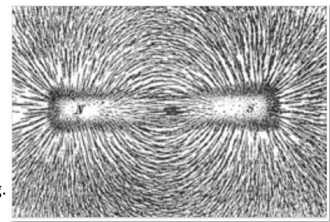
Superparamagnetické nanočástice pro diagnostiku a terapii

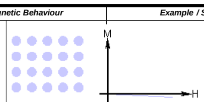
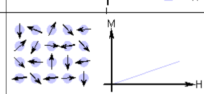
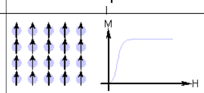
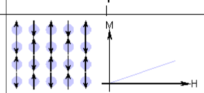
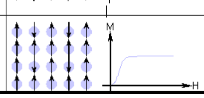
Kamil Záruba

2017

Magnetismus

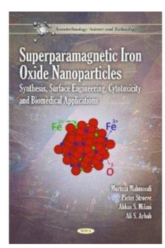
- nenulový spinový moment elektronu
- AO – párování elektronů – Pauliho princip
- vlastnosti materiálů
  - diamagnetické
  - paramagnetické
  - ferromagnetické
- Curieova teplota feromag.



Type of Magnetism	Susceptibility	Atomic / Magnetic Behaviour		Example / Susceptibility
Diamagnetism	Small & negative.	Atoms have no magnetic moment		-2.74×10^{-6} -0.77×10^{-6}
Paramagnetism	Small & positive.	Atoms have randomly oriented magnetic moments		0.19×10^{-6} 21.04×10^{-6} 66.10×10^{-6}
Ferromagnetism	Large & positive, function of applied field, microstructure dependent.	Atoms have parallel aligned magnetic moments		~100,000
Antiferromagnetism	Small & positive.	Atoms have mixed parallel and anti-parallel aligned magnetic moments		3.6×10^{-6}
Ferrimagnetism	Large & positive, function of applied field, microstructure dependent	Atoms have anti-parallel aligned magnetic moments		~3

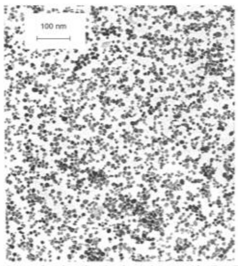
Magnetické nanočástice

- superparamagnetismus
- 2 – 300 nm; obv. 50 nm (magnetické jádro 2 – 20 nm)



Magnetické nanočástice

- maghemit (γFe_2O_3), magnetit (Fe_3O_4)
- komerčně dostupné, klinicky testované
- příprava
  - termální rozklad org. prekurzorů
  - spolusrážení z homogenní fáze
  - mikroemulzní techniky
  - 2 – 20 nm
- video (wifi)



SEM-picture confirms the uniform size of magnetite nanoparticles. (From T

Tiefenauer, L.X., et al., Bioconjugate Chem., 4, 347, 1993

MagNP – povrchová modifikace

- biokompatibilita, cílení

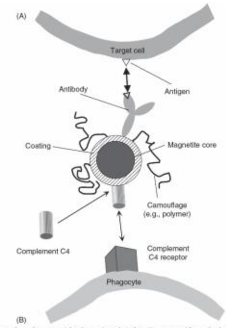


FIGURE 29.4 The surface of nanoparticles determines their fate. Tumor-specific antibody molecules conjugated to a coating recognize a target cell (A). A camouflage (polymer) reduces unspecific adsorption of complement factors,

MagNP – povrchová modifikace

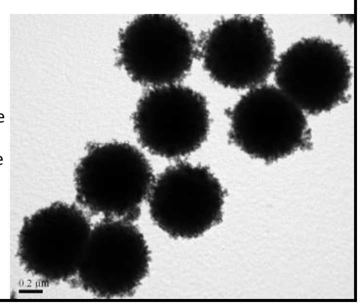
Materials used for coating or encapsulating SPIONs and their applications.

