop. The DMH probe utilizes a combination of AC and DC magnetic fields generated by an excitation coil. Consequently, to excitation magnetic field, a sample will generate a magnetization acquired as a RF signal at a gradiometric coil setup in the DMH probe. A DMH count was generated as a difference between the excitation by a DC magnetic field and a field at an AC offset.

Two single-core iron-oxide particles (SHP, Ocean Nanotech, USA) with core sizes 25 and 30 nm were diluted with water and Glycerol (to enhance sample viscosity observable in clinical situation): total sample volume of 150 μl consisting of 100 μl pure MNP and 50 μl added water or Glycerol. Both SPaQ and DMH data was acquired at a room temperature (21 °C) and at various AC frequencies (i.e. 2.5, 5, 7.5, 10 and 12.5). To compare magnetic properties of MNPs using SPaQ data, two features were extracted from the measured curve, i.e. the maximum signal difference (ΔSmax) and the full width at half maximum (FWHM). The DMH data was directly compared by DMH counts.

Figure illustrates the both systems (SPaQ and DMH probe) including derivative of the magnetization curve and features extracted). SHP-30 produces a significantly higher DMH counts at a excitation frequency of 5 kHz. Derivative of magnetization curve is decreased by increasing the viscosity of particles. However SHP-25 was less sensitive to an increase of viscosity.

Fig. 1. Results of inverse solutions of MNT using (a) NNLS method and (b) combined method (sLORETA plus NNLS).

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Estimation Accuracy Improvement of Magnetic Nanoparticle Tomography by Combining Inverse Solution Methods

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A magnetic nanoparticle (MNP) imaging method is expected to become a new in vivo diagnostic technique for detecting MNPs accumulated in a cancer. An MNP imaging method using a magnetic sensor array, namely magnetic nanoparticle tomography (MNT), has been proposed [1]. To achieve high sensitivity and spatial resolution were achieved using the nonnegative least-squares (NNLS) inverse solution in MNT. However, owing to the presence of measurement noise, certain MNPs were estimated inaccurately, i.e., artifacts were generated.

To suppress the artifacts, a method was proposed to apply a minimum-variance spatial filter (MV-SF), which is a widely used spatial filter in magnetoencephalography (MEG), instead of the NNLS method [2]. The results indicate that the signal was more clearly represented and artifacts were successfully eliminated. However, the performance of MV-SF worsens in the presence of a correlated signal.

To overcome these issues, a method is proposed that combines the inverse solution, spatial filter, and NNLS methods to compensate for their individual weaknesses. First, a spatial filter method is applied to estimate the positions of MNPs approximately, and the analysis region is restricted. Second, the NNLS method is applied to estimate the amount and positions of MNPs in the restricted region. In this study, standardized low resolution brain electromagnetic tomography (sLORETA), which is also used in MEG studies, is chosen as the spatial filter. sLORETA has a lower spatial resolution compared with MV-SF; however, it can detect correlated signals, such as several clusters of MNPs.

The developed MNT system has one excitation coil and 16 detection coils. The excitation coil magnetizes the MNPs, and the third-harmonic magnetic field from MNPs is detected using the detection coils. The inverse problem is solved using the detected third harmonics to estimate the amount and positions of the MNPs. The estimation result, shown in Fig. 1, demonstrates that the proposed method successfully suppresses the artifacts and adequately estimates the amount and positions of MNPs.

Fig. 1. Results of inverse solutions of MNT using (a) NNLS method and (b) combined method (sLORETA plus NNLS).
The Impact of MNP Agglomerations inside Magnetic Fibers on MRI, MPI and Hyperthermia Performance

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Magnetic nanoparticles (MNP) are of high interest as additives for the production of magnetic scaffolds, as they promise to enable the control and monitoring of therapies in nanomedicine. For example, using MNP magnetic hyperthermia and thermo-sensitive drug release from the scaffolds can be achieved by controlled heating in an alternating magnetic fields (AMF). Scaffold visualization is enabled via magnetic particle imaging (MPI) and magnetic resonance imaging (MRI). Recently, it was reported that MNP interactions inside agglomerations significantly affect their magnetic response. In this work, we investigate this impact on MPI, MRI and hyperthermia performance with a focus on the influence of the MNP agglomerate orientation inside hybrid fibers relative to the direction of the applied magnetic field. For this, hybrid fibers consisting of polypropylene and MNP were produced [1] and characterized with the above-mentioned techniques. Figure 1 shows the MNP agglomerate orientation inside fibers and the MPI system matrix models used for the reconstruction of the image for differently oriented fiber snips. From the reconstructed images it can be concluded that MPI signal quality significantly depends on the orientation of the MNP agglomerates in the hybrid fiber. Similarly, the hyperthermia investigations showed different heating outputs for different orientations of MNP agglomerates. The results were consistent with simulation data. These effects are attributed to magnetic interactions of MNP in agglomerates which cause a collective relaxation behavior and a preferential orientation of the easy axes and the magnetic moments of the MNP in elongated agglomerates. In comparison to MPI and MFH, the MRI signal did not show such clear dependency. In conclusion, MNP agglomerate orientation and thus fiber orientation plays a significant role for their MPI and hyperthermia performance. For an optimized application of magnetic scaffolds, such effects must be considered as the orientation of the agglomerations strongly depends on the type and position of the scaffold.

Figure 1: A) Sketch of a MPI setup. B) MPI system matrix sample containers with fiber snippets in x- and y-orientation. C) TEM image of the fiber (adapted from [1]). The inlay shows an elongated MNP agglomerate. θ is the angle between the major axis orientation of the agglomerates and the magnetic field. D) Sketch of the simulated MNP agglomerates.


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Reference:


Small Iron Oxide Nanoparticles as MRI T1 Contrast Agent

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Most common aqueous synthetic methods, i.e., the co-precipitation method, are rather simple from an experimental point of view, as they use relatively cheap and non-toxic chemicals, temperatures < 100°C, and require solely a pH increase of a precursor solution containing ferous and/or ferric ions. However, particles produced by co-precipitation are often polydisperse, and of a restricted size range, i.e., larger than 7 nm and therefore too large for clinical use as T1 MRI contrast agents. To obtain a reproducible, and scalable production of IONPs in water, which are preferred when targeting biomedical applications is non-trivial.

In our original research we demonstrated that IONPs of ~5 nm can be produced via the co-precipitation method, when quenching the growth of IONPs by adding an acidic solution (e.g. citric acid) rapidly after the initiation of co-precipitation. Furthermore, this continuous synthesis enables the low-cost (~£10 per g) and large-scale production of highly stable small IONPs without the use of toxic reagents. The flow-synthesised small IONPs showed high T1 contrast enhancement, with transversal relaxivity ($r_2$) reduced to 20.5 mM$^{-1}$ s$^{-1}$ and longitudinal relaxivity ($r_1$) higher than 10 mM$^{-1}$ s$^{-1}$, which is among the highest values reported for water-based IONP synthesis.

Schematic of precisely-timed quenching of particle growth at different times after the initiation of the co-precipitation.
Low Frequency AC Susceptometry with Optically Pumped Magnetometers

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Due to their sensitivity, small size and flexibility, Optically Pumped Magnetometers (OPMs) have become attractive as sensors in many applications. In magnetocardiography [1] and magnetoencephalography [2] complex arrangements of OPM-arrays are used whereas single detectors have been employed for detecting magnetic properties [3,4].

Another promising application we are investigating is online monitoring of magnetic properties during synthesis of magnetic nanoparticles (MNP). One synthesis route to produce MNP of high quality is microfluidics. In this process, the reaction mixture passes through capillary tubes, which composes the chemical reactor at a certain temperature. Transient time and temperature, among other factors, determine the physical properties (size, magnetization, etc.) of the produced NMPs. We suggest here OPM measurement of the magnetic susceptibility as an online method to detect magnetic properties during MNP synthesis. The susceptometer is composed of a gradiometric coil arrangement with an anti-Heitler spiral coil (10 turns, 13.5 mm radius) with one OPM (QuSpin Inc., Louisville, Colorado, USA) at its center (null field point). The setup is opened in a small magnetically shielded chamber (three-layer mu-metal ZG-206, Magnetic Shield Corporation, Bensenville, IL, USA) with an open end to facilitate accessing and sample handling. Emulsifying a microreactor, we use a plastic silicone microtube with 3.5 mm outer diameter and 2 mm inner diameter passing near the coils. MNP with an effective volume of 100 μl conducted through one of the coils produce a change in the signal detected by the OPM. By using a multturn potentiometer, the current through the coils (balancing the field) can be adjusted so that a common mode rejection up to 10^-4 can be achieved. The presence of MNPs in one coil produces a magnetic field imbalance that is detected by the OPM and the field intensity can be used to calculate the magnetic susceptibility. Finally, the frequency of operation is below 100 Hz, typically at about 10 Hz, which makes this susceptometer unique to study low frequency magnetic phenomena of MNP.

Tabletop setup for Thermal Noise Magnetometry of magnetic nanoparticles based on Optically Pumped Magnetometers

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Magnetic nanoparticles are very useful in biomedical applications, where they are employed in both diagnosis (contrast agent in Magnetic Resonance Imaging, tracer in Magnetic Particle Imaging) and therapy (heat generator in magnetic hyperthermia, carrier in magnetic drug targeting). To improve the performance of these applications, the particle properties need to be precisely characterized, for which numerous magnetic measurement techniques are employed. All methods have the disadvantage that they require the application of an external field to measure the magnetic response of the particles, which may change the magnetic state of the particles. To overcome this limitation, the method of Thermal Noise Magnetometry (TNM) has been developed to characterize magnetic nanoparticle ensembles without any use of an external magnetic excitation [1].

Thermal energy in the system causes the magnetic moment of the particles to change direction, which results in fluctuations of the magnetic signal of the ensemble detected in TNM. The total switching rate of these fluctuations depend on the physical and chemical properties of the particles and their state in the suspension. The characteristics of the nanoparticle ensemble thus greatly influences the magnetization dynamics of the sample, which can be mapped by measuring its thermal noise. Such measurements have been proven to be feasible, and complementary to other characterization techniques due to its diminutive impact on the sample [2].

Until now, TNM measurements have been performed with SQUID sensors because of the small sensor system attractive for TNM. In this contribution, we present a tabletop TNM setup working with commercially available OPMs (QuSpin Gen-2 Zero-Field Magnetometers) in a laboratory magnetic shielding (Twinfoil MS-2).

Since our spectral measure is phase insensitive, we are able to use the OPMs above their bandwidth specified by the manufacturer by compensating for their frequency response profile in the power spectrum. As an example, in the figure we compare the TNM spectrum of a Resovist sample measured in the OPM based setup with that measured in an in-house developed SQUID system and find a very good agreement. The OPM setup with high accessibility complements the SQUID setup with high sensitivity and bandwidth, thereby expanding the field of TNM to possible other magnetic noise related applications.

References:
Characterising magnetic nanoparticles using data-driven methods

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Achieving industrial-scale manufacturing of reproducible and standardised magnetic nanoparticles (MNP) has been among the key challenges in developing diagnostic and therapeutic applications for healthcare. New progress requires devising advanced characterisation techniques to allow precise and efficient determination of intrinsic properties of MNPs [1]. Properties of MNPs are often inferred based on a variety of measurement techniques frequently available only at different laboratories. Data analysis is commonly based on fits to models founded on linear response theory, which is often only truly applicable far from operational conditions in applications. In addition, the presence of magnetic interactions in MNP aggregates also severely complicates data interpretation in most sizing measurement methods. It is therefore clear that accurate MNP characterisation is essential not only to guide our understanding of the behaviour of MNPs in various application scenarios but also for laboratory measurement consistency checking and MNP standardisation.

We will discuss our efforts to develop a machine learning-based MNP characterisation tool utilising standard magnetometry data, such as magnetisation vs magnetic field hysteresis loops or ZFC-FC data, for example (Fig. 1). The approach is data-driven and combines datasets from experiments and large-scale computational modelling. We will discuss the achievable accuracy of the parameter estimation and various challenges encountered in the design and training of machine-learning algorithms. We will also address the prospects for using the technique for guiding the real-time production of standardised MNPs for healthcare and other applications.

Figure 1 – Machine learning-based characterisation methodology for identifying intrinsic properties of MNPs, such as particle volume \( V \), anisotropy \( A \), saturation magnetisation \( M_s \), and interactions through packing fraction \( \rho \) or fractal dimension of aggregates \( D_f \). Standard magnetometry data from measurements or computational modelling can be analysed within the developed framework.

References:

Construction of a broadband 3D magnetic particle spectrometer

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Magnetic particle spectroscopy (MPS) is an important method to analyze the properties of magnetic particles. Especially for Magnetic Particle Imaging (MPI) the measuring of the dynamic magnetization response at sinusoidal excitation frequencies around 25 kHz is a standard process in nanoparticle characterization [1]. While most spectrometers are only able to transmit a single frequency, the use of different frequencies or waveforms like rectangular pulses gained more interest in the field of MPI due to better resolution performance with specific tracer material [2]. We therefore designed and built a 3D field generator which is capable of creating arbitrary field waveforms. The device is extremely flexible in the characterization of magnetic nanoparticles and will be capable of diverse applications such as AC susceptibility measurements, hysteresis curves or measurement of MPI system matrices for arbitrary trajectories.

