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Quantification of inhomogeneous iron oxide uptake over a 3D volume in a small animal arthritis model using dUTE MRI and customized segmentation software

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Introduction

Iron oxide nanoparticles (SPION) as MRI contrast agents target macrophages in antigen-induced-arthritis (AIA) in rat

Easily detectable on MRI as dark regions

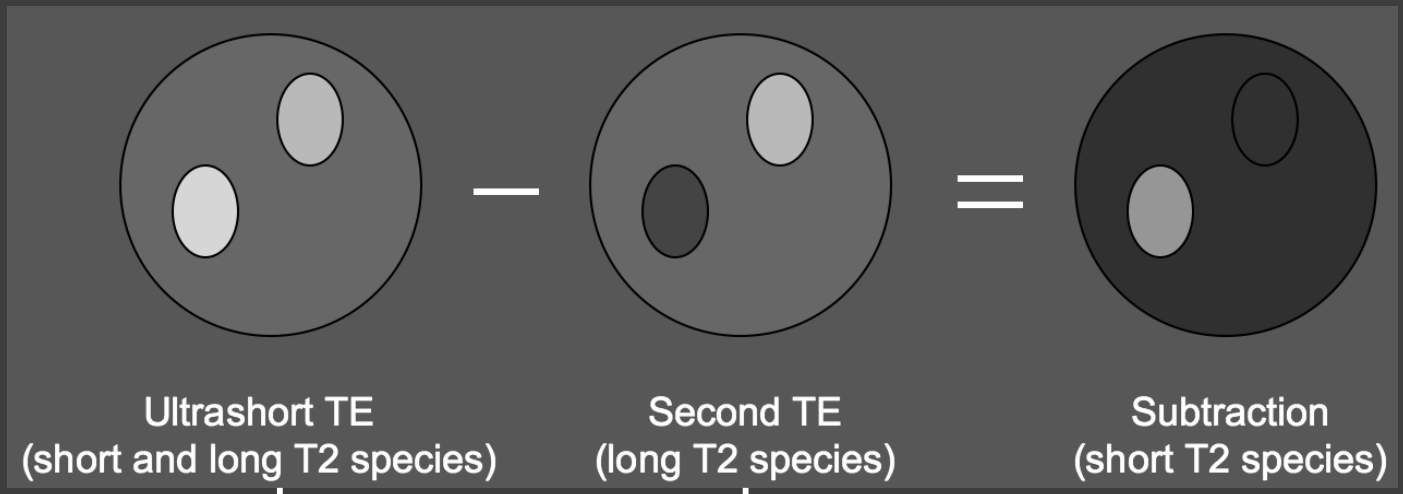
Quantification in vivo remains extremely challenging

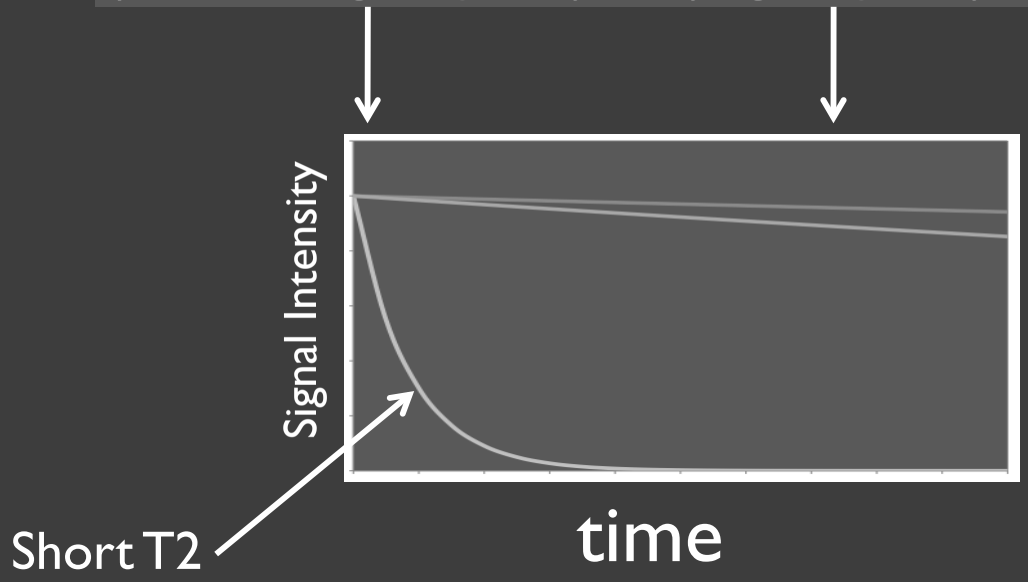
low concentration => signal saturation

Developed and validated quantification based on positive contrast dUTE with semi-automated segmentation