Materials used	Size and size distribution	Applications	Advantages
Amorphous silica	20–200 nm, broad	Isolation of biomolecules, e.g. genomic and plasmid DNA, extraction of nucleic acids from soil, drug delivery, extraction of phenolic compounds from environmental water	Does not require any organic solvents and eliminates the need for the repeated centrifugation, vacuum filtration or column separation
Mesoporous silica	10–300 nm, broad	Controlled drug delivery, removal of mercury from industrial effluent, support for enzyme immobilisation for bio-catalysis, fluorescence, isolation of genomic and plasmid DNA	Uniform pore size, large surface area, and high accessible pore volume
Polyethylene glycol (PEG)	10–50 nm, narrow	*In vivo* NMR imaging, *in vivo* contrasting	Improves the biocompatibility, blood circulation time and internalization efficiency of the NPs, easy to functionalise
Polyvinyl alcohol (PVA)	10–50 nm, narrow	*In vivo* imaging and drug delivery	Prevents coagulation of particles, giving rise to monodisperse particles
Polyvinyl pyrrolidine (PVP)	10–20 nm, narrow	Contrasting and drug delivery	Enhances the blood circulation time and stabilises the colloidal solution
Polyacrylic acid	~250 nm, narrow	Target thrombolysis with recombinant tissue plasminogen activator	Increases the stability and biocompatibility of the particles and also helps in bioadhesion
Polystyrene	10–20 nm, narrow	Cellular imaging and DNA hybridisation	Stable and uniform size particles in suspension
Polymethyl methaacrylate	10–50 nm, narrow	DNA separation and amplification	Novel, simple and labour-saving; can be applied in automation system(s) to achieve high throughput detection of single nucleotide polymorphisms
Polydipyrrole/dicarbazole	20–100 nm, broad	DNA hybridization	Molecular diversity for engineering functional polyDPyr-/polyDCbz-shell outer layers of magnetic nanocomposites
Ethyl cellulose	20–50 nm, broad	Extraction of pharmaceutical chemicals	Enhanced the drug absorption into the surrounding tissues for a prolonged period of time
Chitosan	20–100 nm, broad	Tissue engineering, hyperthermia	A natural cationic linear polymer that is widely used as non-viral gene delivery system, biocompatible, hydrophilic, used in agriculture, food, medicine, biotechnology, textiles, polymers, and water treatment
Dextran	10–200 nm, narrow	Isolation of *E. coli*, drug delivery, imaging	Enhances the blood circulation time, stabilises the colloidal solution

Mahmoudi et al., *Advanced Drug Delivery Reviews* 63 (2011) 24–46

Aplikace

- MRI
- cílený transport léčiv
- magnetická hypertermie
- biomagnetická separace



1. MRI (Magnetic Resonance Imaging)

- Superparamagnetic iron oxide nanoparticles (SPIONs, SPIOs)
- ferromagnetické částice <15 nm = superparamagnetické
- orientace dle vnějšího pole
- vyšší magnetizace než u paramagnetických
- superparamagnetický materiál ovlivňuje relaxaci magnetického spinu jádra atomu vodíku z vody

SPIONs

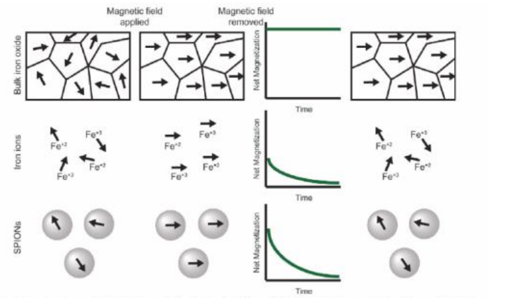


Fig. 1 The effects of an external magnetic field on bulk magnetite (top), Fe ions (middle), and SPIONs (bottom). Before application of the magnetic field all magnetic moments are randomly aligned. Application of an external magnetic field aligns the moments along the z-axis of the magnetic field. The initial net magnetization of SPIONs is greater than Fe ions, but less than bulk magnetite. Upon removal of the magnetic field, the moments of bulk magnetite remain fixed along the z-axis while both Fe ions and SPIONs magnetic moments relax over time to equilibrium.

MaterialsToday, 2011, *14*, 330

Relaxace vektoru magnetizace

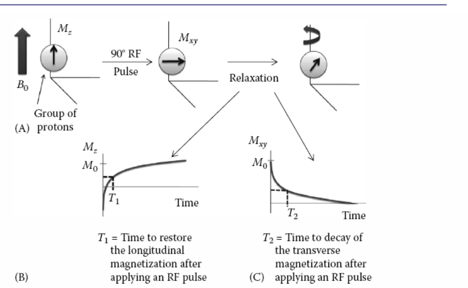


FIGURE 19.1 Graphic representation of the two types of magnetic relaxations. (A) A nuclei of protons are aligned due to an external magnetic field, and after applying a RF pulse, protons tend to relax. (B) Longitudinal relaxation time (T_1). (C) Transverse relaxation time (T_2). (Figure adapted from Cheon, J. and Lee, J.H., *Acc. Chem. Res.*, 41, 1630, 2008.)