The field generator of the presented system consists of three orthogonal transmit and receive coils each, with the whole coil assembly being just 23 mm in size. The transmit coils are wound from litz wire and held in shape with epoxy. They can be driven with arbitrary current waveforms due to the absence of any impedance matching circuits present in existing spectrometers which would limit the excitation waveforms to a small frequency range. Due to the small inductances of the excitation coils they can be directly driven by a power amplifier (AETechron 7224). Currently, the bandwidth of the system is limited by the frequency bandwidth of the amplifier. First experiments show a bandwidth of 127 kHz, 68 kHz, and 50 kHz (12 mT sinusoidal current wave) for x,y,z coil respectively. To achieve the small size of the coil assembly the y- and z-receive coils were manufactured on a flexible PCB. Feedthrough suppression is handled by a cancellation approach with a second set of transmit and receive coils which can be geometrically adjusted to fine tune the coupling between the transmit and receive paths.

First measurements show the capability of the system for the evaluation of different excitation schemes in 2D for MPI, with a successful triangular excitation with a base frequency of around 2.5 kHz. With further optimisation of the power amplifier the transmit bandwidth will be increased allowing higher frequencies or more challenging waveforms like rectangular pulses. The setup will enable sequence studies for optimizing resolution and sensitivity for specific nanoparticle systems by allowing the superposition of low frequency and high frequency fields in one broadband setup.

Figure 1 – Constructed excitation coil assembly with three orthogonal channels optimized for low inductance. (b) Recorded spectrum of Lissajous trajectories, with triangular and sinusoidal excitation wave forms of around 2.5 kHz (trajectories have been thinned for visualisation).

References:
Resolving ambiguities in core size determination of magnetic nanoparticles from magnetic frequency mixing data

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Frequency mixing magnetic detection (FMM) has been widely utilized as a measurement technique in magnetic immunoassays. It can also be used for characterization and distinction (also known as “colorization”) of different types of magnetic nanoparticles according to their core sizes. Typically, 90% of the signal stems from the largest 10% of the particles [1]. This leads to ambiguities in core size fitting since the contribution of the small sized particles is almost undetectable among the strong responses from the large ones. In this work, we report on how this ambiguity can be overcome.

Magnetic nanoparticle samples from Micromod (Rostock, Germany) were prepared in liquid and filter-press form. Their FMMID response at mixing frequencies \( f_1 + f_2 \) to magnetic excitation \( H(t) = H_0 + \dot{H}_0 \sin(2\pi f_1 t) + \dot{H}_1 \sin(2\pi f_2 t) \), with \( H_0 = 1.8 \text{ kA/m} \), \( H_1 = 5 \text{ kA/m} \), at \( f_1 = 40.5 \text{ kHz} \) and \( f_2 = 63 \text{ Hz} \), was measured as a function of offset field strength \( H_0 = (0, -1 ... 24) \text{ mT} \). The signal calculated from Langevin model in thermodynamic equilibrium [1] with a lognormal core size distribution \( f(d) \propto \sigma d^{6/3} \exp(-\frac{(\ln d - \mu)^2}{2\sigma^2}) \) was fitted to the experimental data. For each choice of median diameter \( d_m \), pairs of parameters \((\sigma, \mu)\) are found which yield excellent fit results with \( R^2 > 0.99 \). All the lognormal core size distributions shown in Figure (a) are compatible with the measurements because their large-size tails are almost equal. However, all distributions have different number of particles and different total iron content. We determined the particles' iron mass with inductively coupled plasma optical emission spectrometry (ICP-OES) and, out of all possible lognormal distributions, determined the one with the same amount of iron. With this additional externally measured parameter, we resolved the ambiguity in core size distribution and determined the parameters \((d_m, \sigma, \mu)\).

Figure 1 shows an example of the impact of one of those parameters: inhibiting rotation of the particles (i.e. the Brown relaxation process). As can be seen, it leads to a slower saturation of the magnetization in samples with a high size dispersion parameter \( \sigma < 0.5 \). Likewise, the presence of dipolar interaction between particles also leads to slower saturation in such samples, as does drying samples under a magnetic field perpendicular to the measurement field (as opposed to drying them under a field parallel to the measurement field, which yields the opposite effect). These various modifications of the curves result in a large size dispersion parameter when fitting them to an integrated Langevin equation. The simulations compare well with experimental results, as can be seen on figure 2. In future work, the simulations could be improved by changing the anisotropy model from uniaxial to a more realistic cubic anisotropy.

Monte Carlo and Experimental Study of the Magnetic Behaviour of Superparamagnetic Nanoparticles

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Superparamagnetic Iron Oxide Nanoparticles (SPION) are nanosized crystals of magnetite or maghemite. Their peculiar magnetic properties make them particularly suited for a variety of biomedical applications, ranging from cellular imaging to cancer treatment by hyperthermia [1]. The usual theory used to describe their magnetic behaviour is that developed by Paul Langevin [2], which only applies to idealized, monodisperse in size and non-interacting nanoparticles at high temperatures. Reality however always deviates from that theoretical framework; real samples exhibit polydispersity in sizes, particles usually have at least one anisotropy axis, and, particularly in biological media, they tend to aggregate, leading to highly particle volumic fractions and therefore interaction between their magnetic moments [3]. All those phenomena impact the magnetization of particle ensembles in a non-trivial way and are impossible to model simultaneously theoretically.

In this work, these deviations from the Langevin law are studied numerically, at thermodynamic equilibrium and at 300K, using a Metropolis algorithm, and compared with experimental data obtained using a Vibrating Sample Magnetometer for real SPION, whose size distribution was evaluated by transmission electron microscopy. Thorough tests are led on the simulations to ensure convergence of the magnetization. The effect of each parameter on the field-dependent magnetization curves is then studied. The simulations compare well with experimental results, as can be seen on figure 2. In future work, the simulations could be improved by changing the anisotropy model from uniaxial to a more realistic cubic anisotropy.

References


Poster #09

Figure 1: Impact of the particle's ability to rotate in the magnetic field on the magnetic behaviour of superparamagnetic nanoparticles, and simulations differing in the particle size distribution.

Poster #10

Figure 2: Comparison between experimental results and simulations for magnetic behaviour of superparamagnetic nanoparticles using different core size distributions.
Nanorheology monitoring using magnetic nanoparticles and AC susceptometry

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We have developed a nanorheological characterization method to extract frequency and temperature dependent rheological properties of soft materials. The measurement system consists of two differentially connected detection coils centered coaxially with the excitation coil aligned in the middle of the detection coils. A lock-in amplifier is used to both generating the excitation ac magnetic field and measuring the voltage from the detection coils. To investigate the effect of temperature on the sample, the sample is placed inside a water jacketed flask which is connected to a temperature-controlled circulating water bath. The flask is located directly above one of the two detection coils. By measuring the dynamic magnetization of magnetic nanoparticles blended in the matrix material, the viscosity and storage module can be determined in the matrix material [1-3]. Commercially available iron-oxide multicomponent nanoparticles (MNP) of 100 nm (micromod, BNF Starch) are used as tracer in the excitation frequency range of 1 Hz-10 kHz. As an example, we show the result of mixing 2% gelatin to the MNP tracer. The out-of-phase ac susceptibility vs frequency and temperature for both MNP systems with and without gelatin can be seen below. The frequency and temperature dependent dynamic magnetic properties are affected by the mechanical interaction with the gelatin-matrix. The rheological properties of the matrix can be estimated using theoretical models [1, 2]. The remote magnetic sensing of the MNP tracers and the estimation of the rheological properties allows rheological monitoring of food matrices under oral processing.

Figure:

Left) out-of-phase ac susceptibility vs frequency and temperature of MNP system. Right) out-of-phase ac susceptibility vs frequency and temperature of MNP/gelatin system.


Novel methodologies to determine the magnetic anisotropy of iron oxide nanoparticles in colloidal suspensions

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The potential of magnetic nanoparticles for acting as active agents in catalysis, magnetic particle imaging or magnetic hyperthermia grounds on their superparamagnetic behaviour under alternating magnetic fields (AMF). In spite of the application potential of this magnetic phenomenon, the identification of fingerprints specifically related to the transition from unblocked to blocked states at room temperature under alternating magnetic fields remains a challenge to provide easy access tools for characterising magnetic properties of nanomaterials.

Here, we report an experimental and theoretical study to determine the effective magnetic anisotropy from iron oxide nanoparticles (IONPs) in colloidal suspensions at room temperature. The experimental methodology is based on magneto-optical measurements of IONP suspensions based on Faraday effect under alternating magnetic fields in a six decades frequency range from hundreds of mHz to kHz with field intensities up to 40 kA/m. Our measurements demonstrate a room temperature transition from unblocked to blocked magnetic states in magnetic suspensions under alternating magnetic fields. The transition is characterised by AC anhysteretic (unblocked magnetic state) magnetization cycles at low frequencies and AC hysteretic (magnetically blocked state) magnetization cycles beyond an onset frequency (f onset) value which depends on nanoparticles size (see Figure). Thus, f onset values vary from 13 kHz for 12 nm IONPs to 30 Hz for 22 nm IONPs. Our experimental observations are predicted by a theoretical model based on modified Landau-Lifshitz-Gilbert equation that explains the experimental results in terms of the magnitude of the effective magnetic anisotropy barrier (K eff) from f onset. K eff = 2π τ 4 Δf eff [−2.4064 × log(f onset) + 15.745]. The narrow IONP size distribution, and the negligible contribution of Brownian mechanism to relaxation process of the studied IONPs benefit the good agreement between the experimental and theoretical values. Our results provide alternative methodologies to determine experimental parameters. At the same time, numerical simulations significantly improve the understanding and the description of superparamagnetic behaviour in magnetic suspensions.

Figure:

Left) Frequency dependence of AC magnetization cycles of 22 nm IONP suspension at 0.4 g Fe/L. Right) Experimental (filled dots) and theoretical (empty dots) frequency dependence of coercivity obtained for 12 nm (black dots) and 22 nm (blue dots) IONP sizes (H0 = 40 kA/m). Theoretical values for 12 and 22 nm IONPs are highlighted with red arrows.
Portable MPS device for radical innovation in medical point-of-care diagnostics

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Superparamagnetic iron oxide nanoparticles have received a substantial attention during the past two decades in biomedical applications due to their unique magnetic properties and high biocompatibility. Saturation magnetization, magnetic anisotropy, magnetic susceptibility, and colloidal stability are of the most relevant properties determining their use for different applications in biomedical research area. Magnetic nanoparticles with higher susceptibilities (achieving values close to their saturation magnetization at lower applied magnetic field) can be suitable candidates for magnetic particle imaging (MPI). Higher saturation magnetization with moderate effective magnetic anisotropy is a key feature for magnetic nanoparticles to be used in magnetic hyperthermia. A larger magnetic moment in the particles is a desirable property for magnetic navigation systems for targeted delivery using the gradient field. Although tremendous research has been devoted to development of biocompatible iron oxide nanoparticles with tailored physical and chemical properties to requirements of each application, not many have been approved for preclinical or clinical use. In addition, despite the fact that some commercially available particles for research and preclinical purposes have shown promising results in the past, but cannot reach the sensitivity of above-mentioned preclinical purposes have shown high performance in different applications such as magnetic resonance imaging (MRI), MPI, and magnetic hyperthermia, their intrinsic properties have not been fully provided by the producer company. Moreover, no quantitative data regarding their performance in biomedical applications has been presented by the provider. In recent years, some research groups have reported on characterization and examination of the performance of some commercially available nanoparticles. However, most of these works either have studied particles from small number of companies or they lack the study of the performance of the particles in conditions where the particles are immobilized. The latter is of crucial importance because in vivo application the particles are immobilized in tissue and because of suppressing the Brownian relaxation mechanism, their performance may differ from the condition in colloidal condition substantially. Therefore, a comprehensive characterization of various commercially available iron oxide nanoparticles investigating their performance under different conditions can provide valuable information for research groups who are willing to use these particles. This can accelerate the process of choosing the suitable nanoparticles based on their need and also may considerably reduce the cost by not going through the trial and error method.

In this study, we analyzed five frequently used commercially available particles (BNF, Resovist, Synomag, Nanomag, Sio) in three biomedical applications. Figure shows a portion of the results of MPS experiments. The single experiments of the measuring sequence (ref, 1:2000, 1:5000, 1:10000, 1:20000 (equivalent 50 ng/ml), neg. control) show a clear trend in phase difference of the 7th and 9th higher harmonics. Each sample was measured 5 times without any averaging (acquisition time 10 ms each).

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Poster #74

Characterization of physical properties of commercial nanoparticle for biomedical application

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Superparamagnetic iron oxide nanoparticles have received a substantial attention during the past two decades in biomedical applications due to their unique magnetic properties and high biocompatibility. Saturation magnetization, magnetic anisotropy, magnetic susceptibility, and colloidal stability are of the most relevant properties determining their use for different applications in biomedical research area. Magnetic nanoparticles with higher susceptibilities (achieving values close to their saturation magnetization at lower applied magnetic field) can be suitable candidates for magnetic particle imaging (MPI). Higher saturation magnetization with moderate effective magnetic anisotropy is a key feature for magnetic nanoparticles to be used in magnetic hyperthermia. A larger magnetic moment in the particles is a desirable property for magnetic navigation systems for targeted delivery using the gradient field.