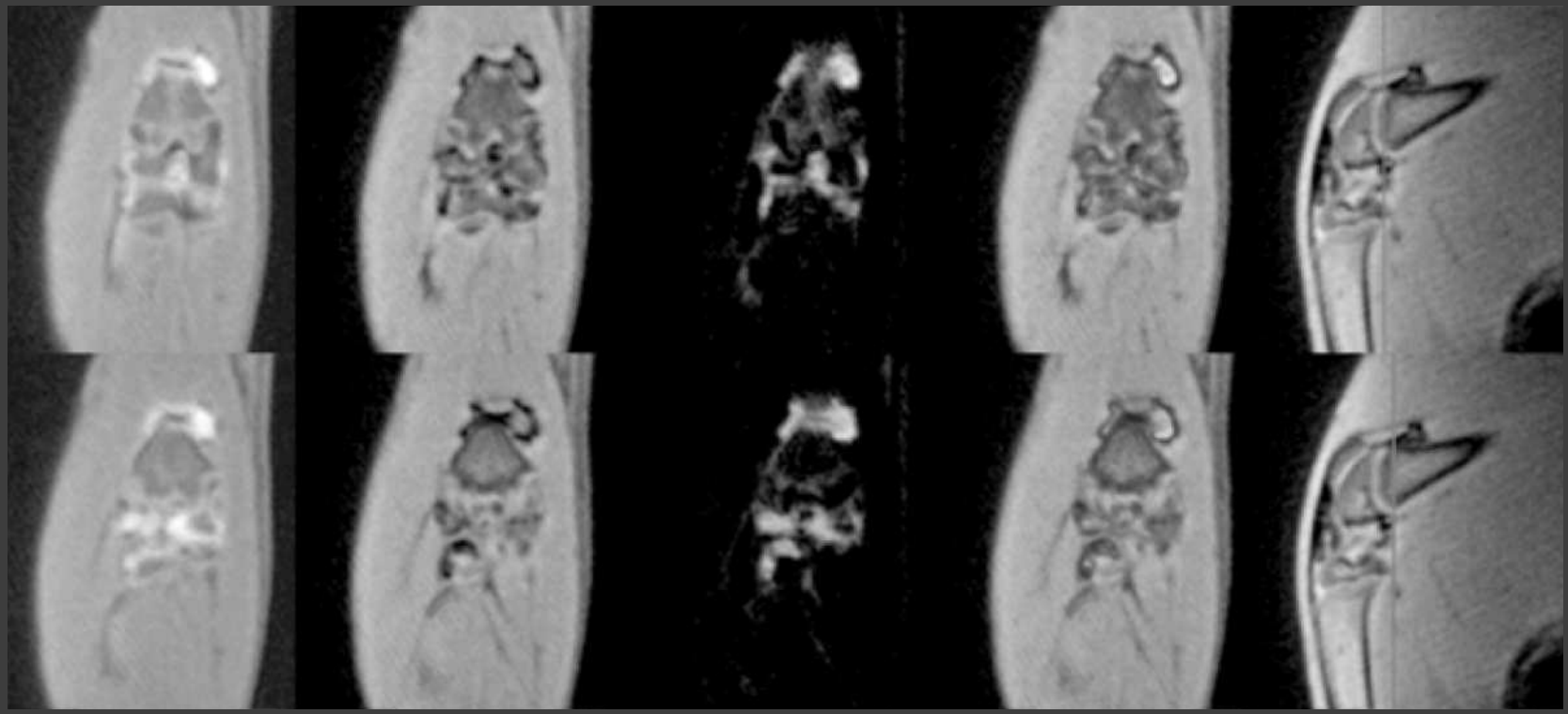
- Purpose: in vivo quantification of SPION uptake after intra venous injection in the clinically relevant antigen-induced arthritis (AIA) model in rat.

dUTE


Ultrashort TE
(short and long T2 species)
Second TE
(long T2 species)
Subtraction
(short T2 species)


