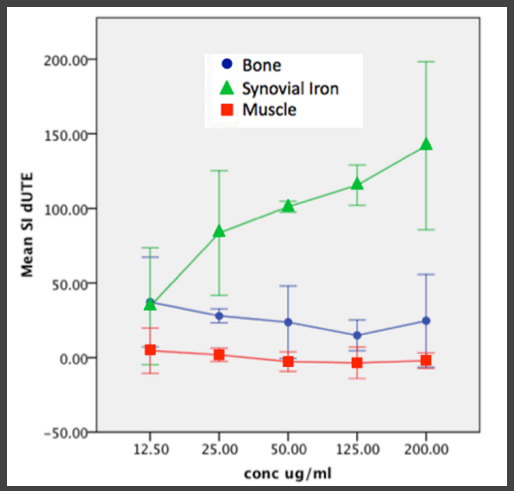
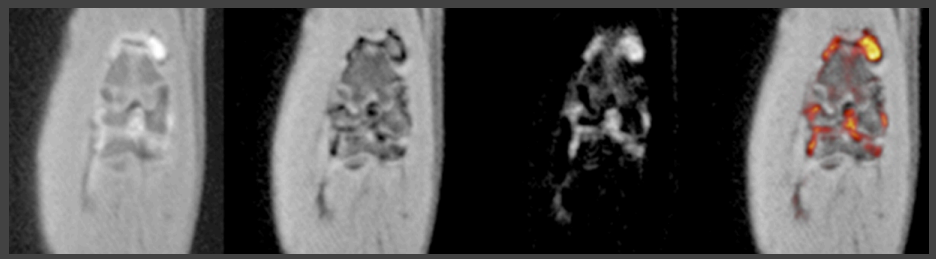
Concentration dynamic response assessment for intra-articular injected iron-oxide nanoparticles.

Lindsey A Crowe[1]
Frank Tobalem[1]
Wolfgang Wirth[2]
Azza Gramoun[1]
Benedicte M A Delattre[1]
Kerstin Grosdemange[1]
Jatuporn Salaklang[3]
Anthony Redjem[3]
Alke Petri-Fink[3]
Felix Eckstein[2]
Heinrich Hofmann[4]
Jean-Paul Vallée[1]





Radiology Department
Geneva University Hospitals
[1]Faculty of Medicine/Department of Radiology, University of Geneva, Geneva, Switzerland,
[2]Institute of Anatomy & Musculoskeletal Research, Paracelsus Medical University, Salzburg, Austria,
[3]Adolphe Merkle Institute, University of Fribourg, Fribourg, Switzerland,
[4]Powder Technology Laboratory, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

SPION concentration dynamic
 # 4351, monitor 41
Thursday 10 May 13.30

Summary

- Introduction
- Methods
- Images
- Quantification
- Conclusions

Introduction

Nanoparticle technology, including superparamagnetic iron oxide nanoparticles (SPIONs), is of emerging importance for monitoring onset, progression and treatment of inflammatory diseases such as arthritis and drives development of imaging techniques.

Studies require sensitive imaging protocols for the detection and quantification of particles over a range of concentrations.

Intra-articular injections of iron were compared to a concentration phantom using a difference-Ultrashort Echo Time sequence.

Particles

All particles described in this work are amino-PVA-SPIONs provided by EPFL/Uni Fribourg with or without coupled fluorophore dye

The superparamagnetic iron oxide nanoparticles were manufactured by an aqueous co-precipitation method.

(Chastellain M, Petri A, Hofmann H. J Colloid Interface Sci 2004;278(2):353-360).

The colloidal particles were further coated with a mixture of poly(vinyl alcohol) (PVA) and vinyl alcohol/vinyl amine copolymer. Surface derivatization of polymer-coated particles with a dye in a magnetic bed reactor.

(Steitz B, Salaklang J, Finka A, O'Neil C, Hofmann H, Petri-Fink A. Bioconjug Chem 2007;18(5):1684-1690).

Methods

15 female Lewis rats (2 months old) were scanned immediately after intra-articular injection in the knee of iron oxide nanoparticles.

Amino-PVA-SPION, 5 concentrations in 50µl of physiological NaCl ranging from 12.5 to 200µg/ml).

Scanning used a Siemens Magnetom Trio 3T clinical scanner and the manufacturers 4cm loop coil.

A phantom was constructed with the same solutions as those injected, plus water. Numerical analysis was carried out using ANOVA with post-hoc Bonferroni (PASWStatistics 18.0) and a $p < 0.05$ was considered significant. Ethical committee approval was obtained for the complete protocol and animals were kept in the institutions animal facility with free access to food and water.