Although tremendous research has been devoted to development of biocompatible iron oxide nanoparticles with tailored physical and chemical properties to requirements of each application, not many have been approved for preclinical or clinical use. In addition, despite the fact that some commercially available particles for research and preclinical purposes have shown high performance in different applications such as magnetic resonance imaging (MRI), MPI, and magnetic hyperthermia, their intrinsic properties have not been fully provided by the producer company. Moreover, no quantitative data regarding their performance in biomedical applications has been presented by the provider. In recent years, some research groups have reported on characterization and examination of the performance of some commercially available nanoparticles. However, most of these works either have studied particles from small number of companies or they lack the study of the performance of the particles in conditions where the particles are immobilized. The latter is of crucial importance because in vivo application the particles are immobilized in tissue and because of suppressing the Brownian relaxation mechanism, their performance may differ from the condition in colloidal condition substantially. Therefore, a comprehensive characterization of various commercially available iron oxide nanoparticles investigating their performance under different conditions can provide valuable information for research groups who are willing to use these particles. This can accelerate the process of choosing the suitable nanoparticles based on their need and also may considerably reduce the cost by not going through the trial and error method.

In this study, we analyzed five frequently used commercially available particles (BNF, Resovist, Synomag, Nanomag, Sio) in three biomedical applications. Figure shows a portion of the results of the hyperthermia, magnetic navigation control and MPI. Comprehensive structural, magnetic characterization of the particles have been provided and their performance in the three application in colloidal condition and using tissue mimicking gelatin phantom have been investigated.

Figure (a): Temperature increase of each particle for hyperthermia. (b) particle movement control under gradient field. (c) MPI image comparison at different concentration.

Poster #74
Studies aggregation mechanism of magnetic nanoparticles under possible scenarios during magnetic drug targeting

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Magnetic drug targeting (MDT) is a method by which magnetic drug carriers in the body are manipulated by external magnetic fields to reach the target area. This method is potentially promising in applications for treatment of disease like cancers, nervous system diseases, sudden sensorineural hearing loss, and so on, due to the advantages in that it can improve efficacy, reduce drug dosage and side effects. Therefore, it has received extensive attention in recent years. However, there are restrictions for using individual magnetic nanoparticles for MDT due to lack of imaging devices and small magnetic actuation forces.

Recently, aggregation phenomena of magnetic nanoparticles under the magnetic field has been considered as one of the great mechanisms to overcome lack of actuation force problems and imaging resolution problems. However, it is significant problems that aggregation could occur clogging or sticking inside the blood vessel during MDT. Therefore, aggregation phenomena during MDT should be considered carefully for improving targeting efficiency and safety especially in case for navigating magnetic nanoparticles inside the blood vessel under dynamic magnetic fields. Although magnetic nanoparticles were aggregated as magnetic chains and these magnetic chains reach equilibrium state (no grows) after few milliseconds under the static magnetic field (uniform magnetic field), in case of using dynamic magnetic field, the relations (distance or angle) between magnetic chains are continuously changed. Therefore, magnetic chains may not reach equilibrium state. In this paper, we have analyzed aggregation mechanism (dipole force, time, velocity, trajectories) of magnetic chains under possible two scenarios during MDT: using uniform magnetic field, using magnetic gradient field. Furthermore, the length of aggregated magnetic nanoparticles is different under the magnetic field so that we set length of aggregated magnetic nanoparticles as a variable. The photo-graphs have been taken during the motion with respect to time (Figure 1). It can be seen that given the initial relative position and initial angle, time required for magnetic chains to aggregate with each other increased as length of magnetic chain increased under the uniform magnetic field. Furthermore, it affects to trajectory of both magnetic chains. Whereas, under the magnetic gradient, aggregation can be hinder. These simulation results show that length of magnetic chain and presence or absence of magnetic field can affect to overall aggregation mechanisms.

Iron-carbides, especially cementite (Fe₃C), are well known for their hardness and chemical resistance. They also attract much interest due to their tunable magnetic properties. Iron/iron carbide nanoparticles are also good candidates for preparing multifunctional electrocatalysts for oxygen catalysis. In this study, we analyze the structural and magnetic properties of carbon coated Fe/Fe₃C “core-shell” nanoparticles, to examine their perspectives as biomedical heating carriers possessing high losses of magnetic energy under AC field, i.e. magnetic particle hyperthermia cancer modalities. To start with, carbon encapsulated iron-cementite (Fe-Fe₃C) nanoparticles with “core-shell” architecture, were synthesized by a single-step solid-state pyrolysis at variable temperatures (700, 800, 850, 900, 950, 1100 oC) and duration (5, 15, 30 min). X-ray diffraction outlined the tunable crystallinity with respect to synthesis parameters. Dimensional and morphological features have been investigated using high resolution transmission and scanning transmission electron microscope (HRTEM, STEM) showing Fe-Fe₃C nanoparticles with an average diameter less than 30 nm embedded in a carbon matrix. Mosauer spectroscopy, XANES, EXAFS combined with Reactive Force-Field Molecular Dynamics simulations confirm the evidence of “core-shell” architecture, which is further supported by the magnetic features exhibited in low (10 K) and high (300) K temperatures. The biomedical applicability is examined by magnetic particle hyperthermia experiments (375, 765 kHz and 30-60 mT) where the structural features directly reflected to superior magnetic features also conclude to enhanced heating efficiency.

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Mind the Solvent Impurity and Never Give Up on Catechol Anchor: 3D Nano-Assembly and Aqueous Dispersion of Cobalt-Ferrites

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In nanomedicine, the goal is to develop multimodal nanoparticles (NPs) to speed up targeted diagnosis, to increase its sensitivity, reliability and specificity for a better management of the disease. Besides being excellent T2 contrast agents for MRI, iron oxide NPs are promising as therapeutic agents by magnetic hyperthermia when correctly designed (high magneto-crystalline anisotropy) and they also have an interest for photothermal diagnostics probes in biology and biomedicine. However, to meet the application needs, designing therapeutic efficiency of both treatments[2][3]. So, defect evaluation on different sized and shaped NPs is a crucial requirement. In addition, when cobalt is employed as a second transition metal to generate magnetically blocked nanoparticles and enhance magnetic anisotropy, they are not open to surface modification with classical catechol-based ligands. Therefore, the use of MNPs-based platforms with diverse metal components for intracellular and bioanalytical research and diagnostics is still limited.

Here, we provide insights into designing highly monodisperse cobalt-ferrite (Co-Fe) magnetic nanocubes (NCs) with precise shapes by decoupling influence of solvent impurity in classical synthesis recipes. Additionally, we showcase how to assemble the nanocubes into a three-dimensional (3D) cubic nano-assembly by selectively choosing a series of solvent impurities. We then transfer these particles from an organic medium to aqueous medium using custom-designed catechol-based polyethylene glycol ligands. Combining high-resolution transmission electron microscopy (HRTEM), proton nuclear magnetic resonance spectroscopy, and ex-situ monitoring of the particle growth, we elucidate the formation mechanism of the 3D nano-assemblies. Their 3D formation is further validated by zero-field-cooled (ZFC) and field-cooled (FC) magnetic susceptibility measurements, where 3D nano-assemblies show an initial magnetic transition that resembles single nanocubes, suggesting the existence of multiple nanocubes within the nano-assemblies of Co-Fe. We will furthermore unravel the effect of solvent impurities on the formation mechanism of the 3D assemblies using X-ray photoelectron spectroscopy.

Figure 1. HRTEM and respective magnetic susceptibility of mixed NCs: Cu3Fe4O12 (left panel) and Co1.33Fe1.67O4 (right panel).

Effects of Size, Shape and Defects of Iron Oxide Nanoparticles on Photothermal and Magnetothermal therapies

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In nanomedicine, the goal is to develop multimodal nanoparticles (NPs) to speed up targeted diagnosis, to increase its sensitivity, reliability and specificity for a better management of the disease. Besides being excellent T2 contrast agents for MRI, iron oxide NPs are promising as therapeutic agents by magnetic hyperthermia when correctly designed (high magneto-crystalline anisotropy) and they also have an interest for photothermal diagnostics probes in biology and biomedicine. However, to meet the application needs, designing therapeutic efficiency of both treatments[2][3]. So, defect evaluation on different sized and shaped NPs is a crucial requirement.

We thus optimized the reproducible synthesis of iron oxides NPs with different sizes (3D and 20 nm) and shapes (nanocubes and nanoplates) by the thermal decomposition approach by tuning synthesis parameters such as the reaction temperature, the heating rate and the nature of surfactant. Defects such as dislocation or antiphase boundaries were evaluated by XRD and HRTEM images and by calculating band gap and Urbach energies. NPs behaviors towards the different kinds of therapies were investigated both in suspension in water and viscous media and in cancerous cells allowing to establish the key role of defects and NPs design for multimodal therapy.

Figure 2. TEM images of various sized and shaped NPs: 1- 12 nm spherical NPs, 2- 22 nm spherical NPs, 3- 20nm nanocubes, 4- 20nm nanoplates. B) 1- HRTEM image of 22nm NPs. 2- FIT of the area of HRTEM image. 3- Mask of the FIT. 4- Zoom of inverse FIT showing defects in the plane (2 1 2).

References:

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Synthesis of Size-Controlled Iron Oxide Nanocubes for MPI-MFH Applications

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Magnetic particle imaging (MPI) is a newly developed tracer-based modality which has emerged as a promising tool for many potential therapeutic and diagnostic applications.1 Standardly, the tracers employed by MPI are superparamagnetic iron oxide nanoparticles (SPIONs). MPI implements a gradient field with strong gradients and weak field strengths, and the non-linear magnetic response of these SPIONs to the gradient field is detected directly for image generation. Overall MPI performance and imaging quality is greatly influenced by the magnetic properties of the SPION implemented. By improving these properties of SPIONs through tailoring of their physical and chemical characteristics, including the iron oxide core size and shape, it is possible to significantly improve the sensitivity and imaging resolution properties of MPI. These particles can also be optimised for improved performance in specific MPI applications. The application of interest in this study is MPI in combination with magnetic fluid hyperthermia (MFI), known as MPI-MFH. This refers to MFI performed using the MPI gradient system which permits localised heating to a desired region in biological tissue, mitigating some of the issues with standard MFH application paradigms.

In this work, we aim to synthesise and optimise single-core superparamagnetic iron oxide nanocubes (IONCs) towards both MPI, and combination MPI-MFH application. Due to their lower spin disorder at the surface and smaller surface anisotropies, IONCs have a greater overall performance in terms of saturation magnetisation and magnetic susceptibility compared to equivalent spherical SPIONs. However, IONCs have not been optimised yet for these mentioned applications, which is the focus of this study. The effect of changing the core size of spherical SPIONs on MPI performance and sensitivity is well-documented with monodisperse single-core SPIONs having an increasingly improved MPI performance up to a magnetic core diameter of ~25 nm.2 With this in mind, an array of IONCs with sizes smaller than 25 nm were synthesised in our study. For good MPI-MFH performance, the nanoparticle must demonstrate both impressive MPI spatial resolutions, so heat can be localised more specifically using the MPI gradient field system, and heating performance, individually.

Reaction parameters in a thermal decomposition process were altered to obtain decanoic acid-coated magnetite IONCs of different sizes. TEM images of the syntheses are shown in Fig. 1. In all syntheses, there is clear formation of majority cubic shapes with narrow size distributions. The MPI properties have been measured for the largest and smallest synthesised IONCs. The heating performance for the 7 nm IONCs (Fig. 1d) was poor, with an intrinsic loss parameter (ILP) value of ~0.17 W/mKg. The ILP value was much larger for the 24 nm IONCs (Fig. 1a), at ~2.75 W/mKg. The 34 nm size of our IONCs is also close to the optimal size of ~25 nm for MPI, indicating their potential application in MPI, and because of the good heating properties, MPI-MFH also.

Fig. 1. TEM images of the IONCs synthesized under various conditions, with sizes of (a) 24 nm, (b) 18 nm, (c) 11 nm, (d) 7 nm, (e) 18 nm.


A tunable acid-etching procedure for the preparation of partially hollow magnetic nanostructures

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Nanostructures with hollow core and outer shell are an exciting type of nanoparticles. The central void is a space available for the incorporation of various functional cargo(s), such as drugs and catalysts. However, a wider applicability of the hollow nanostructures is delayed due to scarce and challenging synthetic procedures needed to obtain such complex nanostructures. So far, various approaches have been utilised to prepare hollow nanostructures. The most widely used etching methods rely on the synthesis of nanoparticles that have a shell and a sacrificial core, which gets selectively removed while the shell is kept intact. If the removal of the sacrificial core is only partial, we obtain a partially hollow structure, commonly referred to as yolk-shell or multishell nanostructures. These partially hollow nanostructures are also attractive as they may offer combined functionalities of the shell and the residual core part. The procedures for the preparation of partially hollow nanostructures are generally more challenging than obtaining completely hollow nanostructures, as the core removal process needs to be precisely controlled and should offer the possibility for rapid termination of the core removal. An elegant way to control the core removal process is to utilise core-shell nanoparticles, where the shell and the sacrificial core are composed of chemically different materials. In such a way we achieve a selective core removal and, moreover, the core removal rate can be nicely controlled by changing the thickness and morphology (porosity) of the shell.