Signal Intensity
time
Short T2

dUTE

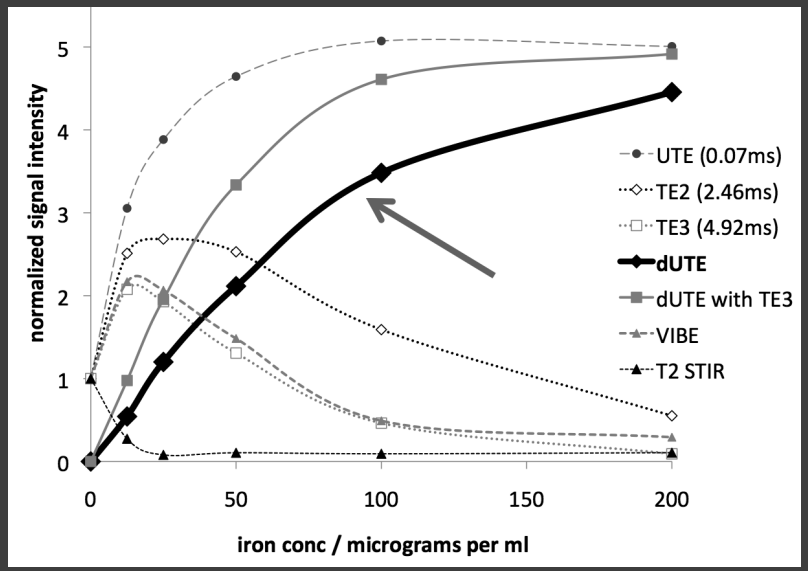


UTE | TE(2) | dUTE | overlay | orthogonal

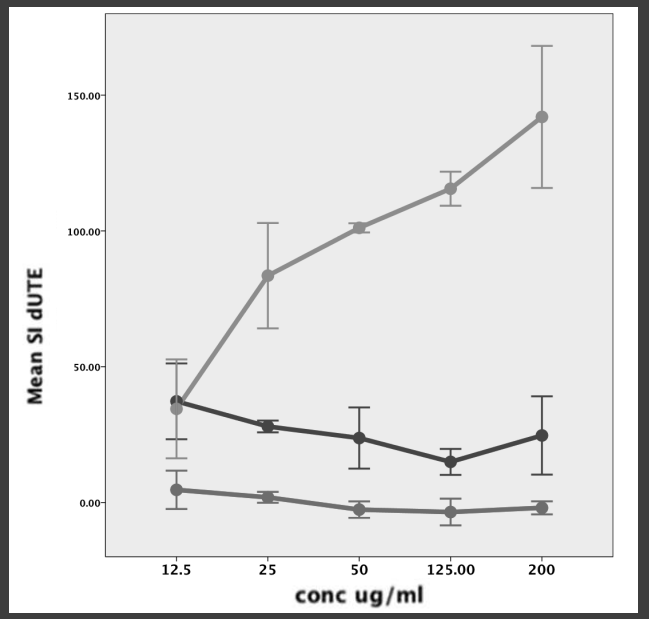
dUTE gives high-resolution 3D anatomical images with suppressed background, reduced artifacts and high iron contrast, and allows quantification of iron oxide

Previous work

Phantom



Intra-articular known concentration



Concentration phantom study and regional mean signal intensity after ia injection = monotonic signal increase with iron concentration

dUTE positive contrast method and automatic segmentation give pixel intensity histograms => quantification of both size and intensity of SPION biodistribution

Crowe LA, et al. Magn Reson Med 2012; 68 (5): 1544-1552.

Model

- Model
  - 23 Female Lewis rats (Janvier, France, weighing 150-175g, age 2 months) with right knee antigen-induced arthritis
  - Intravenous (iv) injection of 7mg SPION on day 5 after AIA induction.
  - iv injections = low, unknown and irregular uptake in the synovium, complex shape that requires 3D quantification.
- Particles
  - All particles described in this work were amino-PVA-SPIONs provided by EPFL, Lausanne, and University of Fribourg (7).

Ethical committee approval was obtained for the protocol and animals were kept in the institutions animal facility with free access to food and water.