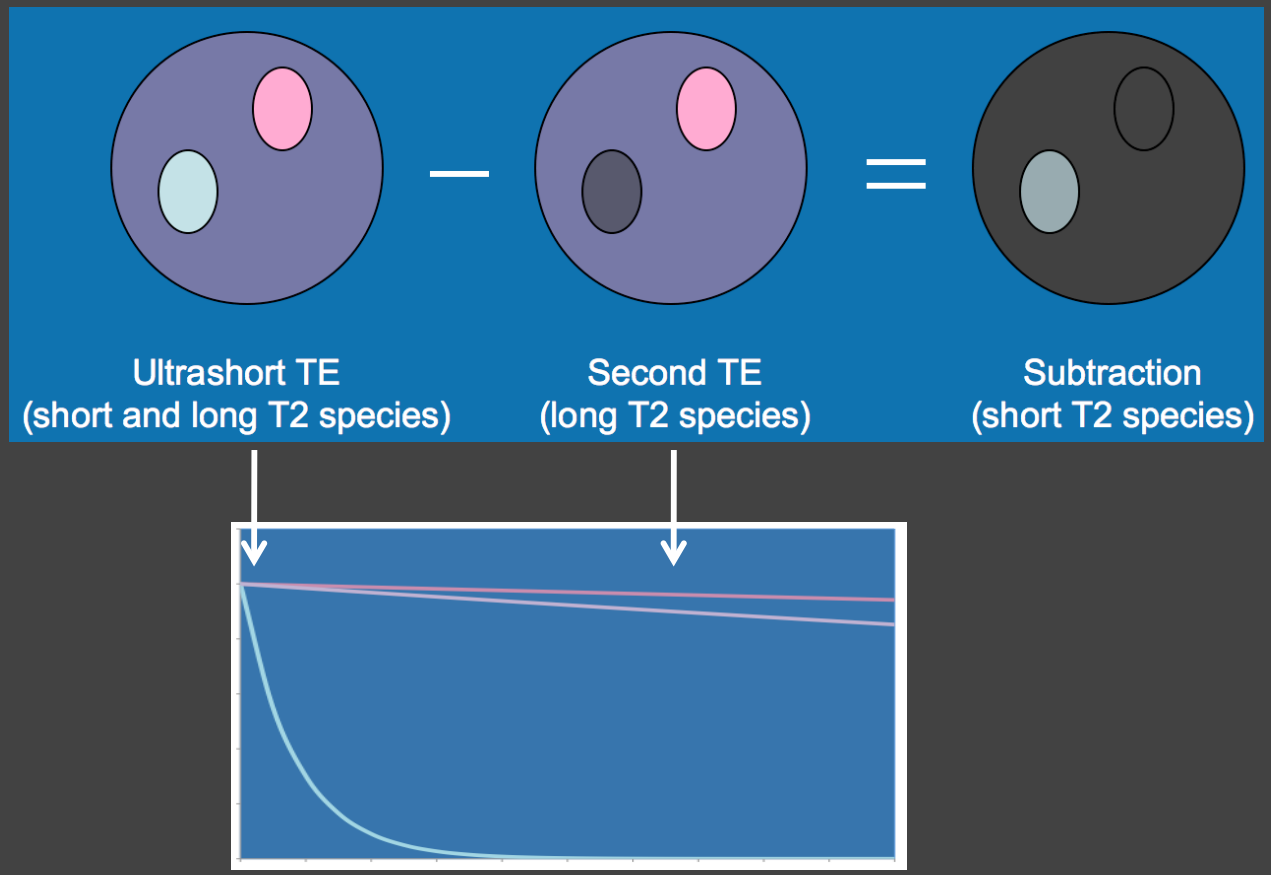
Methods

The protocol included 3D T1 gradient echo (VIBE) with parameters:
TR/TE 14.3/5.9ms, flip angle 12°
fat suppression,
isotropic resolution 0.31mm, and FOV 100mm.

dUTE consisted of the acquisition and subtraction of two echo times (ultrashortTE, and short TE2) leading to positive contrast from short T2* species and reduced signal elsewhere.

Parameters were:
3D isotropic resolution of 0.18mm, an 80mm FOV, 50000 radial projections, UTE/TE2 0.07ms/2.46ms (for in-phase fat/water image), TR 9.6 ms and flip angle 10°