In our work, we synthesised hollow and partially hollow magnetic silica nanostructures (Figure). These structures were prepared from silica-coated magnetic nanocubes by using an acid etching method to partially dissolve iron oxide cores. The iron oxide cores were either completely or partially dissolved using hydrochloric acid. Iron oxide dissolves readily in the hydrochloric acid while the silica shell remains intact. The silica porosity affects the rate of the iron oxide dissolution. Moreover, the protective ability of silica shells with different thicknesses (ranging from ~3 nm to ~60 nm) and morphologies (low-porous and mesoporous) was systematically studied by using different durations of the etchings and different hydrochloric acid concentrations. We have figured out some differences in the protective ability of different silica shells towards the acid dissolution of iron oxide cores. Our findings can be further applied to efficiently adjust the preparation procedures for obtaining partially hollow magnetic nanostructures. Finally, we conducted preliminary drug-loading experiments to test the ability of such hollow silica nanostructures to be used as drug delivery system for the model drug ibuprofen.

Figure. Transmission electron microscope micrographs of hollow silica nanostructures. (A) ~60 nm thick low-porous silica shell, (B) ~30 nm mesoporous silica shells, and (C) ~3 nm thin low-porous silica shells. All scale bars are 500 nm.

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Poster #89
Synthesis and characterisation of BaTiO$_3$ – CoFe$_2$O$_4$ magnetoelectric nanoparticles for biomedical applications.

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Magnetoelectric nanoparticles (MENP) have magnetic and electric properties coupled together[1] Here, the significant coupling between the two properties will allow direct control of ferroelectricity and magnetism. MENP are of significant interest in biomedical applications as they exhibit new functionalities such as magnetic field control of electric polarisation used in on-demand drug release among others.[2] Although there are several ways of achieving the magnetoelectric (ME) effect, combining a magnetic material with a ferroelectric one in a core-shell structure has gained significant interest in recent years due to its large ME effects.[3] The magnetic phase used in this study will be cobalt ferrite (CF) due to its high magnetostrictive coefficient and the ferroelectric phase barium titanate (BT) due to its high piezoelectric coefficient.[4, 5]

First, we present an optimisation of the synthesis protocol for the ferroelectric and the ferrimagnetic phase to control morphology of the nanoparticles. The effect of morphology and size on the properties of MENP will be studied by using different characterisation techniques (TEM, SQUID, STM, XRD, Raman, DLS).

![Figure 1: Schematic of magnetoelectric coupling causing the direct magnetoelectric effect.](image)

When a magnetic field is applied on a MENP, CF undergoes magnetostriction which causes the material to strain and elongate. This mechanical energy is transferred to BT which then exhibits polarisation. This is called strain-mediated magnetoelectric coupling (figure 1). The shape and size of the core-shell nanostructure is controlled using synthetic parameters.

References:

Synthesis of flower-like manganese ferrite nanostructures for enhancing chromium bio-reduction by *Shewanella oneidensis*

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Chromium is a common environmental pollutant deriving from several industries including plating, tanning and metal finishing. Human exposure to hexavalent chromium (Cr(VI)) can cause cancer and neurotoxicity. Leaking chrome from industrial sites into water can lead to soil and groundwater contamination which is a risk currently being considered in several industries. Integrating both adsorption and biological reduction of highly toxic Cr(VI) into the less toxic trivalent one (Cr(III)) together has been proposed as a promising strategy to tackle the aforementioned issue. In this context, nanoscale materials possess special features that make them promising candidates for such applications; nanoclusters have been gaining much attention due to their simple preparation, high surface to volume ratio, high stability and enhanced efficiency due to the complex interparticle interactions which depend on the single crystal particle size, orientation and spacing. Herein we report a simple route for the robust, single-step and scalable preparation of Mn$_x$Fe$_{3-x}$O$_4$ nanoflowers via a polyol-assisted solvothermal method. Our results revealed that the one gram of nanoflowers (60 ± 12 nm diameters) can adsorb 12 mg of Cr(VI). The effect of nanoflowers on the Cr(VI) reduction and tolerance by *Shewanella oneidensis* have been explored as a safe and integrated way with good performance in heavy metal removal from water.

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![Figure 1. Representation of an integrated adsorption bio-reduction method for safe removal of hexavalent chromium](image)
Effect of Iron Oxide Nanoparticle Surface Chemistry on Magnetic Property and Cytotoxicity on HeLa Cells

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Abstract: Superparamagnetic iron oxide nanoparticles (IONPs) with appropriate surface chemistry are in the field of great interest due to the high potential for a wide range of biomedical applications such as drug delivery, magnetic fluid hyperthermia, magnetic resonance imaging and stem cell therapy. Surface properties of nanoparticles (NPs) (i.e. surface chemistry, charge) provide them not only stability and biocompatibility but also conjugation capability for drug molecules and/or targeting ligands. Surface properties are also important to avoid or delay the interaction of NPs with the reticuloendothelial system, which might prolong their circulation half-life in the blood stream. Optimization of surface properties of NPs allows to use these NPs not only in separate application but also in combined modalities.

The aim of this study is to synthesize superparamagnetic IONPs with different surface properties (i.e. carrying carboxyl, hydroxyl, and amine groups) convenient for biomedical applications and to investigate the effects of surface chemistry on magnetic properties and in vitro cytotoxicity on HeLa cells. For this purpose, three types of IONPs (IONP@DMSA, IONP@DMSA-DG, IONP@APTES) were prepared. First, 8.4±1.0 nm spherical oleic acid coated-IONPs were synthesized by thermal decomposition method and then coated with meso-2,3-Dimercaptosuccinic acid (DMSA) or (3-Aminopropyl) triethoxysilane (APTES) via ligand exchange reaction. DMSA-coated IONPs were further conjugated with 2-deoxy-D-glucose (DG) by esterification reaction to impart functionality. Structural and magnetic properties of all IONPs were characterized by X-ray diffraction, transmission electron microscope, Fourier-transform infrared spectroscopy, zeta sizer, thermogravimetric analysis and vibrating sample magnetometer. Cytotoxicity of the IONPs with three types of coatings was assessed through 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The results showed that all NPs exhibited a typical superparamagnetic property at room temperature. Surface modification with DMSA resulted in a magnetization increment of 22% while DG conjugation and APTES coating caused a reduction of magnetization (6.5% and 32%, respectively). HeLa cells remained more than 80% viable relative to the control group when incubated with all nanoparticle types with the nanoparticle concentrations of 2.5 μg ml⁻¹, 5 μg ml⁻¹ and 10 μg ml⁻¹ for 24, 48, and 72 h. The results showed a promising potential for the use of IONP@DMSA and IONP@DMSA-DG NPs for biomedical applications. To the best of our knowledge, this is the first study to compare IONPs with these three types of surface coatings.

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Multifunctional “core/shell”-like nanocomposites based on magnetic Fe₃O₄ nanoparticles (MNP)s and cerium dioxide (CeO₂) attract significant scientific interest due to the possibility to combine the simultaneous ability of MNP-s to heat up effectively in AC magnetic field with the antioxidant and anti-amyloid activity of CeO₂. Such composites can be promising for biomedical investigations, particularly, in the therapy of diseases caused by oxidative stress and amyloidogenesis. The aim of this study was the synthesis of “core/shell”-like nanocomposites based on Fe₃O₄@CeO₂, examination of their physical-chemical properties and morphology as well as evaluation of their antioxidant and anti-amyloid activity. A set of Fe₃O₄@CeO₂ “core/shell”-like nanocomposites with the theoretically calculated thickness of CeO₂ “shell” of 3, 5, and 7-layers was fabricated by the precipitation of CeO₂ NPs onto the surface of the Fe₃O₄ MNP-s. According to XRD data, signals of both Fe₃O₄ and CeO₂ were present in XRD patterns of the composites, but the intensity of the main peak of Fe₃O₄ at 20 equal to ~ 35° reduced with the growth of CeO₂ “shell” on the surface of MNP-s. HR TEM and EELS studies revealed that Fe₃O₄@CeO₂ nanocomposites consist of Fe₃O₄ NPs core with an average size ~ 16 nm surrounded by CeO₂ NPs with an average size of ~ 3 nm forming the “core/shell”-like structures. Increasing CeO₂ “shell” thickness is manifested by the increased hydrodynamic diameter of NPs in aqueous suspensions and better stability of nanocomposites in the suspensions exposed as zeta-potential (DLS) measurements. DLS measurements with the 5- and 7-layers “shell” formed highly stable suspensions without any additional stabilizers (ζ +30 mV) in Opposite to Fe₃O₄, NPs which had zeta-potential values +17.7 mV. The thickness of the CeO₂ “shell” affected also the heating efficiency of nanocomposites under applying of AC magnetic field (H=9.3 kA/m, 300 Hz). The maximal heating temperature values were 40-50°C and decreased with increasing of the “shell” thickness. The specific loss power (SLP) values reduced from 33 W/g for Fe₃O₄ NPs to 18 W/g for Fe₃O₄@CeO₂ NPs with the theoretically calculated “7-layers shell”. Bioactivity of prepared nanocomposites as the antioxidant and anti-amyloid effect has been examined. All tested NPs significantly inhibited the formation of insulin amyloid aggregates in vitro. The anti-amyloid activity was highly dependent on the thickness of CeO₂ layers on the core of Fe₃O₄. The highest activity to inhibit the process of fibrils formation was observed for nanocomposites with the theoretically calculated “7-layers shell”. The antioxidant activity of Fe₃O₄ and Fe₃O₄@CeO₂ nanocomposites was evaluated by monitoring their catalase- and superoxide dismutase-like activity.

From a translational perspective, magnetic nanoparticles (MNP) require manufacturing processes that can be performed reliably and at scale. Continuous and automated manufacturing processes are particularly well suited for this purpose compared to batch processes, which have high technical variability and low throughput production. In this study, a continuous MNP manufacture approach based on oxidative precipitation is presented. For this, a setup was built consisting of a 10-meter-long coiled tube and a mixing element. Air (20.95 vol.-% oxygen) and a mixture of iron sulfate and ammonia solution were alternately pumped into the tube coil (Figure 1 A). Over the 10-minute continuous flow in the mixing element, superparamagnetic iron oxide nanoparticles (SPION) were then formed. The fluid exchange rate for the reaction was varied by changing the volume ratios between gas and liquid bubbles and by increasing the total number of bubbles per tube length. For different rates, SPION were synthesized and physico-chemically characterized (Figure 1 B). Transmission electron microscopy (TEM), dynamic light scattering (DLS), and iron concentration based on complexation of Fe³⁺ was determined. Exemplary results are depicted in Figure 1 B demonstrating the influence of oxidation on SPION formation. Tuning gas transfer into the liquid indicates that the diameter of the resulting SPION can be controlled. SPION can be used for the delivery of therapeutics and for imaging applications.

**Figure 1:** A) Sketch of the continuous MNP synthesis. Precise adjustment of the gas and liquid bubbles allows the reaction environment to be varied. A1: 1.85 cm³ liquid and 0.5 cm³ gas bubble (volume ratio: 0.27); A2: 1.4 cm³ liquid and 0.65 cm³ gas bubble (volume ratio: 0.68); A3: 1.0 cm³ liquid and 0.75 cm³ gas bubble (volume ratio: 0.75). B) Representative transmission electron microscopy (TEM) images of the settings A1 (TEM image B1), A2 (TEM image B2) and A3 (TEM image B3) without purification or coating. Images show different SPION morphologies.

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**From a translational perspective, magnetic nanoparticles (MNP) require manufacturing processes that can be performed reliably and at scale. Continuous and automated manufacturing processes are particularly well suited for this purpose compared to batch processes, which have high technical variability and low throughput production. In this study, a continuous MNP manufacture approach based on oxidative precipitation is presented. For this, a setup was built consisting of a 10-meter-long coiled tube and a mixing element. Air (20.95 vol.-% oxygen) and a mixture of iron sulfate and ammonia solution were alternately pumped into the tube coil (Figure 1 A). Over the 10-minute continuous flow in the mixing element, superparamagnetic iron oxide nanoparticles (SPION) were then formed. The fluid exchange rate for the reaction was varied by changing the volume ratios between gas and liquid bubbles and by increasing the total number of bubbles per tube length. For different rates, SPION were synthesized and physico-chemically characterized (Figure 1 B). Transmission electron microscopy (TEM), dynamic light scattering (DLS), and iron concentration based on complexation of Fe³⁺ was determined. Exemplary results are depicted in Figure 1 B demonstrating the influence of oxidation on SPION formation. Tuning gas transfer into the liquid indicates that the diameter of the resulting SPION can be controlled. SPION can be used for the delivery of therapeutics and for imaging applications.