MRI kontrast

- sledování rychlosti relaxace T_1 a T_2

Hodnoty pro B_0 = 1,5 T

Tkáň	ca. T_1 v ms	ca. T_2 v ms
Tuková tkáň	240-250	60-80
Krev neokysličená	1350	50
Krev okysličená	1350	200
Mozkomíšní tekutina (jako čistá voda)	4200 - 4500	2100-2300
Šedá hmota mozková	920	100
Bílá hmota mozková	780	90
Játra	490	40
Ledviny	650	60-75
Svaly	860-900	50

http://en.wikipedia.org/wiki/Relaxation_(NMR)

Princip relaxace

- Dva příspěvky k T_1 a T_2

1. Neélova doba relaxace τ_N

$$\tau_N = \tau_0 \cdot e^{\frac{K_u V}{k_B T}}$$

τ_0	konstanta
K_u	anisotropní konstanta
V	objem částice
k_B	Boltzmanova konstanta
T	abs. teplota

Princip relaxace

2. Brownova doba relaxace τ_B

$$\tau_B = \frac{3\eta V_h}{k_B T}$$

η	viskozita
V_h	hydrodynamický objem
k_B	Boltzmanova konstanta
T	abs. teplota

Efektivní relaxační čas

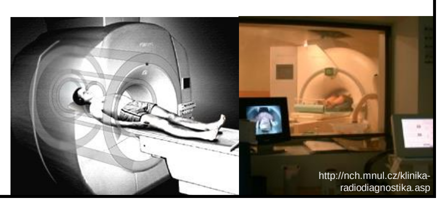
- efektivní relaxační čas τ

$$\tau = \frac{1}{\tau_N} + \frac{1}{\tau_B}$$

- Neélova doba relaxace τ_N významná pro malé NP a vyšší frekvence
- Brownova doba relaxace τ_B významná pro velké NP a nižší frekvence

MRI

- aplikace
  - trávicí trakt (300 nm)
  - játra, slezina (40 – 150 nm)
  - rakovinná tkáň (20 – 40 nm)
  - průtok krve mozkem, srdcem (<20 nm)



http://nch.mnul.cz/klinika-radiodiagnostika.asp

MRI
cirhóza jater

bez SPIONs

se SPIONs

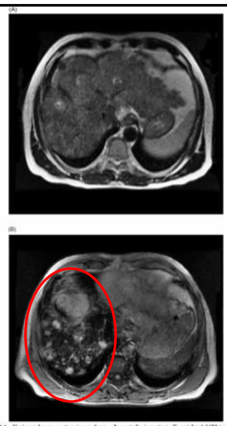


FIGURE 29.6 Horizontal cross-section image from a liver cirrhosis patient. T_2-weighted MRI images acquired using a spin echo sequence before (A) and after (B) administration of SPIONs (Endorem®). The lesion in the right liver lobe (left side of the picture) is clearly delineated after the administration of the contrast agent and some small carcinomic foci (5–15 mm) additionally appear.

MRI pro překonání BBB
(blood brain barrier = hematoencefalická bariéra)

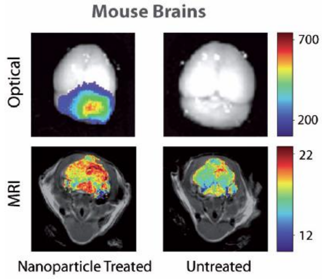


Fig. 7 Ex vivo optical imaging and in vivo MR imaging of brain tumors from a mouse treated with Cy5.5 labeled SPIONs (left) and an untreated mouse (right). The optical spectrum gradient bar corresponds to increasing fluorescent intensity. The color gradient bar for MR images corresponds to increasing r_2 values. Adapted with permission from[32], © 2010 American Association for Cancer Research.

Veiseh, O., et al., Cancer Res (2009) 69(15), 6 200.

MRI

Commercialized SPIONs.