dUTE

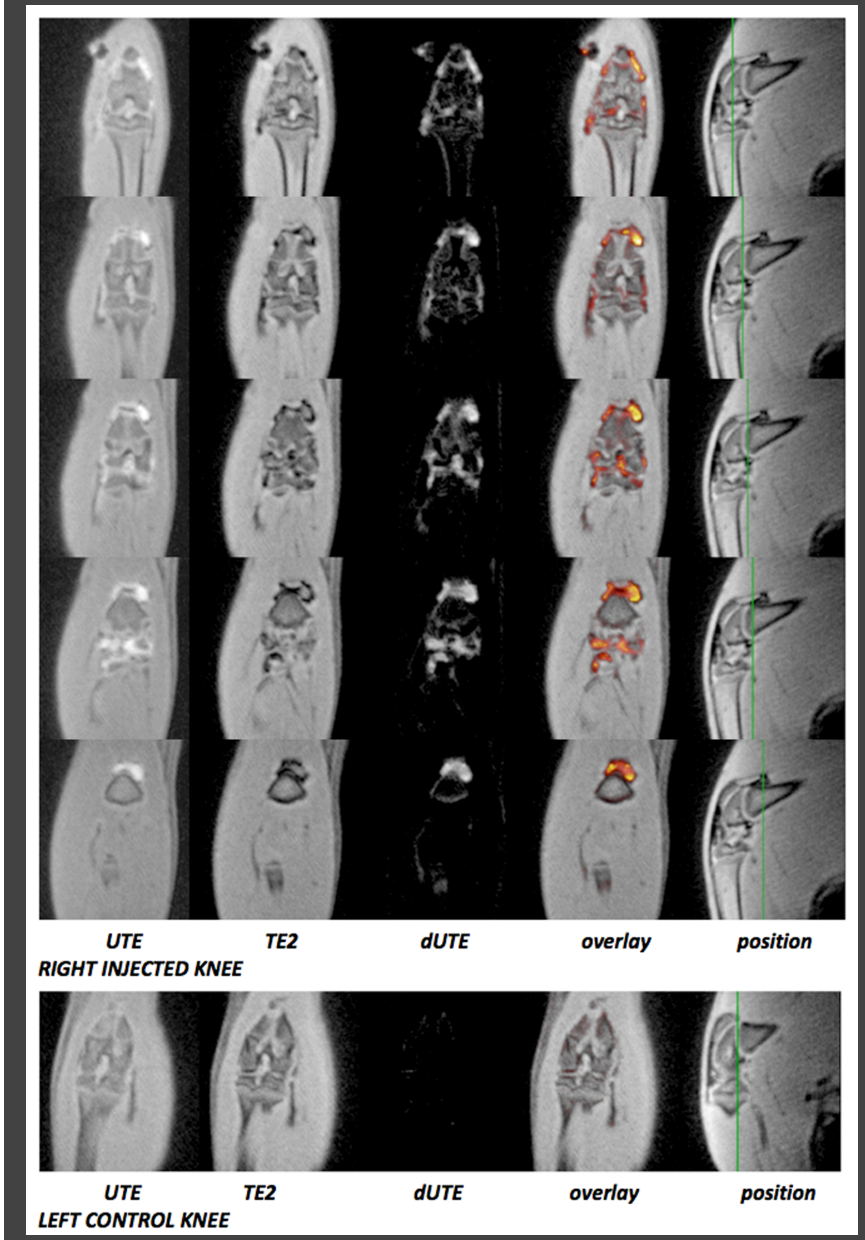


dUTE gives high-resolution 3D anatomical images with suppressed background, reduced artifacts and high iron contrast, and allows automatic quantification of iron oxide

Methods

Non-normalised signal intensity of synovial iron region is measured in a region of interest as a function of concentration (μg/ml) of solution injected intra-articular into the knee joint of healthy rats.

Signal intensity on MRI is measured immediately after injection of 50μl of amino-PVA-SPION in PBS.



Images

In-vivo results at 50μg/ml concentration. Iron oxide volume 50μL injected.

UTE, TE(2), dUTE, dUTE fusion on anatomy and sagittal for localization.

Region of synovial iron is clearly delineated. Several example slices are given throughout the knee.

Red is low iron signal, through yellow to white for high iron concentration.

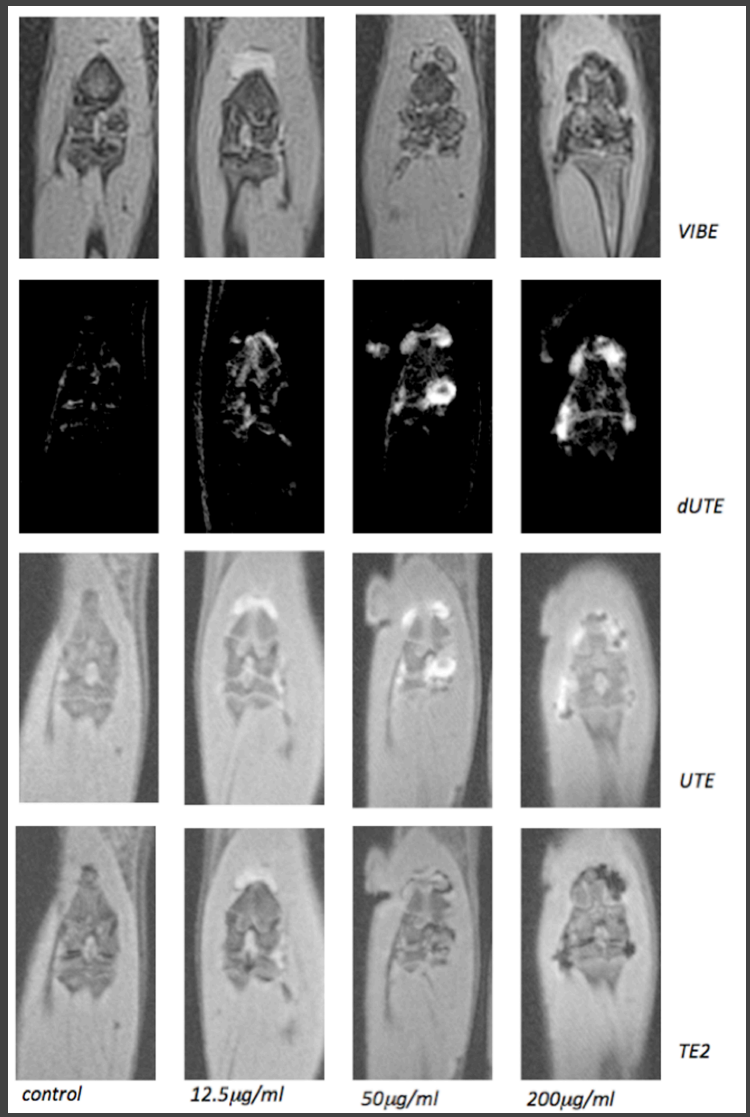
Last image row shows also the contralateral knee without injection.