**Figure 1**

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Synthesis and characterization of gold-coated superparamagnetic iron oxide nanoparticles for magnetic drug targeting treatment

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Treating cancer is still a major challenge for modern medicine. Conventional therapies such as chemotherapy are accompanied by severe side effects on healthy tissue as well as ineffective drug accumulation in diseased tissue. The concept of magnetic drug targeting (MDT) provides the means to tackle the disadvantages of conventional chemotherapy while further enhancing the effectiveness of the treatment.

Surface functionalized gold-coated superparamagnetic iron oxide nanoparticles (Au-SPIONs) might offer the possibility of a strong covalent bond for actively transporting drugs towards diseased tissues by an external magnetic field. The gold-coating process increased the hydrodynamic size of pure citrate-stabilized SPIONs (Cit-SPIONs) from an average of 107 nm to 445 nm with a broadened size distribution and resulted in non-uniform particle aggregates. While magnetic properties could be maintained after the gold-coating, particle size control and stability against sedimentation of the particles were challenges. Thus, Au-SPIONs were surface stabilized with additional citrate to create Cit-Au-SPIONs. These synthesized nanoparticles were found to be controllable in size by the variation of the added citrate concentration accompanied by a higher long-term stability and moderate pH values of the dispersion as well as reproducible particle sizes of around 150 nm.

Investigating procedure parameters during the gold-coating process revealed a strong influence of the concentration of the used gold salt on the hydrodynamic particle size, pH value and reproducibility of the particle dispersions. With an increase in gold content, the particle size increased while the reproducibility decreased. After further characterization, a promising Cit-Au-SPION system was tested for cell toxicity. No major toxic effects were found on the cell viability and proliferation of Jurkat T cell leukemia cells even after 48 h of exposure. Early functionalization of the gold surface with the thiol-containing amino acid cysteine demonstrated a 6-fold higher cysteine binding on Cit-Au-SPIONs in comparison to pure Cit-SPIONs. Binding a cysteine termined peptide on 95 nm large Cit-Au-SPIONs still resulted in stable nanoparticles with a size of 114 nm bearing 45 nm of peptide per mg of iron. Thus, gold-coating SPIONs might present a way to strongly bond thiolated molecules to their gold surface. These molecules or proteins could e.g. be specialized for carrying drugs for the usage in magnetic drug targeting treatments.

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Figure 1: Scanning electron microscope image of citrate-stabilized gold-coated SPION aggregates. Cit-Au-SPIONs show no severe toxic effects on Jurkat T cell leukemia cells and a 6-fold higher cysteine binding when compared with pure citrate-stabilized SPIONs.

Figure: SEM image of MMS with 33 wt% MNP (top) Z-contrast micrograph of a FIB prepared MS section across MNP appear bright (bottom)

Polymeric microspheres (MS) are of great interest for several medical and biotechnological applications. By incorporating drugs into the MS, they can be used for drug delivery, where diseased organs are targeted in a controlled manner by linking specific antibodies to the MS surface. Additionally, magnetic nanoparticles (MNP) can be embedded into the MS, leading to magnetic microspheres (MMS), that can be used for hyperthermia and to enhance the drug release out of the MMS. Antibody conjugated MMS can also be utilized for immunomagnetic separation and pathogens can be extracted out of a specimen. For all mentioned applications, a high concentration as well as a homogenous distribution of the MNP inside the spheres is needed. Therefore, we are working on MS made of poly(lactic-co-glycolic acid) (PLGA) or poly(lactic acid) (PLA) with embedded oleic-acid coated MNP and antibodies linked to their surface. Microspheres were produced by an emulsion-evaporation method, where the polymer, MNP and a drug are suspended in an oil phase that is homogenized in an aqueous phase containing PVA. The oil droplets are allowed to harden and finally form the MS. The homogeneity of the MS size was studied by varying several synthesis parameters, using static light scattering for size measurements. To incorporate the MNP, a hydrophilic coating is needed, why we established an oleic-acid coating of the MNP, characterizing the resulting particles with VSM, DLS and TGA. The incorporation of oleic acid coated MNP into the MS was investigated with SEM on focused ion beam cross sections and VSM. Last, an antibody conjugation was evaluated using a click chemistry approach as well the biotin-avidin adsorption mechanism. As a proof of principle, the release of an anticancer drug out of MMS by magnetic heating to 43 °C compared to 37 °C was investigated. We found that mainly the homogenization speed and method (mechanical or ultrasonic) and PVA concentration can be used to control the MS size, enabling the synthesis of MS between 0.5 and 6 μm. Coating the MNP with oleic acid enables monodisperse and stable particles in organic solvents with a mean diameter of 190 nm (z-average), a PDI of 0.12 and approx. 8 wt% oleic acid relative to the overall particle weight. SEM images revealed a homogeneous distribution of MNP throughout the spheres while maintaining a perfect spherical shape (see figure) with concentrations of MNP up to 33 wt%. Antibodies were conjugated on PLA microspheres, confirmed by photometry (ELISA). Drug release was increased by 30% due to magnetic heating, compared to release at body temperature, confirming the use of magnetic particles to accelerate drug delivery mechanisms. Summarized, we developed a toolbox of MS that can be adapted to several applications by tuning their size, incorporating magnetic nanoparticles and conjugation of antibodies to their surface.

Acknowledgements

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Ferrimagnetic iron oxide nanoparticles for heating applications: large single domain particles prepared by the green rust method

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During recent decades, the ability of magnetic particles to generate heat when exposed to alternating magnetic fields has been studied intensively, primarily because of its potential use in magnetic hyperthermia therapy. The temperature elevation in a magnetic material is caused by the magnetic relaxation and hyperthermia losses and depends on the size of particles, their mass concentration as well as the arrangement of particles. For instance, in Pickering droplets where magnetic particles are attached to the droplet surface, the heating efficiency was worse for a more dense particle shell [1]. By using proper particles it is possible to obtain a temperature high enough to partially sinter thermo-responsive particles (e.g., polymer particles) that make the particle shell around the droplets more rigid. In this manner, the microcapsules are prepared from Pickering droplets (Fig. 1a). What is more, in this approach the capsules can be inherently responsive to the external magnetic fields which is crucial when it comes to their applications in targeted therapies.

Here, we will show the proof-of-concept results for fabricating microcapsules with polymer shells from oil-in-oil Pickering droplets used as precursors. The stable Pickering droplets were prepared via oil-in-oil Pickering droplets used as precursors. The stable Pickering droplets were prepared via oil-in-oil Pickering droplets used as precursors. The stable Pickering droplets were prepared via oil-in-oil Pickering droplets used as precursors. The stable Pickering droplets were prepared via oil-in-oil Pickering droplets used as precursors.

Figure: MS for varying synthesis temperatures

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<thead>
<tr>
<th>Temperature (°C)</th>
<th>MS (Am²/kg)</th>
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<tr>
<td>5</td>
<td>54</td>
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<td>25</td>
<td>76</td>
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<tr>
<td>45</td>
<td>85</td>
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For temperatures below 45 °C, MS values are in the range of 54 Am²/kg to 85 Am²/kg. Above 45 °C, MS decreases sharply to 50 Am²/kg at 55 °C followed by a slower decrease above 55 °C, reaching 25 Am²/kg at 65 °C. Saturation magnetization Ms can be classified into three regions (see figure): synthesis temperature below 45 °C does not enable the complete transformation to magnetic material. For temperatures above 45 °C, high magnetization values around 85 Am²/kg are obtained, whereas for temperatures above 45 °C, Ms decreases, indicating the formation of a non- or weak magnetic phase apart from magnetic magnetite. This non-magnetic phase was observed using Mössbauer spectroscopy, showing an additional to high-temperature increase was tested under electric fields (Fig. 1b). After magnetic heating, the shells were much more resistant to the applied electric stress [2]. For the fabrication of capsules in bulk quantities, more efficient techniques of controlling successful capsulation should be developed and one of the potential approaches is to use a non-destructive ultrasound testing.

Acknowledgments

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STEM cells carriers of Fe-Cr-Nb-B ferromagnetic particles for cancer cell destruction by mageto-mechanical actuation

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Magnetic particles (MPs) can be used in different cancer treatment applications, such as magnetic hyperthermia, magnetic controlled delivery and release of antitumoral drugs at the targeted site of a tumor, or through mageto-mechanical actuation.

Recently, we have introduced a new type of magnetic particles (MPs) for cancer treatment by mageto-mechanical actuation (MMA) [1]. The rectangular shapes of the MPs, and the magnetic anisotropy of the glassy ribbons of which they are made induce important magnetic shape anisotropies which, along with a large saturation magnetization, generate an improved torque in a rotating magnetic field, producing important damages on the cellular viability of tumor cells. In this work we studied the possibility of transporting Fe-Cr-Nb-B MPs to areas with cancer cells (human osteosarcoma - HOS), using adipose-derived stem cells (ADSC) as carriers, considering their tumor-targeting capacity [2], and the MPs-mediated mageto-mechanical effect on HOS viability.

The Fe-Cr-Nb-B MPs were used to obtain a ferrofluid which was added with cell culture media in the cell cultures. Then, HOS and ADSC cells were incubated for 24h with the MPs, and a specific cellular viability assay MTT was performed. No cytotoxic effect was observed while the MPs upload by HOS was confirmed using TEM. By using a “wound healing” model, the migration of ADSC, both loaded and unloaded with MPs, was recorded by time-lapse imaging. The recorded films showed that ADSC were able to easily target osteosarcoma cells. The traveled distance of MPs-loaded ADSC is twice the length of the MPs-free ADSC, due to the higher mobility of the loaded cells induced by the presence of iron (Figure 1a). Mageto-mechanical actuation led to the destruction of ADSC and to the release of MPs on HOS cells, the latter incorporating the released MPs, further leading to the destruction of 80% of HOS cells (Figure 1b).

In conclusion, after checking for the biocompatibility of Fe-Cr-Nb-B magnetic particles (MPs), we have shown that MPs were successfully incorporated by ADSC and HOS cells and MPs-loaded ADSCs displayed increased mobility towards tumor cells, compared with their unloaded counterparts. The mageto-mechanical actuation led to the release of the MPs towards tumor cells, the latter being destroyed in high proportion (about 80%) by immediate application of MMA.

Acknowledgements: Work supported by UEFISCDI under contract no. PCE20/2021 (PN-III-P4-ID-PCE-2020-2381).

References

Figure 1. (a) In vitro cell migration of ADSC loaded and non-loaded, respectively, with MPs towards tumor cells. (b) Cell viability of HOS and ADSC cell controls and cells with MPs after MM actuation.

In conclusion, after checking for the biocompatibility of Fe-Cr-Nb-B magnetic particles (MPs), we have shown that MPs were successfully incorporated by ADSC and HOS cells and MPs-loaded ADSCs displayed increased mobility towards tumor cells, compared with their unloaded counterparts. The mageto-mechanical actuation led to the release of the MPs towards tumor cells, the latter being destroyed in high proportion (about 80%) by immediate application of MMA.

Acknowledgements: Work supported by UEFISCDI under contract no. PCE20/2021 (PN-III-P4-ID-PCE-2020-2381).

References

Figure a) Schematic of the drug loaded ferromagnetic nanocapsules components and their functionalities. b) TEM images of the ferromagnetic nanocapsules. c) In plane and out-of-plane magnetization loops showing the ferromagnetic behavior, the magnetic anisotropy and the vortex magnetic structure (inset image shows a schematic magnetic vortex configuration). d) Demonstration of the efficient optical heating in the first and second biological windows.
Magnetic hyperthermia as a combinatorial tool to develop new therapies against cancer

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In the last decades, magnetic nanoparticles (MNPs) have been widely investigated in the field of cancer therapy. Among their several applications, MNPs have shown a great potential in magnetic hyperthermia treatment (MHT), an adjuvant tumor therapy now undergoing clinical trials. The therapeutic effects provided by MNPs in MHT are based on their ability to heat up at therapeutic relevant temperatures (40-45°C) at the tumor site when exposed to an alternating magnetic field (AMF). This leads to apoptotic and necrotic processes of cancer cells.1,2 To improve the antitumor therapeutic effect of MNPs-based MHT, combinatorial strategies with drug delivery, immunotherapy, photothermal, and radiotherapy, are exploited.3,4 In particular, MHT can trigger the release of chemotherapeutic drugs at the tumor site or boost immune system response against tumoral cells.

In this regard, here, we present two approaches. In a first strategy, an electrospun polycaprolactone (PCL) fiber mat was co-loaded with iron oxide nanocubes (IONCs) and doxorubicin (DOXO), and the resulted platform was exploited as a scaffold to combine MHT with the heat-mediated delivery of the anti-cancer drug (Figure 1A).5 Thanks to the outstanding heating properties of the scaffold, which allow to reach the therapeutic temperature (45°C) and to induce the subsequent DOXO release, we were able to use a lower dose of the drug than that administered intravenously. Moreover, this significant cytotoxic effect against the DOXO sensitive HeLa cell line was reached under clinical conditions for MHT. In the other strategy, MHT was used in combination with immunotherapy (Figure 1B). In our group, indeed, we have demonstrated that MHT at 43°C performed on Glioblastoma cancer cells (U87 cell line) can induce the upregulation of specific stress ligands on U87 cells, making them more susceptible to macrophages and NK cell killing.6 This study suggests the possible use of MHT with MNPs as a tool to remotely switch on the immune response at the tumor by mild temperature increase, thus providing full-body coverage.