MR Imaging Protocol

- MR Imaging: Siemens Magnetom Trio 3T clinical scanner, 4cm loop coil.
  - 3D T1 gradient echo (VIBE) parameters were: TR/TE 14.3/5.9ms, flip angle 12°, fat suppression, isotropic resolution 0.31mm, and FOV 100mm.

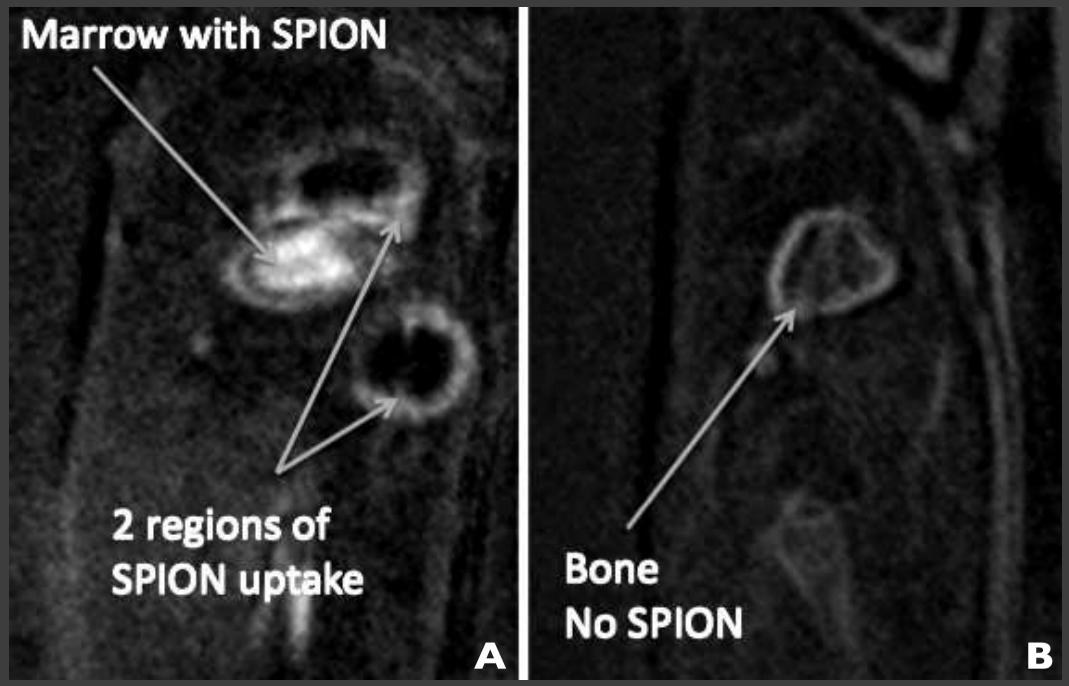
  - Quantifiable SPION image from dUTE MRI
    - simultaneous acquisition then subtraction of 2 TEs
  - 3D dUTE parameters were: 3D isotropic resolution of 0.18mm, an 80mm FOV, 50000 radial projections, UTE/TE2 0.07ms/2.46ms (for in-phase fat/water image), TR 9.6 ms and flip angle 10°.

Analysis

- Analysis software allowed simultaneous all three images (UTE, TE(2), dUTE)
- Important features included:
  - Semi-automatic segmentation
    - Thresholding: single pixel click region fill, intensity threshold and radius constraint
    - Quantification of volume and signal intensity for all images
    - Export of signal measurements for statistical analysis

- Manual segmentation (n=16) was used as a gold standard for the validation of the analysis software.