Images: In-vivo results

Synovial iron

VIBE, dUTE, UTE and TE2 images of a control

and at 50μL volume i.a. injection 12.5μg/ml, 50μg/ml and 200μg/ml

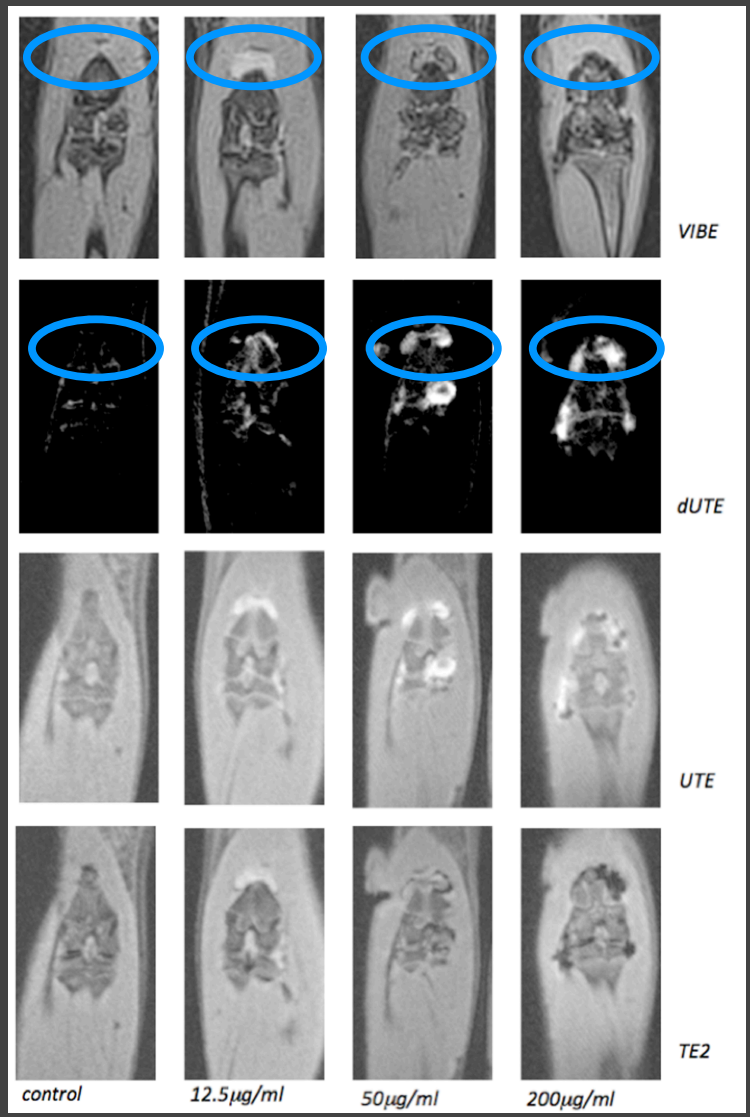


Images: In-vivo results

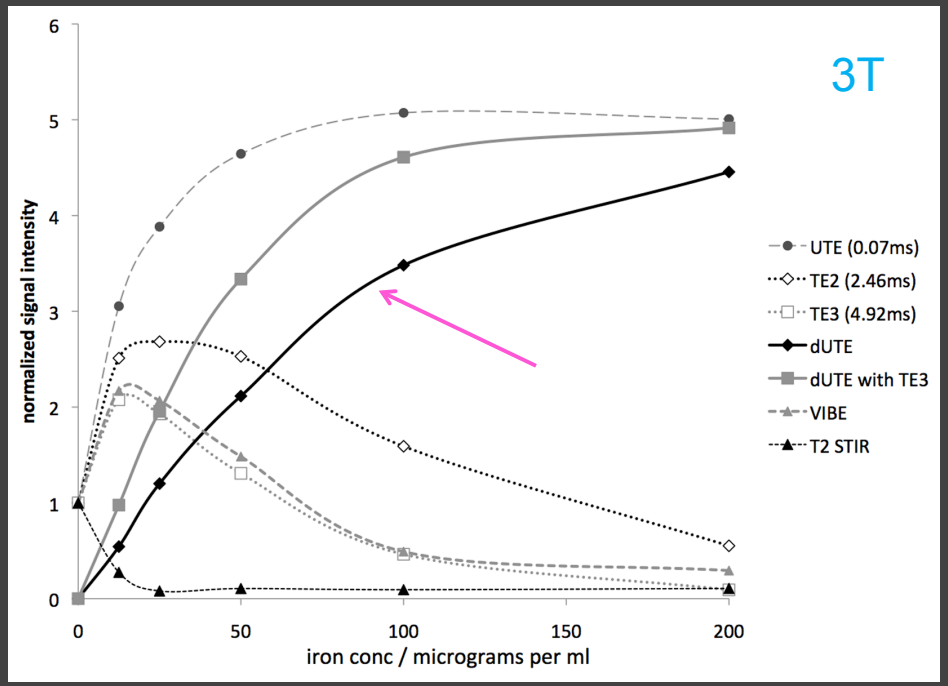
Synovial iron

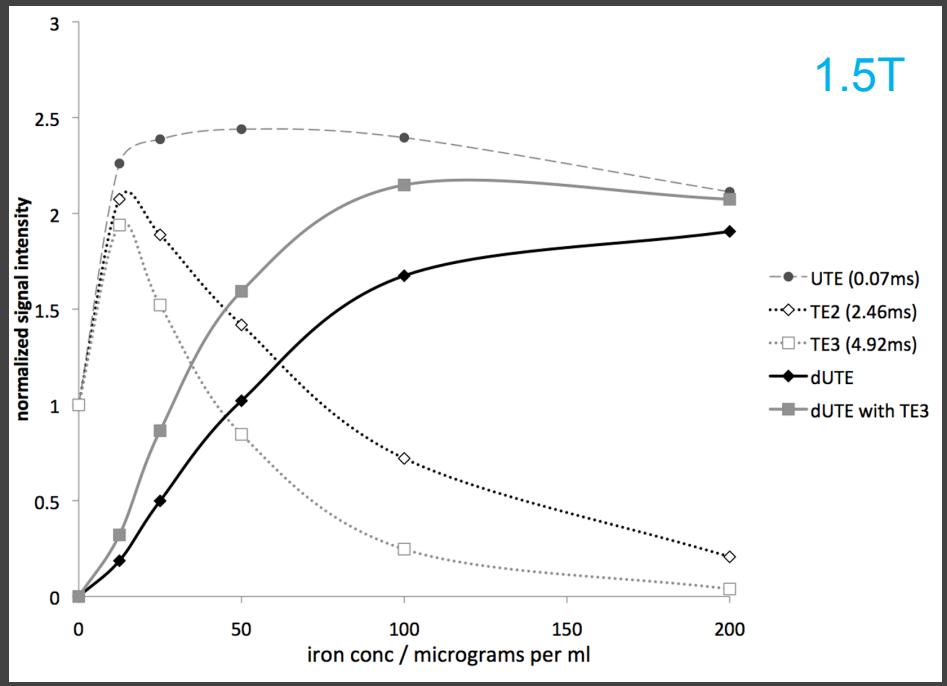
VIBE, dUTE, UTE and TE2 images of a control