References:

Poster #93

Oriented immobilization of cadherin fragments on magnetic nanoparticles as novel magneto-mechanical cell actuators

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Magnetic nanoparticles (MNPs) can be used in a multitude of applications in the field of nanomedicine due to their unique characteristics. Among them, their ability to generate heat or tensile forces when manipulated by external magnetic fields are highly interesting. The forces generated by the remote stimulation of the MNPs can be harnessed to convert the MNPs in mechanostimulation platforms, able to exert forces directly on the cell membranes. By targeting receptors that convert mechanical stimuli into biochemical signals (mechanotransduction), MNPs could be used to activate intracellular pathways in a controlled way. In this context, mechanotransduction can take place in the adherent junctions, which relies on the role of E-cadherin. In fact, E-cadherin mechanotransduction is critical to mediate collective epithelial remodeling that takes place during tissue repair. Functionalizing MNPs with cadherins would allow to attach the nanomaterials to the cadherins on the cell membrane in an orientation-dependent manner, prior to an external mechanical stimulation that could be used to activate intracellular pathways implicated in regeneration processes.

In the present work, we generated different fragments of E-cadherin, composed of the first two extracellular domains, which are enough to establish stable homophilic interactions with the cadherins present on the cellular membrane. We used the wild-type E-cadherin recombinant fragment, and two E-cadherin mutants generated by site-directed mutagenesis, in order to control the binding affinity. The cadherin fragments were modified with a histidine tag (His-Tag) at the C-terminus to allow their oriented attachment via metal-chelate affinity to the MNPs. 15 nm iron oxide MNPs were coated with poly(ethylene glycol) (PEG) and functionalized with a nitrilotriacetic acid derivative (NTA), a molecule able to chelate metal ions like Ni2+ or Co2+. Then, His-tagged cadherin fragments were bound in an oriented fashion to the MNPs, controlling at the same time the number of proteins/MNP. In order to use the MNPs as potential cellular mechanostimulation devices, besides controlling the number and orientation of cadherins over the MNPs surface, the strength of the union protein-MNP surface is another crucial step. Thus, we stabilized these links to reach a higher union strength, through two different strategies.

Finally, we immobilized the E-cadherin-MNPs on membrane of living cells that express E-cadherin. The selective binding of the MNPs functionalized with the wild type fragment on cells was assessed, while MNPs functionalized with E-cadherin mutants did not bind to them. This is the first step towards the selective activation of intracellular pathways linked to cadherins using MNPs.
Synthesis and characterisation of Fe@FePt nanocubes for synergistic magneto-phototherapy.

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Magnetic hyperthermia (MHT) and photothermal therapy (PTT) are two promising techniques for the treatment of cancer. Compared to conventional therapies including surgery, chemo- and radiotherapy, they offer fewer side-effects considered harmful to the human body. Furthermore, the synergistic effect of both techniques offers a novel pathway for therapeutic enhancement by combining magnetic nanoparticles (MNPs) and plasmonic nanoparticles (PNPs) in one nanocomposite.

Herein, a novel nanocomposite system is proposed. Based on a core-shell principle, Fe@FePt nanocubes were synthesised for a synergistic magneto-photothermal response. The selected materials offer a possibility to establish an effective therapeutic treatment whilst remaining biocompatible. The iron-platinum shell is reported to destroy cancer cells at a threshold laser energy comparable to that of gold nanorods and have similar saturation magnetisation comparable to permanent magnets. These metal alloys are chemically stable against oxidation, however, the key point that favours these metal alloys over the mentioned comparisons is their enhanced biocompatibility.

Furthermore, the soft magnetic (low coercivity) iron nanocubes possess higher magnetic moment compared to iron oxide NPs and ferrites and are biocompatible. Through the tuning of the magnetic properties of an Fe@FePt core-shell nanocomposite, the combination of a soft magnetic iron core and a hard bimetallic shell can effectively enhance the coercivity compared to their hard-core and a soft-shell counterpart. In addition to this, cubic anisotropy is favoured over their spherical and other geometrical counterparts, showing lower magnetic and surface anisotropies (surface spin disorders). Iron nanocubes are reported to reach their bulk saturation value at around 20 nm (where maximum magnetic properties are observed).

The chosen path of synthesis is via organometallic route (Scheme 1), whereby an iron dimmer will undergo thermal decomposition to form iron NPs seeds. With the variation of long chain amines and amines, the control of the a/d ratio will favour the formation of an anisotropic shape over an isotropic one, controlling the formation of cubic-shaped species. Additionally, monitoring the temperature below will favour the anisotropic growth of iron nanocubes along with the pH controlling the formation of an FePt cubic lattice.

NP seeds
20 nm iron nanocubes
Iron@Platinum.

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References:

Poster #85

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Poster #88

Figure 1: NP growth by molecular imaging techniques like PET and SPECT.
Using Magnetic Torques to Enhance Tumor Infiltration of Cargo-Carrying Magnetotactic Bacteria

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Tumor-targeting bacteria are appealing therapeutic vectors because of their capacity to produce or transport a wide range of payloads and their ability to modulate an intratumoral inflammatory response. Nevertheless, translation of this approach has been hindered by difficulties in achieving sufficient tumor colonization. Developing strategies to enhance accumulation at the target site is essential for facilitating robust colonization, while concurrently decreasing the required initial dose and associated toxicity.

Recently, magnetotactic bacteria (MTB), which biomimic the magnetic-based nanostats, have been manipulated with external magnetic fields as guidable drug carriers. Thus far, control strategies have either relied on poorly scalable magnetic field gradients that diminish rapidly with increasing distance from their source, or have employed directing magnetic fields with propulsive forces limited by the bacterial motor. Here, we employ a magnetic torque-driven actuation scheme based on rotating magnetic fields (RMF) to wirelessly control Magnetospirillum magnetotacticum AMB-1 bearing versatile liposomal cargo.

By studying extracellular with computational models (Fig. 1A) and in vitro (Fig. 1B), we find that the main mechanism driving the enhancement of translocation is increased surface exploration resulting from torque-driven translational motion at the cell interface. We then assess the spatiotemporal characteristics of MTB infiltration and find that fluorescently labelled bacteria colonize core regions in 3D tumor models, with 9-9 fold higher signal in samples exposed to RMF (Fig. 1C). Finally, to better recapitulate in vivo conditions, we study magnetically-enhanced penetration of MTB in a microfluidic chip containing spheroids embedded in a collagen matrix (Fig. 1C). Overall, our findings suggest that scalable control strategies that harness magnetic torque-driven motion and autonomous axis-based locomotion can be leveraged advantageously for improved targeting and colonization of living therapeutics in tumors.

![Figure 1](image1.png)

**Figure 1.** (A) Computational model and velocity profiles of MTB transport under RMF across an endothelial monolayer. (B) Translational for control (no field), directing magnetic field (DMF, 12 mT) and RMF (20 mT, 24 Hz). VE-cadherin (green) on HRECC-1 cells (magenta, scale bar = 50 μm). (C) Top: Z-projection of spheroids and corresponding fluorescent mouse collagen (red) extruded for 24 hours after RMF exposure (bottom, scale bar = 200 μm).


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Poly-histidine functionalized γ-Fe₂O₃@SiO₂ nanoparticles to access the cell cytoplasm

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Magnetic nanoparticles (MNPs), as any other type of nanoparticles, are internalized by cells through endocytosis, and thus are trapped in intracellular vesicles called endosomes[1]. But for a number of bio-applications, such as cellular engineering or magnetic hyperthermia treatments, it can be of great interest to have particles able to reach the cell cytoplasm. This would allow to have less dipolar interactions between the MNPs, and hence increase their intracellular heating properties[2]. It would also enable the possible diffusion of the MNPs in the cytosol and the targeting of specific intracellular proteins of organelles, which would open the door to intracellular engineering with MNPs[3,4].

In this study, we studied the effect of the functionalization of γ-Fe₂O₃@SiO₂ core-shell nanoparticles with poly-histidine moieties through two types of functionalization: a permanent bound made by strain-promoted azide-alkyne cycloaddition (SPAAC) or an intracellularly labile disulfide link. After careful characterization of the functionalized MNPs, we showed, by means of confocal microscopy and transmission electron microscopy, that the poly-histidine peptide promoted cytosol access to the MNPs probably through the proton sponge effect[5]. In the case of the disulfide bound, the peptide was cleaved from the surface of the MNPs thanks to intracellular glutathione, decreasing the possible interactions between the MNPs and the intracellular membranes.

**Figure:** a) Transmission electron microscopy image of γ-Fe₂O₃@SiO₂ core-shell MNPs. b,c) confocal microscopy image of fluorescent γ-Fe₂O₃@SiO₂ core-shell MNPs 6 h after internalization in CHO cells: b) non functionalized MNPs, c) MNPs functionalized with peptides through click chemistry. d) Scanning transmission electron microscopy image showing MNPs escaping from a ruptured endosome.

Optimal particles for highly sensitive biosensing application in mixed frequency excitation: Insights from a fundamental simulative approach
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Magnetic nanoparticles (MNPs) are widely investigated for biomedical applications in diagnostics (e.g., imaging), therapeutics (e.g., hyperthermia), and general biosensing. For all these applications, the MNPs unique magnetic relaxation mechanism in an alternating magnetic field (AFM) is stimulated to induce desired effects. Whereas magnetic fluid hyperthermia (MFH) and magnetic particle imaging (MPI) are the most prominent examples for biomedical application, we investigate the relatively new biosensing application of frequency mixing magnetic detection (FMMD) from a fundamental perspective. Generally, we ask how specific MNP parameters (core size, magnetic anisotropy) influence the signal, specifically we predict the most effective MNP core size for signal generation.

In FMMD, simultaneously two AFM are applied: a low-frequency magnetic driving field, driving MNP close to saturation, and a high-frequency excitation field that probes MNP susceptibility: $H_{\text{eff}} = H_0 + H_{\text{mip}} \sin(2\pi f_1 t) + H_{\text{mip}} \cos(2\pi f_2 t)$. Resulting from the nonlinear magnetization of the MNP, harmonics of both individual incident frequencies as well as intermodulation products of these frequencies are generated. In this work, we present numerical Monte-Carlo (MC)-based simulations of the MNP relaxation process, solving the Landau-Lifshitz-Gilbert (LLG) equation to predict FMMD signals: $\frac{d\mathbf{m}_p}{dt} = -\gamma (\mathbf{m}_p \times \mathbf{H}_{\text{eff}} + \alpha \mathbf{m}_p \times (H_{\text{eff}} \times \mathbf{m}_p))$. Details on the method can be found in [1].

As Figure 1 shows for the first four intermodulation signals $f_1 + n \cdot f_2$, with $n = 1, 2, 3, 4$, we can clearly see that larger core sizes generally increase the signal intensity. This trend is predicted by a simple Langevin-function based thermal equilibrium model. Both predictions include a lognormal size distribution, the effect of core size distribution presumably dominates the effect of magnetic anisotropy. The findings are supported by comparison with experimental data and help to identify which MNPs are best suited for magnetic biosensing applications using FMMD.

Reference:

Figure 1: ACS spectrum of the normalized imaginary part of the magnetic susceptibility over frequency. Each color represents a different virus concentration (in viruses per ml). With increasing virus concentration, a broadening of the maximum of the imaginary part and a shift to lower frequencies is measured.

Figure 2: MC-simulated core size-dependent FMMD signal for the first four intermodulations $f_1 + n \cdot f_2$ with $n = 1, 2, 3, 4$. Input parameters for 4000 particles: $f_1 = 2000$ Hz, $f_2 = 40000$ Hz, $H_0 = 36$ kA/m, $H_{\text{mip}} = 3.3$ mT.
Point-of-need detection of pathogen-specific nucleic acid targets using magnetic particle spectroscopy

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The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strongly demonstrates the need for a sensitive, fast and reliable pathogen diagnostics tool. Ultra-flexible giant magnetoresistance biosensors exhibit great potential for the detection of various biomarkers with the ability to adapt to different surface textures. Here, a lab-on-a-needle biosensing platform based on ultra-flexible giant magnetoresistance (GMR) biosensors is developed for the detection of osteosarcoma cells (OSCA-8) cells (see Fig. (a)-(c)). The fabricated flexible GMR sensors remain unchanged after 500 cycles of compressive and tensile stress, indicating strong robustness even when applied to a surface that’s constantly in motion. The platform’s capability in cell detection is validated through the detection of different concentrations of OSCA-8 cells with a LOD of 10^4 cells/ml, which corresponds to 200 cells in the sample, as shown in Fig. (d)-(i). The ability to perform real-time, sensitive cell detection based on the developed platform makes it possible to realize cell tracking in cell metastasis studies as well as on-site biopsies at potential tumor sites with proper cell recognition bioassays.