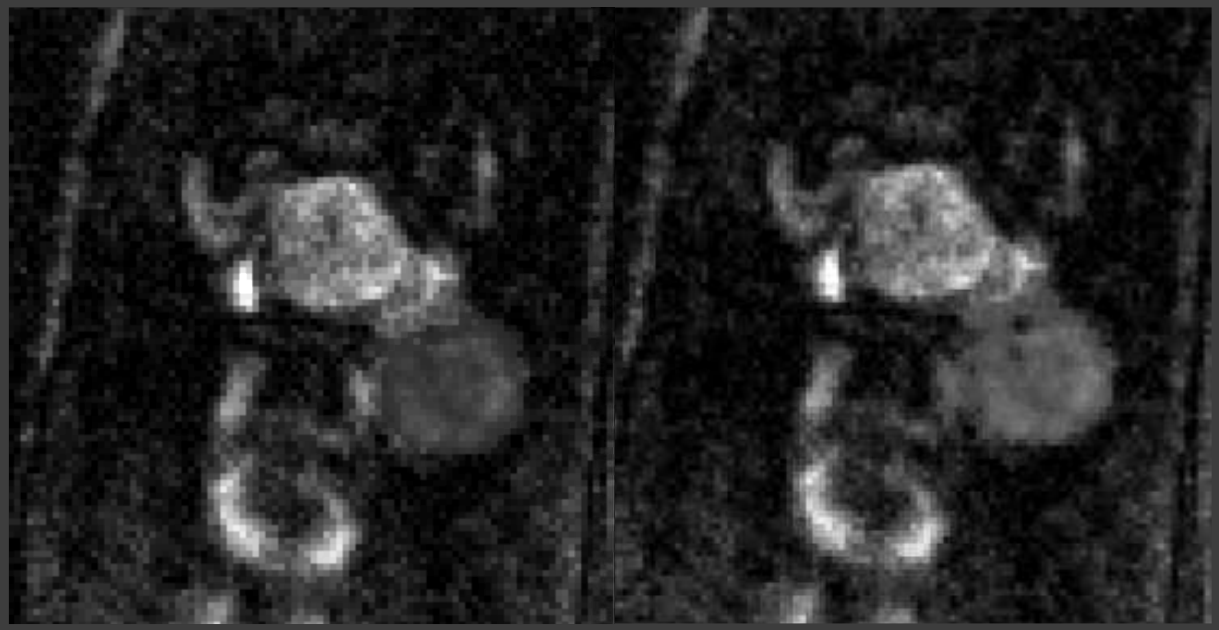
Images – SPION uptake



(A) *Coronal slice from 3D dUTE of AIA knee at day 10 of AIA SPION uptake after iv injections (7mg on day 5)*
Two different regions of the synovium (top and medial side of the knee) and bone marrow

(B) *without SPION, only the cortical bone as hyperintense signal*
Lower than SPION intensity

Images – Manual vs automatic

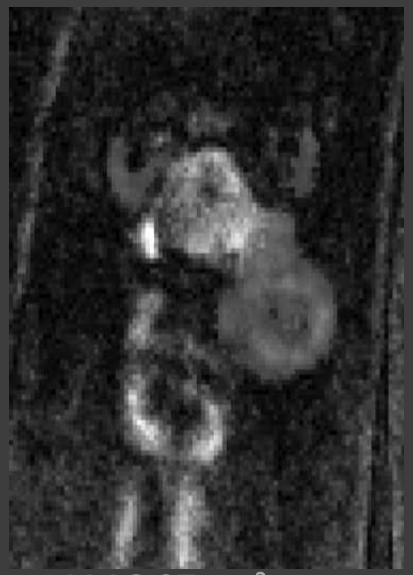


Manual segmentation	Semi-automatic segmentation
Volume = 2.15mm^2	Volume = 2.45mm^2
mean signal (sd) = 175.3 (50.8)	mean signal (sd) = 178.3 (43.8)
Integral = 377.6	Integral = 432.4

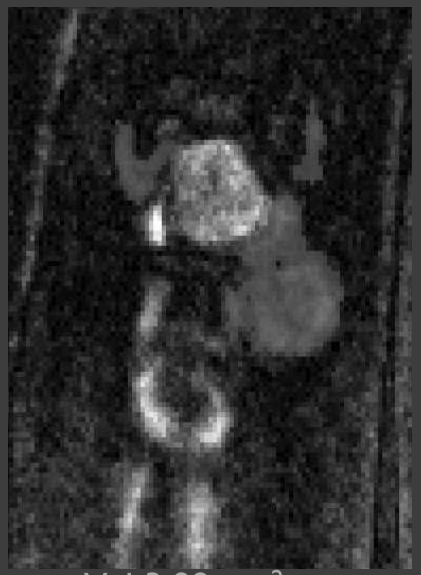
Automatic method successful in all cases