and at 50μL volume i.a. injection 12.5μg/ml, 50μg/ml and 200μg/ml



Phantom calibration

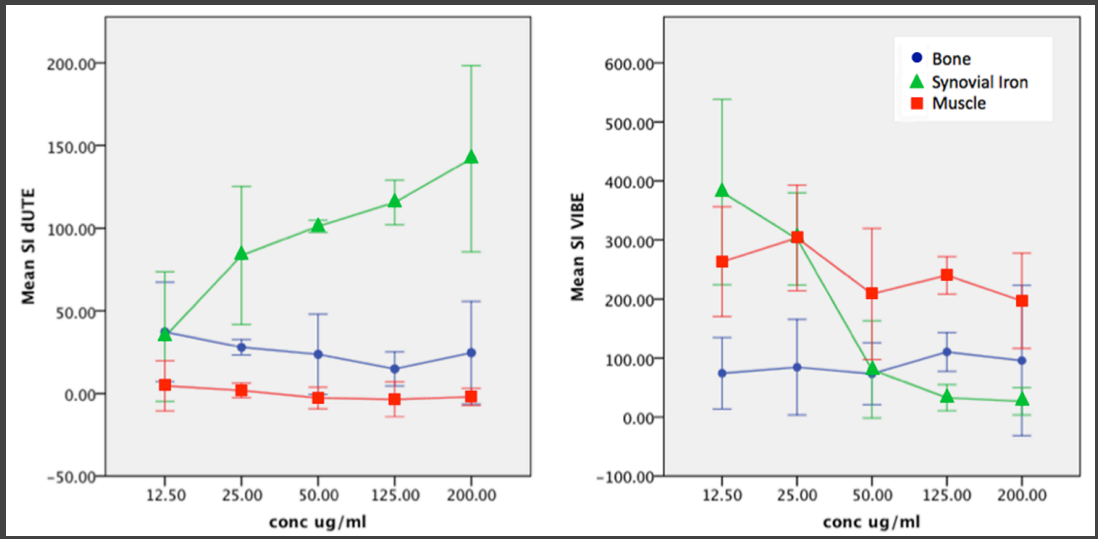




Comparison of signal intensity versus concentration of iron oxide in sample tubes, normalized to the signal at concentration 0 (water).

*Proposed **dUTE** method and conventional signal loss sequences comparing sensitivity and ambiguity at different concentrations showing monotonic concentration dynamic of dUTE.*