Ultra-Flexible Giant Magnetoresistance Biosensors for Realtime Monitoring of Tumor Cells: Method for Future Lab-on-a-Needle Biopsies

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Flexible biosensors exhibit great potential for the detection of various biomarkers with the ability to adapt to different surface textures. Here, a lab-on-a-needle biosensing platform based on ultra-flexible giant magnetoresistance (GMR) biosensors is developed for the detection of osteosarcoma cells (OSCA-8) cells (see Fig. (a)-(c)). The fabricated flexible GMR sensors exhibit a MR ratio of 5.2% and a sensitivity of 0.13%/Ω in the linear region, which are comparable to their rigid counterparts. It is found that the magnetic properties of the flexible GMR sensors remain unchanged after 500 cycles of compressive and tensile stress, indicating strong robustness even when applied to a surface that’s constantly in motion. The platform’s capability in cell detection is validated through the detection of different concentrations of OSCA-8 cells with a LOD of 10^4 cells/ml, which corresponds to 200 cells in the sample, as shown in Fig. (d)-(i). The ability to perform real-time, sensitive cell detection based on the developed platform makes it possible to realize cell tracking in cell metastasis studies as well as on-site biopsies at potential tumor sites with proper cell recognition bioassays.

In this study, MNPs and polystyrene beads were functionalized with single-stranded (ss)DNA. By the addition of a specific target ssDNA sequence, the particles and beads are crosslinked, resulting in increased particle hydrodynamic size and retarded Brownian relaxation mechanism, causing a decrease of odd higher harmonics in the MPS spectrum (Fig. 1A). To exclude the effect of particle concentration, 3rd/1st harmonics ratio is calculated (Fig. 1B). Our preliminary studies show that ssDNA can be detected in a concentration-dependent manner, providing the means to quantify the results, with a limit of detection of 280 pM (Fig. 1C). We show that not only synthetic DNA with an arbitrary sequence, but also RNA can be detected. In addition, SARS-CoV-2-specific DNA as well as saliva as a sample medium can be used for an accurate assay.

Our proof-of-principle experiments demonstrate the potential of MPS-based assays for a reliable and fast diagnostic of pathogens like SARS-CoV-2 in a point-of-need fashion without the need of complex sample preparation.

Figure 1 A) Measurement and assay principle of MPS. B) Exemplary result of the harmonic ratio. C) Target concentration dependence of the relative change δ (difference between the measured harmonic ratio with target present and the blank probe).

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Understanding the dynamic susceptibility of magnetic nanoplatelet suspensions

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Following advances in synthesis techniques, magnetic soft matter research has expanded to increasingly investigate anisotropic and anisometric magnetic colloidal suspensions. The persistent interest in studying and refining anisotropic colloidal systems comes from the knowledge that colloidal anisometry can be used as an effective control parameter to tune both self-assembly scenarios and thermodynamic, rheological and phase behavior of dipolar (magnetic) soft matter[1]. Potential applications for such tailored suspensions include drug delivery[2] and magnetic hyperthermia[3].

One recently prominent example of such a suspension would be that of magnetic nanoplatelets with a dipole oriented perpendicular to the surface, which have recently drawn attention for their potential to form a ferromagnetic nematic phase[4]. This contribution will focus on the computational work to characterise properties such as the static and dynamic magnetic susceptibilities of polydisperse magnetic nanoplatelets, as well as the microstructure of such suspensions. While these properties are well-described by mean-field approaches in conventional moderately concentrated and interacting ferrofluids[5], we see that the interparticle interactions in polydisperse suspensions render the situation significantly more complex.

References

Figure 1: Simulation snapshot of a polydisperse magnetic nanoplatelet simulation.
Safety and efficacy assessment of iron oxide nanoparticles intended for magnetic hyperthermia: a translational story

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Pancreatic ductal adenocarcinoma (PDAC) carries a dismal five-year survival rate of less than 10%, and a median survival time of 10-12 months from diagnosis. At present, efforts to improve overall outcome in these patients have been minimally effective, with five-year survival statistics barely increasing in the last four decades (<4%). Clearly, novel approaches for treating this cancer are required to overcome the lack of success in recent times.

Magnetic hyperthermia is an innovative thermal treatment for cancer that utilizes tumour-residing superparamagnetic iron oxide nanoparticles (SPION) and externally-applied alternating magnetic fields (AMF). This treatment is clinically approved in Europe to treat glioblastoma and is currently undergoing clinical evaluation in prostate cancer in the United States. These are not the only potential indications, however, with many preclinical studies demonstrating efficacy in multiple solid malignancies.

Here we present highlights of the NoCanTher (Nanomedicine upsaling for early clinical phases of multimodal cancer therapy) and Safe-N-MedTech (Safety testing in the life cycle of nanotechnology-enabled medical technologies) projects where magnetic hyperthermia treatment - both SPION and AMF device - were successfully translated to a clinical study currently ongoing for locally-advanced PDAC. Work related to the early contamination screening, blood compatibility analysis, in vitro and in vivo safety and efficacy testing will be presented that resulted in the approval of a clinical study by the Spanish National Competent Authority in 2021.
Basics of Magnetic Nanoparticles

Karen Livesey

13th Magnetic Carriers Meeting, London, 2022

Three tutorials

1. Basics and energies
2. Magnetic nanoparticle dynamics
3. Characterizing magnetic nanoparticles
Basics of Magnetic Nanoparticles

Karen Livesey

Three tutorials

1. Basics and energies

2. Magnetic nanoparticle dynamics

3. Characterizing magnetic nanoparticles

Magnetic materials

- Have atomic magnetic dipoles due to electrons
- Dipoles (left) are equivalent to mini bar magnets (right)

\[ \mu = \text{atomic magnetic dipole moment [A m}^2\text{]} \quad \text{ie. Current \times area} \]
FERROmagnetic materials

- All those dipoles tend to **align**

![Diagram of aligned spins]

- We say there is a net **magnetization**, found by summing up dipole moments $\vec{\mu}$ and dividing by the volume $V$ they occupy:

$$\vec{M} = \frac{\sum_i \vec{\mu}}{V} = \text{magnetization} \ [\text{A/m}]$$

FERRImagnetic materials

- All the dipoles tend to **anti-align**, with different moments on each sublattice

![Diagram of anti-aligned spins]

- Still a net **magnetization**, found by summing up dipole moments $\vec{\mu}$

$$\vec{M} = \frac{\sum_i \vec{\mu}}{V} = \text{magnetization} \ [\text{A/m}]$$
FERROmagnetic materials: exchange energy

- This is what most people mean by “a magnet”

- Alignment is due to an interaction between neighbouring dipoles: the quantum “exchange” energy $E_{ex}$

---

Thermal energy

- Atomic-level *jiggle* affects all systems at finite temperature $T$

- Jiggle reduces the alignment $\rightarrow$ lower net magnetization $\vec{M}$
Magnetization versus temperature

- For large temperatures, thermal energy dominates exchange and magnetization is lost! ($\vec{M}=0$)

Ferromagnet and paramagnet

- Exchange energy in competition with thermal energy
Now make it nano!

- Imagine a tiny ferromagnetic ball

10 – 30 nanometer-wide core
(40 – 120 atoms)

Now make it nano!

- Imagine a tiny ferromagnetic ball

- Since the atomic dipoles are all aligned, replace with one “macrospin” magnetic moment

\[ \vec{m} = V \vec{M} \text{ = macrospin moment [A m}^2\text{]} \]
Now make it nano!

- Imagine a tiny hairy ferromagnetic ball

![Diagram of a ferromagnetic ball with ligands](image)

**Ligands**
- ie. Stabilizing organic molecules
- Vary in length
- Ligand exchange may occur!

One slide for the chemists!

---

Single domain particle

- If nanoparticles are too big, then the magnet splits into **regions of aligned magnetization**, ie. “domains”

![Diagram of magnetic domains](image)

**Single domain**
- $\leq 50$ nm

**Two domains**

**Multi-domain**

- Domains form to reduce stray magnetic field energy
**Stray field energy**

- **Large stray field** energy
  - Low exchange energy

- **Low stray field** energy
  - Large exchange energy

**Single domain**

**Multi-domains**

---

**Anisotropy energy**

- There is a **preferred axis** for macrospin to point, due to underlying crystal structure.

- Usually assume “uniaxial”

- Key to understanding thermal behaviour of magnetic nanoparticles!
**Anisotropy energy**

- Two happy directions
- Energy barrier $KV$ in between

![Energy diagram](image)

$k = \text{anisotropy constant} \quad [\text{J/m}^3]

V = \text{volume} \quad [\text{m}^3]

**Anisotropy energy**

- Consider competition between anisotropy energy and thermal energy

![Energy diagram](image)
Low temperatures...

- Macrospin is stuck in an energy well
- Anisotropy dominates thermal energy
- "Blocked" moment

![Energy diagram for low temperatures](image1)

High temperatures...

- Macrospin jumps over barrier easily.
- Average magnetization $\bar{M} = 0$
- "Superparamagnetic" behaviour

![Energy diagram for high temperatures](image2)

- Onset depends on size
- $\sim 25$ K for 5 nm radius magnetite
Zeeman energy

- Macrospin prefers to align with an applied magnetic field $\vec{H}$

\[
\text{Energy of particle}
\]

![Graph showing energy vs. $\theta$ (rad)]

The two wells are no longer equal

Dipolar interaction energy

- Each macrospin produces a dipolar magnetic field

- Other macrospins want to align with that dipolar field

- Very complicated magnetic arrangements
Dipolar interaction energy – in fluids

Recap of energies

1. Exchange energy
2. Stray field energy
3. Anisotropy energy
4. Thermal energy
5. Zeeman energy
6. Dipolar interaction energy

These energies will be needed to understand dynamics... next time!
Basics of Magnetic Nanoparticles

Karen Livesey

End of part 1

Basics of Magnetic Nanoparticles

Karen Livesey

Three tutorials

1. Basics and energies

2. Magnetic nanoparticle dynamics

3. Characterizing magnetic nanoparticles
Why study dynamics (changes with time)?

• Most applications of magnetic carriers rely on their magnetic or physical response to a stimulus over time

  e.g. Drug delivery through mucus

  30 nm magnetite particles in magnetic field gradient
  Picture courtesy Profs Spendier & Celinski (UCCS)

Why study dynamics (changes with time)?

• Most applications of magnetic carriers rely on their magnetic or physical response to a stimulus over time

  e.g. Hyperthermia

  Oscillating field
  → jiggling particles
  → heat generated

  A. Andrade et al., Biomedical Engineering-Frontiers and Challenges (2011)
Dynamics to reach a steady state = “relaxation”

1. **Magnetization relaxation** $\rightarrow \mathbf{M}$ moves towards a steady value

2. **Physical relaxation** $\rightarrow$ Particle density/microstructure moves towards a steady state

Magnetization relaxation mechanisms

1. **Macrospin** rotation – called Néel relaxation

2. **Physical** rotation – called Brownian relaxation
Macrospin rotation – Néel relaxation time

- **Macrospin** must surmount energy barrier
- Small particles and/or high temperature
- A **stochastic** process!
  So we can only talk about “average time” to relax for a nanoparticle sample

Deutsch and Evans, JMMM 354 (2014)
Brown, Phys. Rev. 130, 1677 (1963)

Average Néel relaxation time

Sample of many thousands or millions of nanoparticles

**Constant Applied Field**

**Constant Temperature**

*NSF DMR-1808412*  
*Artek Chalifour (UCCS)*

**VIDEO**: Thermal Landau-Lifshitz equation simulations
Average Néel relaxation time

H = 50 Oe  \( \tau \rightarrow 14.2 \text{ ns} \)

T = 150 K

Simulations yield an average relaxation time

Constant Applied Field

Constant Temperature

NSF DMR-1808412
Artek Chalifour (UCCS)

Average Néel relaxation time

Fast intra-well dynamics

Longer time hopping over energy barriers

5000 particles
5 nm radius magnetite

Macropin rotation – Néel relaxation time

- Analytic estimate:
  Average time depends on barrier height ($KV$) compared to thermal energy ($k_B T$)

\[ \tau_N = \tau_o e^{\left(\frac{KV}{k_B T}\right)} \]

Deutsch and Evans, JMMM 354 (2014)
Brown, Phys. Rev. 130, 1677 (1963)

Physical rotation – Brownian relaxation time

- Whole particle rotates in a fluid (driven by field or diffusive)
- Larger particles and/or lower temperature
- Average time depends on fluid viscosity ($\eta$) and hydrodynamic volume ($V_h$) compared to thermal energy ($k_B T$)

\[ \tau_B = \frac{3\eta V_h}{k_B T} \]

Frenkel, Kinetic Theory of Liquids (1955)
Physical rotation – Brownian relaxation time

- Whole particle rotates in a fluid (driven by field or diffusive)

![Diagram of particle rotation](image)

VIDEO!

$B=20$ mT

1 particle
(radius = 10 nm)

- Brownian translations are seen here, as well as rotations

An aside on units

- I am using **Standard International (SI)** here... mostly, rather than Centimeter-Gram-Second (CGS)
An aside on units

- Magnetic field (H) and Magnetic induction (B) have SI units of [A/m] [T]
  In a vacuum, $B = \mu_0 H$, where $\mu_0$ is the vacuum permeability

$1.6 \times 10^4$ A/m = 20 mT

= 400 X larger than Earth’s magnetic field in London
= 100 X smaller than in a Magnetic Resonance Imaging machine
= insufficient to dominate Brownian rotations

An aside on units

- Magnetic field (H) and Magnetic induction (B) have SI units of [A/m] [T]
  In a vacuum, $B = \mu_0 H$, where $\mu_0$ is the vacuum permeability

- **Volume magnetization** has units [A/m].