<20 minutes per knee: >3 x faster than manual

Quantification



Vol 3.87mm^2
mean SI 179.5
Integral 694.7



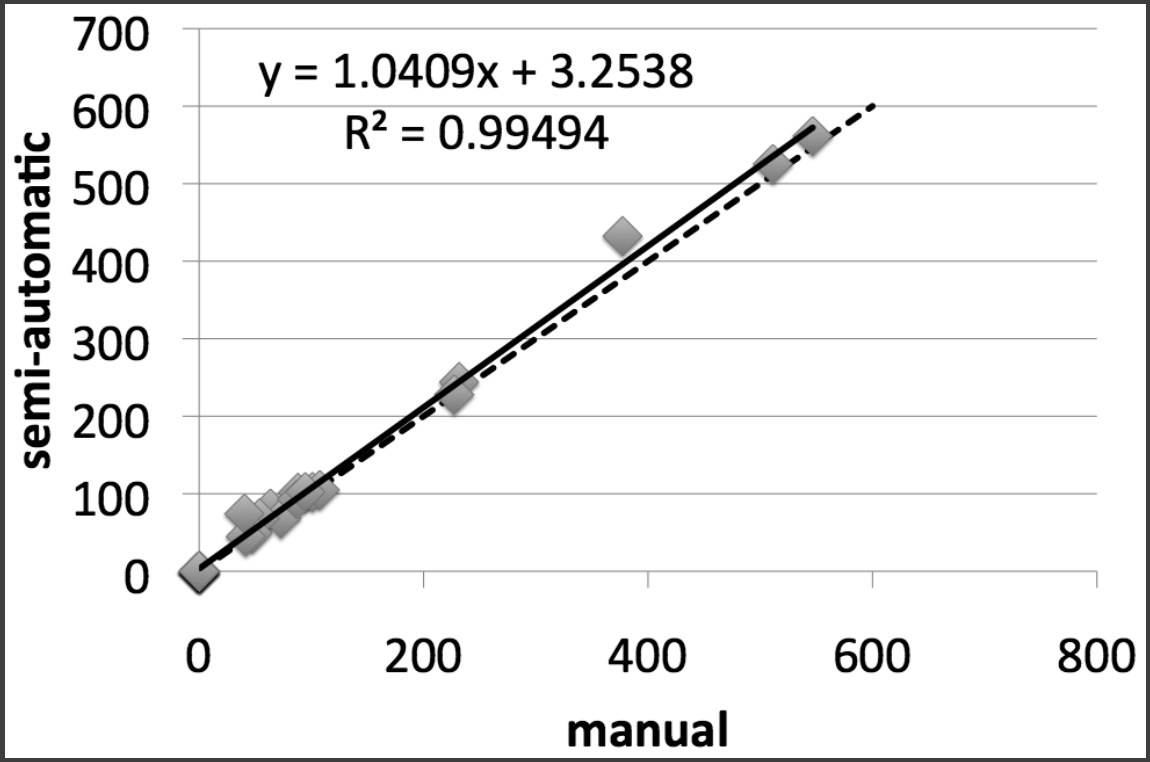
Vol 3.99mm^2
mean SI 162.3
Integral 647.6

Vol 2.86mm^2
mean SI 63.0
Integral 180.2

Vol 0.74mm^2
mean SI 104.8
Integral 77.6

An example of a semi-automatic segmentation of SPION at different locations

Quantification



Significant correlation between manual and semi-automatic segmentation of inhomogeneous uptake (n=16).

*Both axes show pixel intensity*number of pixels.*
Dotted line: x=y, solid line: fit of data showing excellent agreement (p<0.0001).

Discussion

- SPION biodistribution in the AIA knee is a complex process with heterogeneous accumulation of iron all over the synovium.
  - Pixel variation is generally not assessable by traditional GRE T2* MR used to evaluate the SPION distribution due to the saturation induced by even small amounts of iron.
- The dUTE sequence offered the advantage of positive, concentration dependent, signal - useful in the case of heterogeneous iron distribution. Therefore, it became possible with dUTE to quantify both distribution and intensity. The total 'iron quantification integral' gave a more complete assessment.

Conclusion

- The advantages of the dUTE sequence are removal of artifactual hypointense regions in the image and improved delineation of the iron-enhanced synovium from the cortical bone for semi-automated segmentation.
- The efficiency and speed of the semi-automated segmentation was well illustrated by the validation against manual segmentation.

- **Conclusion: We demonstrated 3D quantification of irregular SPION uptake with robust, easier and faster assessment using semi-automated segmentation and dUTE, as applied to intravenous SPION uptake in arthritic rat knee.**

Acknowledgements

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Thank you

Questions?

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