Company	Reference	Applications
Stemcell Technologies	www.stemcell.com	Automated immunomagnetic cell separation
Micromod	www.micromod.de	Drug delivery, biomagnetic separation, nucleic acid purification and protein separation
Chemicell	www.chemicell.com	Bioseparation- and detection systems
Magnisense	www.magnisense.com	Bioassays for human and animal diagnostics, food safety and environmental protection
Diagnostics Biosensors	www.diagnosticbiosensors.com	Diagnostics biosensors
Dexter Magnetic Technologies	www.dextermag.com	Biomagnetic separation
Ocean Nanotech	www.oceannanotech.com	Synthesis, production as well as R&D of magnetic NPs
Imego	www.imego.com	Medical diagnostics
Integrated Engineering Software	www.integratedsoft.com	Electromagnetic, electromechanical and electrothermal analysis software
EMD chemicals	eshop.emdchemicals.com	Immunoassay and immunoreagent development
Magsense	www.magsenselifesci.com	Bioseparation, diagnostic, immunoassay, and bioanalytical measurements
TurboBeads	www.turbobeads.com	Efficient magnetic separation
European Institute of Science	www.biotechniques.com	Hyperthermia
Magnabeat Inc.	www.magnabeat.com	Separation of many different bio-substances
nanoTherics Ltd.	www.nanotherics.com	Magnetic gene transfection
SEPMAG technologies.	www.sepmag.eu	Large volume magnetic separation systems
Magforce	www.magforce.de	Hyperthermia
AMAG Pharmaceuticals (Advanced Magnetics)	www.amagpharma.com	MRI contrast agents; Diagnosis of cardiovascular disease and cancer
Estapor	www.estapor.com	Application of magnetic microspheres in immunoassays
Miltenyi Biotec	www.miltenyibiotec.com	Reagents and instruments development for use in immunology, cell and molecular biology, bioinformatics, and stem cell technologies
Invitrogen and Dynal Biotech (bought by Invitrogen in 2005)	www.invitrogen.com	In vitro diagnostics, protein, cell and biomolecular purification and separation

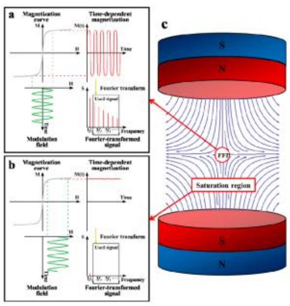
Mahmoudi et al., *Advanced Drug Delivery Reviews* 63 (2011) 24–46

2. MPI (Magnetic Particle Imaging)

- Superparamagnetic iron oxide nanoparticles (SPIONs, SPIOs)
- složitá topologie generovaného magnetického pole
- oblast saturace a oblast nulového pole
- excitace a detekce signálu z oblasti nulového pole
- rychlé proměření velkého objemu vzorku (možnost 3D zobrazování v reálném čase)

MPI

- FFP = field free point



MPI

- úzká oblast, kde NP nejsou saturovány vnějším polem

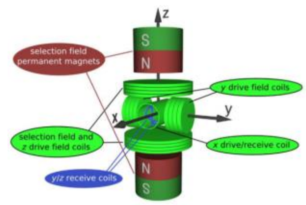
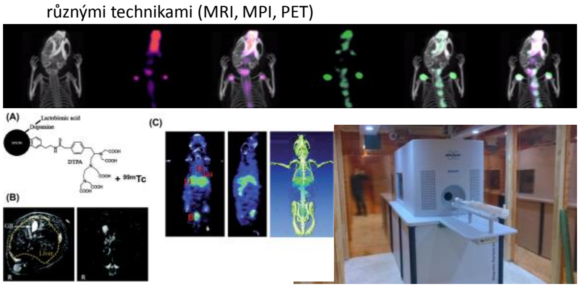


Figure 1. Schematic scanner setup. The mouse was inserted into the x drive/receive coil cylinder using an animal support. The bore diameter is 32 mm. The selection field is generated by both the permanent magnets and the coil pair in the z direction. The drive field coils can move the FFP in all three spatial directions. For signal reception, each spatial component of the magnetization is detected by a respective receive coil. In the x direction, the drive field coil is also used for signal reception.

Zobrazování magnetických NP

- přenos vyšetřovaného zvířete v kyvetě – kombinace zobrazení různými technikami (MRI, MPI, PET)



J. Mater. Chem. B, 2015,3, 939-958 http://capi.lf1.cuni.cz/en/in-vivo-imaging-capi1lf

3. Cílený transport léčiv

Various SPIONs-assisted drug delivery systems.