- **Mass magnetization** (total moment per unit mass) has units [Am²/kg].

You may see emu/g (CGS) regularly... ...I’m sorry.
Combined magnetic relaxation time

- Fastest process dominates relaxation.

\[
\frac{1}{\tau} = \frac{1}{\tau_N} + \frac{1}{\tau_B}
\]

Dynamics to reach a steady state = “relaxation”

1. Magnetization relaxation $\rightarrow \vec{M}$ moves towards a steady value

2. Physical relaxation $\rightarrow$ Particle density/microstructure moves towards a steady value
**Physical relaxation mechanism**

- Macrospins feel a **force** due to **magnetic field gradients**
- Gradients are depicted by a changing density of magnetic field lines
- Most bar magnets produce a gradient field – especially at sharp edges/changes

**Self-assembly by magnetic field gradients**

- e.g. magnetic substrate with magnetization transitions produces large field gradients there
**Video: Simulation of self assembly in a fluid**

- Field gradient generated by 2 magnetic transitions

---

**Dipolar interactions**

- Particles are attracted/repelled by the field gradients of others

- Presence of a static OR oscillating applied field can aid in the formation of chains
Chain formation

VIDEO!

25 nm radius particles

1.25 kHz field of 100 kA/m

Anderson et al., Nanomaterials 11 (2021)

Physical structures affect magnetic relaxation

VIDEO!

$B=20 \text{ mT}$

1 particle (radius = 10 nm)
Physical structures affect magnetic relaxation

Magnetization relaxation takes much longer than for the isolated particle

Dynamics summary

- **Magnetization relaxation** $\rightarrow \vec{M}$ moves towards a steady value
  Brownian and Néel mechanisms

- **Physical relaxation** $\rightarrow$ Particle density/microstructure moves towards a steady value
  Magnetic field gradients

- **Relaxation times over 10 orders of magnitude!!!**
  1 nanosecond (Néel) to 1 minute (self-assembly)
Dynamics – implications

- **Hyperthermia example**: maximize energy produced by oscillating the field with a period that matches the magnetic relaxation time.

Then particles can just keep up (left), and there is less static waiting (right).

![Graph showing magnetic field (H) and magnetization (M) over time](image)

Dynamics – implications

- **Characterization methods rely on relaxation processes**: Dynamic Magnetic Susceptibility measurements

How the magnetization keeps up with an oscillating field frequency
- tells us the relaxation time
- tells us the nanoscale energy barriers

![Graph showing magnetization (M) in phase with field frequency](image)
Basics of Magnetic Nanoparticles
Karen Livesey

End of part 2

More on characterization tomorrow!

Basics of Magnetic Nanoparticles
Karen Livesey

Three tutorials

1. Basics and energies
2. Magnetic nanoparticle dynamics
3. Characterizing magnetic nanoparticles
Experiments and what they tell us

- According to a theorist...

- Some useful articles:


What we may want to know

1. Particle size
2. Saturation magnetization
3. Particle interaction strength and sign
4. Anisotropy barriers

E.g. **Hyperthermia**: want a **large saturation magnetization** and **moderate anisotropy** to generate the most heat. **Interactions** may help or hinder!
Particle size

- Transmission Electron Microscopy (TEM) or Scanning Electron Microscopy (SEM)

![TEM image of immobilized particles](image)

**e.g. TEM image**
Immobilized particles

FitzGerald PhD dissertation, University of South Carolina (2021). Fig. 4.2

---

Particle size from TEM

- From images, measure each particle and construct histogram of diameters

![TEM image and histogram](image)
Particle size from TEM

• From images, measure each particle and construct histogram of diameters

• Option: fit analytic function to particle size distribution

Particle size from TEM: notes

• The immobilized particles may be different to when in fluid

• It’s possible to measure magnetic core size, subtracting ligands

• Beware the log-normal size distribution!
  - Mean and mode size are different
  - Diameter distribution is different from the volume distribution
Particle size

- Dynamic light scattering (DLS) of fluids
- Measures the “hydrodynamic” size of particles
- Relies on their Brownian motion in solution

Saturation magnetization $M_s$ [A/m]

- Magnetization versus static applied field measurement
- Performed using a SQuID or VSM magnetometer
M vs H – Low temperature

- The system has a **memory** ... “Hysteresis loop”
- Macrospins are **blocked** at low temperature and for fast field sweep rates
- **Area** inside loop = magnetic work done by the field (heat?)

M vs H – High temperature

- The curve is now **reversible** – no memory
- Macrospins are "**superparamagnetic**" at high temperature and/or slow field sweep rates
- The net moment follows the field
M vs H – High temperature – Langevin function

- Superparamagnetic magnetization can be predicted using the Langevin function (not given)
  Assumes anisotropy barriers negligible & particles are non-interacting

- For small fields, $M$ has linear behaviour

\[
\frac{M}{M_s} \sim \left(\frac{\mu_0 M_s V}{3 k_B T}\right) H
\]

Low field susceptibility $\chi$ – High temperature

- Susceptibility = the rate of magnetization $M$ increase with an increase in field $H$ (unitless slope)

\[
\chi = \frac{M}{H} \sim \frac{\mu_0 M_s^2 V}{3 k_B T}
\]
**Low field susceptibility \( \chi \) – High temperature**

- Susceptibility = the rate of magnetization \( M \) increase with an increase in field \( H \) (unitless **slope**)

\[
\chi = \frac{M}{H} \sim \frac{\mu_0 M_S^2 V}{3kT}
\]

- A plot of \( 1/\chi \) versus \( T \) should be linear and should extrapolate to origin...

\[
\frac{1}{\chi} \sim \frac{3k}{\chi} = \frac{3k}{\mu_0 M_S^2 V} T
\]

**Curie’s Law**

---

**Interaction temperature**

- Often \( 1/\chi \) versus \( T \) does **not** go through the origin!!!!

  - Due to dipolar interactions
  - Can tell their strength and sign
Anisotropy barriers

- Zero-field cooled (ZFC) and field cooled (FC) magnetization versus temperature measurements
- Dynamic Magnetic Susceptibility measurements

Zero field cooled measurement

- Cool sample in zero field, then heat back up in a weak field $H \sim 10$ Oe (CGS) or $\mu_0 H \sim 1$ mT (SI)
Field cooled measurement

- Cool sample in weak field, then heat back up in a weak field

Mean “Blocking temperature” $T_B$

= The average temperature at which particles become unblocked.

- Transition region is smeared because of particle size distribution
**Audience poll: Where is the mean Blocking temperature?**

a) At the ZFC peak, you idiot!
b) To the right of the ZFC peak
c) To the left of the ZFC peak

Vote now!

---

**Left of peak = “Blocking temperature” \( T_B \)**

- The *mean* Blocking temperature tells us about the mean energy barrier \( K \nu \)
- Recall the Néel relaxation time formula

---

It’s not at the peak. Stop it.
Extracting anisotropy constant $K$ [J/m$^3$]

- Important for choosing materials for hyperthermia and other applications!

\[
T_B = \frac{KV}{k_B \ln(\tau_m/\tau_0)}
\]

Volume distribution

Measurement time $\sim 100$ s

Attempt time $\sim 1$ ns


Summary of characterization

1. **Particle size**
   - **Electron Microscopy** and **Dynamic Light Scattering**

2. **Saturation magnetization**
   - Magnetization versus applied field

3. **Particle interaction strength and sign**
   - Low field susceptibility

4. **Anisotropy barriers**
   - Magnetization vs temperature (ZFC and FC) and Dynamic Susceptibility
Thank you for listening

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13th Magnetic Carriers Meeting, London, 2022

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Quantum Design UK and Ireland is part of the Quantum Design International (QDI) group. The company distributes scientific and industrial instrumentation through an international network, with subsidiaries in every major technological centre around the world. QDI’s success in distributing scientific products comes from more than 30 years’ experience in manufacturing and distributing its own industry-leading materials characterisation systems. We also offer the DynoMag instrument which enables determination of the dynamic magnetic properties of liquids, powders and solid samples.

Sepmag
https://www.sepmag.eu/

SEPMAG manufactures constant force biomagnetic separation equipment. Its systems enhance the reproducibility of diagnostic kits eliminating assay variability, recover the maximum of beads and facilitate the validation process through a full scale up technology.

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FerroTec provides customers with advanced technology solutions that make their products work better, more precisely, and more reliably. Founded in 1968 on a technology core of Ferrofluidic magnetic liquid and Ferrofluidic® sealing products, the company and their product portfolio have grown to meet the evolving customer needs.

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Magnet Sales & Service Limited provides magnetic solutions to a wide variety of markets and applications. Over many years we have worked closely with leading magnetic bead manufacturers, developers and users in providing both standard and bespoke separation devices. Whether you’re looking for a rapid or improved separation device for a tube, vessel or plate, or if you require a magnetic separation process as part of your automated equipment or production, then Magnet Sales can help.
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The highest quality iron oxide magnetite (Fe₃O₄) nanoparticles commercially available.

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**Key Applications**
- Superparamagnetic Relaxometry
- Magnetic Resonance Imaging
- Magnetic Particle Imaging
- Magnetically Induced Hyperthermia

**Other Applications**
- Vaccine Adjuvant
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- Magnetic Immuno assays
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PrecisionMRX nanoparticles are manufactured by Imagion Biosystems, Inc., a developer of non-invasive, non-radioactive diagnostic imaging technology. Combining nanotechnology and biotechnology, the company aims to use PrecisionMRX nanoparticles to support clinical research and other biomedical applications.

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It is chemicell’s policy to be open for cooperations with other companies or scientific institutes to maximize the chances and opportunities that evolve from the rapid development of biotechnological procedures and to distribute innovative new products.
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SiMAG-N-DNA particles have been successfully used to isolate SARS-CoV-2 RNA for rapid large scale testing by RT-qPCR and RT-LAMP.

Steffen Klein et al. - July 2020 - SARS-CoV-2 RNA extraction using magnetic beads for rapid large-scale testing by RT-qPCR and RT-LAMP. https://www.mdpi.com/1999-4915/12/8/863

Magnetofection – magnetic transfection of pollen

The simple and efficient Magnetofection technology was successfully applied to the transfection of pollen. This opens the possibility of the rapid and efficient generation of new variations of transgenic crops.


SiMAG / fluidMAG - magnetic nano- and microparticles

Contact

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Germany

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About us

Nanotech Solutions S.L. is an innovation company founded on January 2019 and composed by experts in instrumentation and nanomagnetics research, development and manufacturing.

NTSOL focuses its commercial activities on the development and manufacturing of instrumentation for AC/DC magnetic field generation or Magnetometry. These Systems are used for characterising the magnetic properties of nanomaterials and for its applications in different areas.

A tight interaction with customers to satisfy their requirements is our major fingerprint as manufacturer.

We are committed with magnetic nanomaterial’s users to provide the best to benefit their research and/or industrial activities. NTSOL offers commercial alternatives to suit customer requirements and purchase capabilities: Sales or renting?

For achieving this goal, ‘flexibility’ guides our actions concerning the design, development, manufacturing and commercialization of NTSOL advanced instrumentation.

AC Magnetometry

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Developing a magnetic bead-based process is a laborious task. Users often need to work with a wide range of volumes, starting with small tubes and increasing the sample size. Sepmag® proprietary technology generates constant magnetic force at their inner bore, with minimum stray fields. Processes are monitored and recorded, which enables the operator to explore the effects of bead size, concentration, or buffer conditions on the separation time.

- **Real-time monitoring.** Our Monitor - software and hardware - measures optical changes in the suspension, displaying its behavior and comparing different compositions.

- **Well-defined magnetic separation conditions.** Applying a well-defined magnetic force to the entire sample means variations are restricted to suspension characteristics (particles, buffer, …).

- **Safe System.** Large magnets can be dangerous. Our systems are designed to operate near computers and to protect operators from risks.

Sepmag® LAB, especially suited to viscous media and/or small magnetic beads/particles

<table>
<thead>
<tr>
<th>Model</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepmag® LAB</td>
<td>For small tubes (1.5-50 ml), filled up to 50 mm</td>
</tr>
<tr>
<td>Sepmag® LAB L</td>
<td>For small tubes (1.5-50 ml), filled up to 90 mm</td>
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</table>

Sepmag® A, for the first steps with commercial magnetic beads and water buffers

<table>
<thead>
<tr>
<th>Model</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepmag® A200ml</td>
<td>For 250 ml bottles</td>
</tr>
<tr>
<td>Sepmag® A200ml</td>
<td>For 500 ml bottles</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most popular adaptors</th>
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<tbody>
<tr>
<td>MA211</td>
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<tr>
<td>MA022</td>
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<tr>
<td>MA003</td>
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References:
[3] TEM tomography image of synomag®-D, L. J. Zeng, Chalmers University of Technology, Göteborg

Do you require particle design and modification in compliance with ISO 13485?
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