In vivo quantification

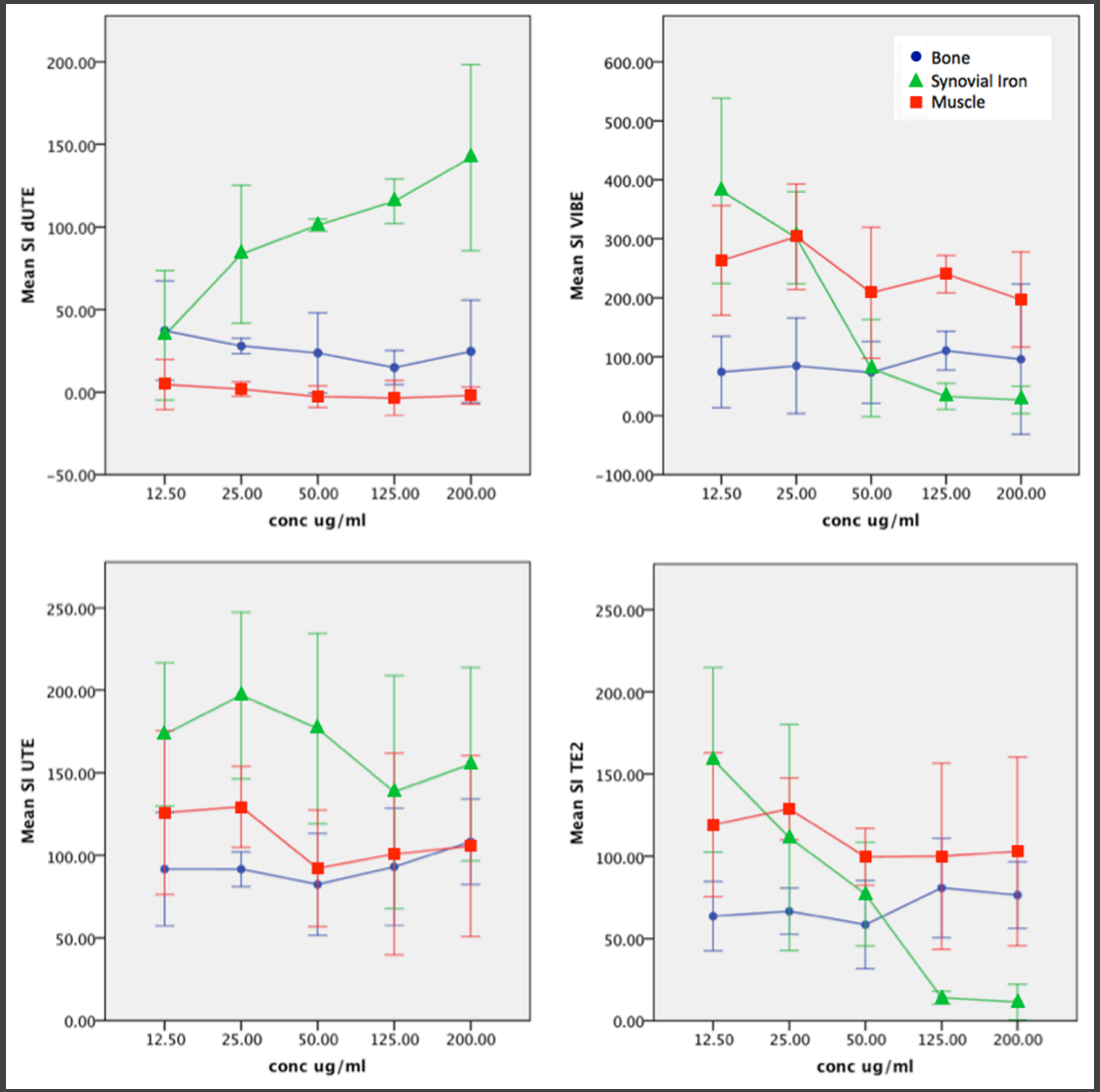


In-vivo results showing synovial iron signal in green emphasizing both the sensitivity to concentration from the slope and the contrast due to the separation of the iron data from the red/blue muscle/bone data. Error bars 95%.

dUTE and VIBE

Each plot shows the effect of injected concentration on the signal intensity in the region of uptake (green) as well as the signal for muscle (red) and bone (blue).

In vivo quantification



In-vivo results showing synovial iron signal in green emphasizing both the sensitivity to concentration from the slope and the contrast due to the separation of the iron data from the red/blue muscle/bone data. Error bars 95%.

Top row, dUTE and VIBE,

Bottom row, the individual echoes for creating dUTE (UTE and TE2).

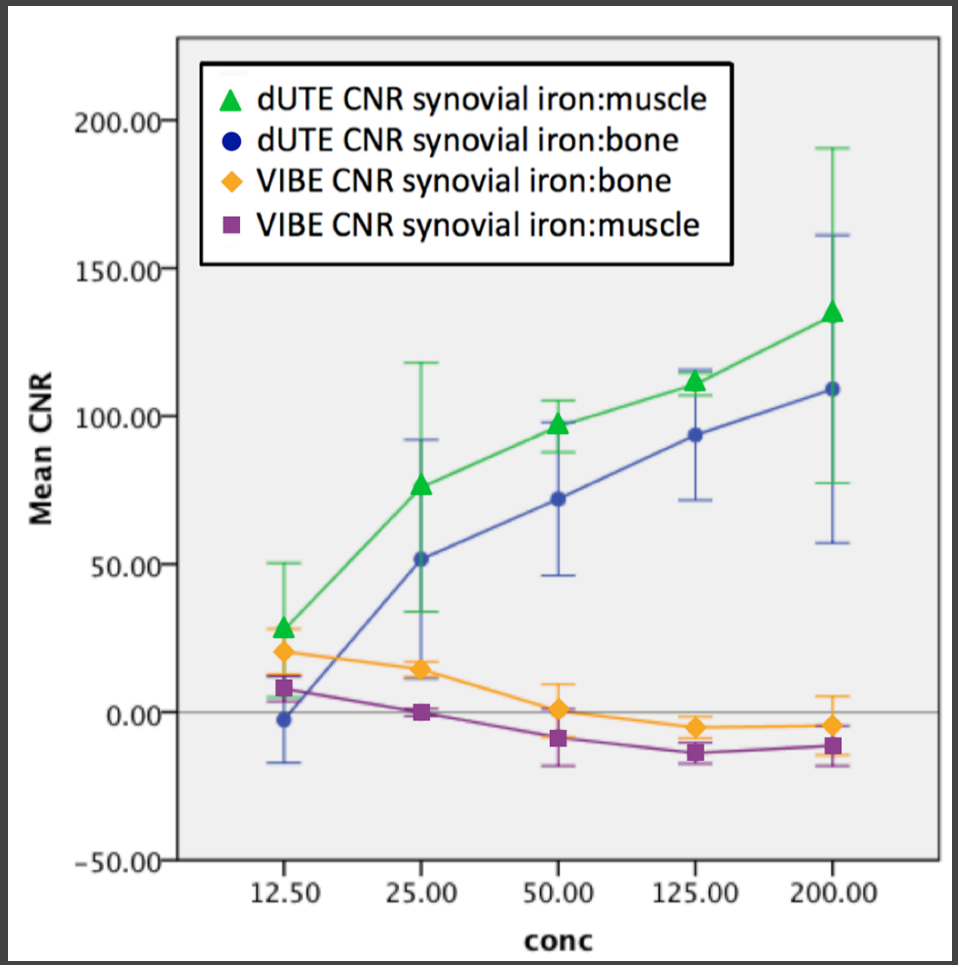
Each plot shows the effect of injected concentration on the signal intensity in the region of uptake (green) as well as the signal for muscle (red) and bone (blue).