Coating	Delivery system	Drug tested	Examination route
Carbon	Aqueous media	Carminomycin and rubomycin	*In vivo* (Rat) Injected into the tail vein
Anhydroglucose	Aqueous media	Epirubicin	*In vivo* (Human) Intravenous injection
Phosphated starch	Aqueous media	Mitoxantrone	*In vivo* (Mice) The magnetic NPs were injected either into the femoral artery close to the tumour or intravenously
Poly(lactic-co-glycolic acid)	Microspheres and microcapsules	Dexamethasone acetate	*In vitro* and *In vivo* (intra-articular)
Amphiphilic block copolymers of maleimide-terminated poly(ethyleneglycol)-block-poly(D,L-lactide) and methoxy-terminated poly-(ethylene glycol)-block-poly(D,L-lactide)	Multifunctional polymeric micelles	Doxorubicin	*In vitro*
Albumin	Microspheres	Doxorubicin	*In vitro*
Polyethylene glycol fumarate	Aqueous media	Tammoxifen	*In vitro*
Oleic acid	Aqueous media	Doxorubicin and paclitaxel	*In vitro*
Oleic acid–Pluronic	Aqueous media	Doxorubicin	*In vitro*
Poly(acrylic acid)	Aqueous media	Taxol	*In vitro*
None	Porous hollow nps	Cisplatin	*In vitro*
Chitosan, O-carboxymethylchitosan and (N-succinyl-O-carboxymethylchitosan	Aqueous media	Camptothecin	*In vitro*
Poly(lactic acid) and poly(lactic-co-glycolic acid)	Microspheres	Interferon alpha-2b	–
Silica	Hollow mesoporous sphere	Ibuprofen	*In vitro*
Cross-linked chitosan	Microspheres	Aspirin	*In vitro*

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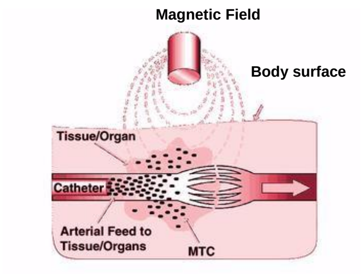
Cílený transport léčiv



Cílený transport léčiv

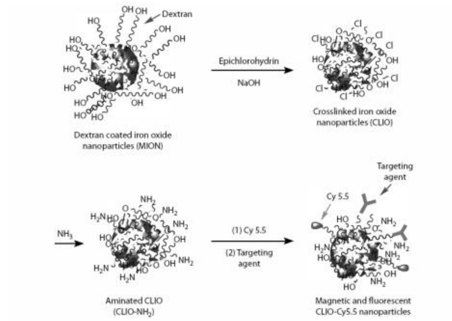
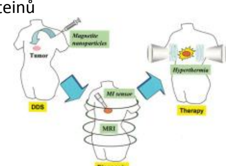


FIGURE 20.1 Schematic. Synthesis of iron oxide nanoparticle-based multifunctional magnetic and fluorescent nanoparticles CLIO-Cy5.5.

Nanobiomaterials Handbook

4. Magnetická hypertermie

- střídavé magnetické pole
- zvýšení teploty – kolaps krevního řečiště
  - špatný odvod tepla
  - nedostatek kyslíku a živin
  - rozrušení cytoskeletu
  - narušení funkce buněčných proteinů
- t > 45 °C, 30 min

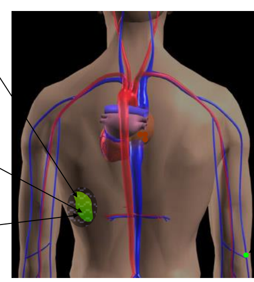


Aplikace magnetických nanočástic

Nádor

Cílení MNP
mag. polem

Terapie střídavým
mag. polem

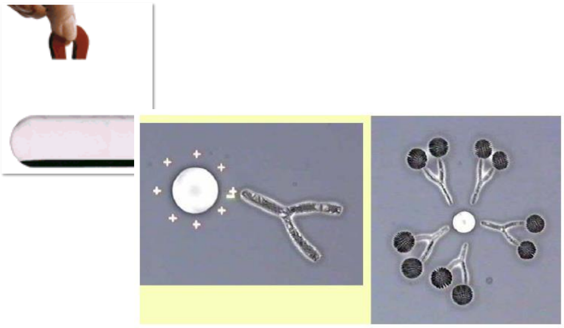


Podání MNP,
cirkulace v krvi

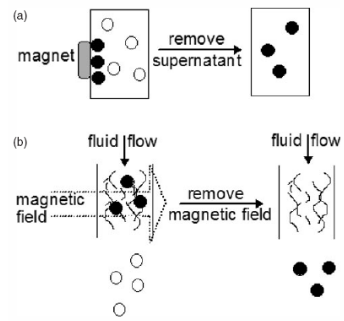
Další způsoby cílení:
1 – Přímá dávkování do rakovinné tkáně
2 – Cílení specifickou protilátkou

Terapie
1 – Uvolnění léčiva
2 – Hypertermie

5. Biomagnetické separace



Biomagnetické separace



Literatura

Review

Magnetic Nanoparticles: Design and Characterization, Toxicity and Biocompatibility, Pharmaceutical and Biomedical Applications

Reddy et al., *Chem. Rev.*, **2012**, *112* (11), pp 5818–5878

http://pubs.acs.org/doi/pdfplus/10.1021/cr300068p