In vivo quantification

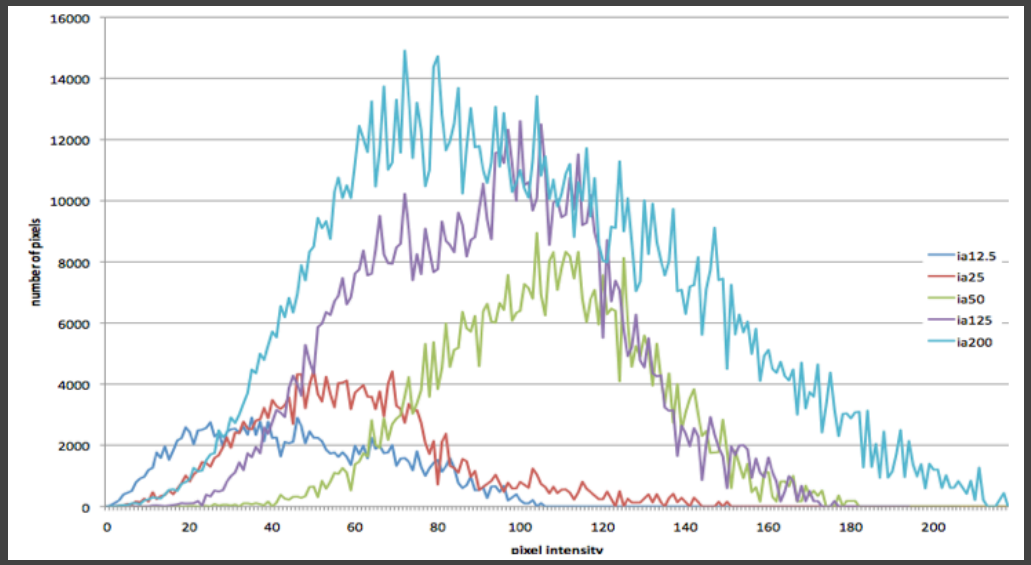
Contrast-to-noise (difference between synovial iron and other tissue, normalised by noise background signal for the appropriate sequence)

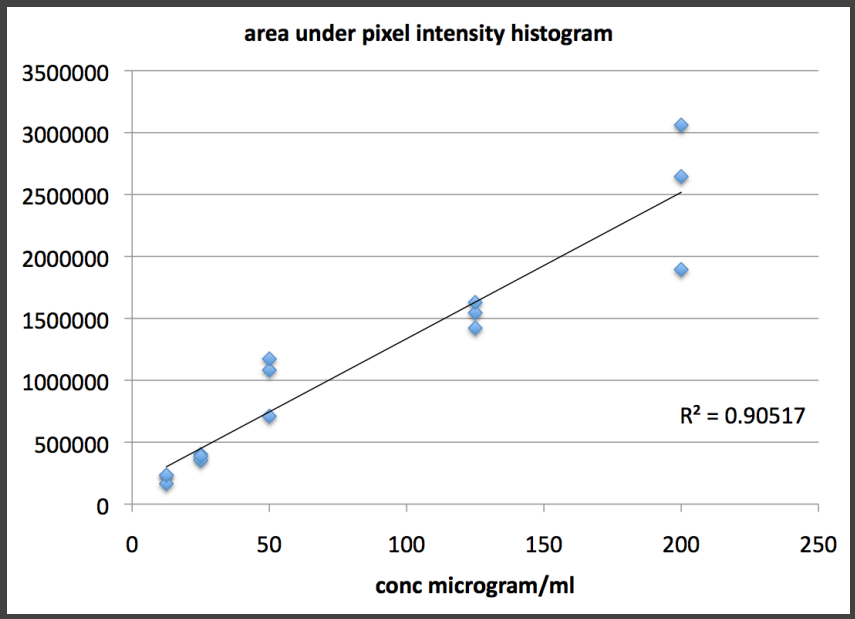
High and positive at all concentrations for dUTE compared to VIBE.

Values are mean of 3 animals per group with 95% error bars.



Heterogeneous signal In vivo quantification

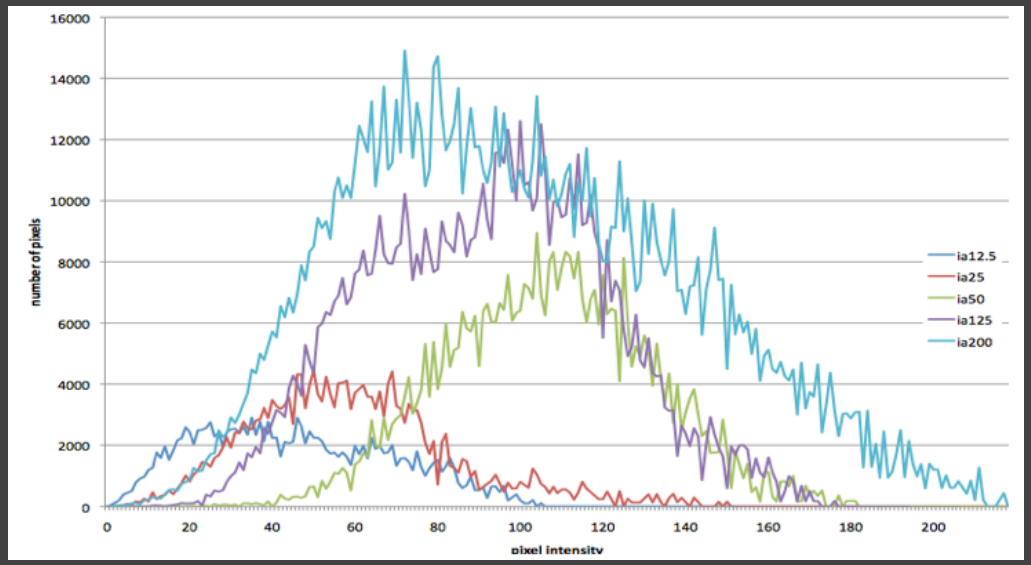


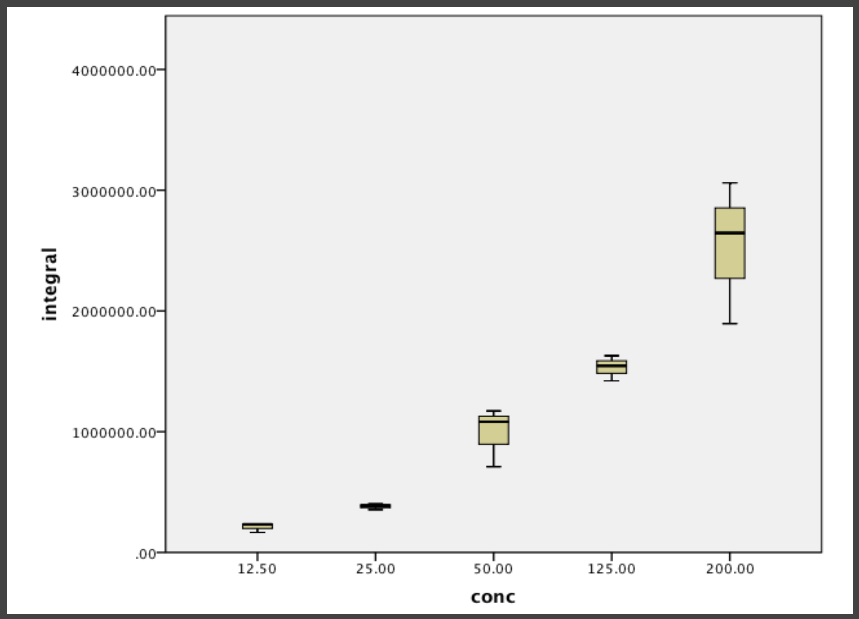


Quantification of whole heterogeneous volume: pixel intensity and frequency, and integral for each concentration.

Illustrates variation in number of pixels and intensity, but total 'iron quantification' integral is linear with concentration. Good correlation.

Heterogeneous signal In vivo quantification





Quantification of whole heterogeneous volume: pixel intensity and frequency, and integral for each concentration.

Illustrates variation in number of pixels and intensity, but total 'iron quantification' integral is linear with concentration. Separation.

Conclusions

An important factor gained by the **dUTE** sequence is the **distinction of synovial iron signal intensity from tissues** (muscle, bone) and noise, unlike any of the classical sequences compared, or the simple single echo of the UTE acquisition.

The dUTE sequence (difference-Ultrashort Echo Time) gives **positive, unambiguous signal characteristics and monotonic increasing concentration response** (linear for physiologically relevant concentrations) over a wide range in a phantom and a rat model,

Limited susceptibility artifacts and **high contrast**, open possibilities for quantification of other heterogeneous regions of iron uptake in more complex models.

Acknowledgements

- HUG Radiology, CIBM
- NanoDiaRA
  - Development of Novel Nanotechnology Based Diagnostic Systems for Rheumatoid Arthritis and Osteoarthritis. The European Commission is funding the collaborative project through the 7th Framework Programme for Research (NMP4-LA-2009-228929 "Nanosciences, Nanotechnologies, Materials and new Production Technologies").

NanoDiaRA

CIBM Centre d'Imagerie BioMédicale

- Work supported in part by the Center for Biomedical Imaging (CIBM), Geneva and Lausanne, Switzerland

- Thank you
- Questions?

UNIVERSITÉ DE GENÈVE

References

Butoescu N, Jordan O, Petri-Fink A, Hofmann H, Doelker E. Co-encapsulation of dexamethasone 21-acetate and SPIONs into biodegradable polymeric microparticles designed for intra-articular delivery. J Microencapsul 2008;25(5):339-350.

Xie J, Lee S, Chen X. Nanoparticle-based theranostic agents. Adv Drug Deliv Rev 2010;62(11):1064-1079.

Beckmann N, Falk R, Zurbrugg S, Dawson J, Engelhardt P. Macrophage infiltration into the rat knee detected by MRI in a model of antigen-induced arthritis. Magn Reson Med 2003;49(6):1047-1055.

Crowe LA, Ris F, Nielles-Vallespin S, Speier P, Masson S, Armanet M, Morel P, Toso C, Bosco D, Berney T, Vallee JP. A novel method for quantitative monitoring of transplanted islets of langerhans by positive contrast magnetic resonance imaging. Am J Transplant 2011;11(6):1158-1168.

Nielles-Vallespin S, Weber MA, Bock M, Bongers A, Speier P, Combs SE, Wohrle J, Lehmann-Horn F, Essig M, Schad LR. 3D radial projection technique with ultrashort echo times for sodium MRI: clinical applications in human brain and skeletal muscle. Magn Reson Med 2007;57(1):74-81.

Crowe et al. In press in MRM 2012.