22.561 Final Project

^{19}F Magnetic resonance imaging of perfluorooctanoic acid encapsulated in liposome for biodistribution measurement

Magnetic Resonance Imaging

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Motivation and Challenges

Visualization of the tissue distribution of perfluorooctanoic acid (PFOA, $C_7F_{15}COOH$) by ^{19}F-MRI for pharmacological studies of similar compounds (many applications; toxicity)

Wide-range distribution of chemical shifts of ^{19}F-containing metabolites → molecular imaging and tissue function evaluations

^{19}F-MRI for image contrast enhancement

- **No background → ^{19}F signal is the contrast for ^{1}H-MR image (anatomy)**
- **^{19}F has the next highest MR sensitivity (83% of ^{1}H)**

Challenges intrinsic to ^{19}F-MRI

- **^{19}F has Long T1 → long acquisition time; Short T2 → signal attenuation**
- **Chemical shifts of ^{19}F NMR → chemical shift image artifacts (although preferred to trace the metabolism)**
- **Signal can only be obtained from the agents retained in tissue → SNR is the major concern for ^{19}F-MRI**

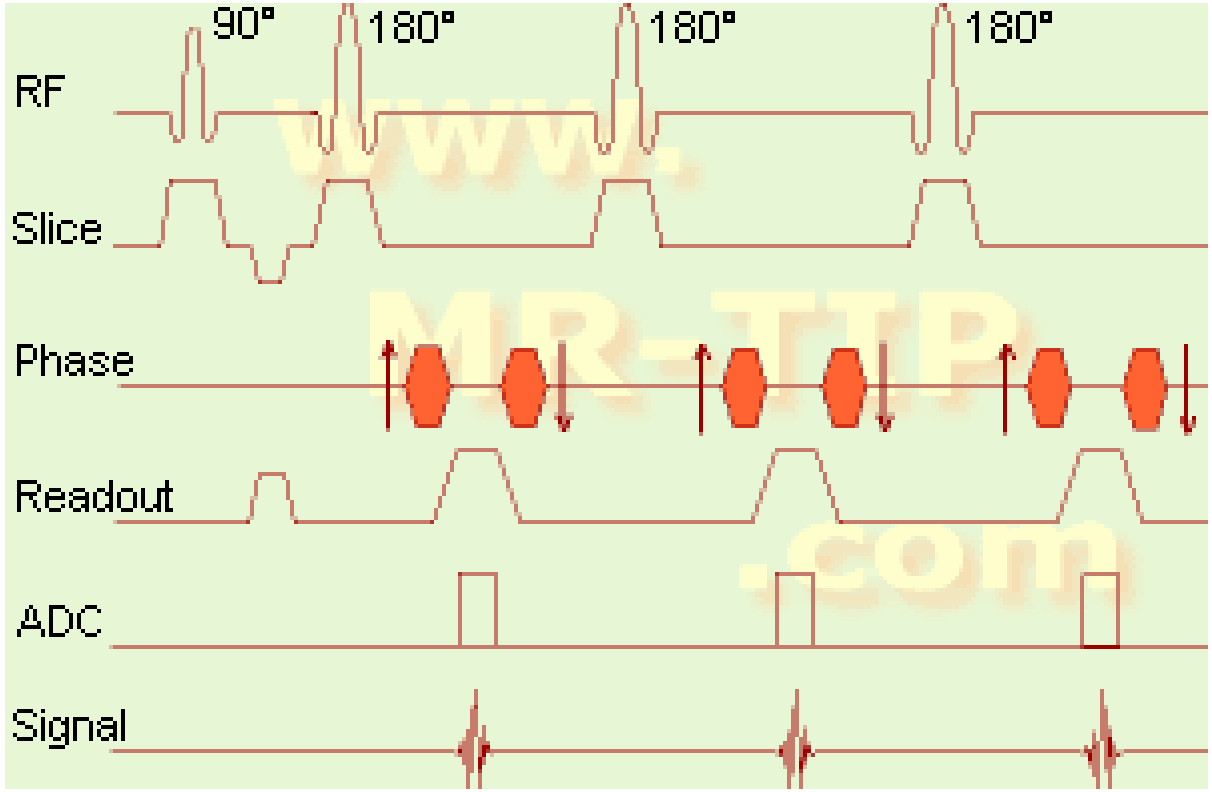
Solution – Chemical Shift Selected Fast Spin-Echo

Chemical shift artifacts

→ chemical shift selected RF pulse

Short T2

→ Spin Echo (SE) to preserve the signal



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Long T1 → Fast Spin Echo (FSE) to shorten acquisition time

Multiple phase-encoding steps with a single excitation (90° RF) and multiple echoes (180° RF), # of echoes per TR = echo train length (ETL)

Acquisition time reduced proportional to ETL

Effective echo time (TE) = maximum TE / ETL

Chemical Shift Selection

9.4T (376.2 MHz)

TR = 0.2 s, 128 scans

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See Kimura, A., M. Narazaki, Y. Kanazawa, and H. Fujiwara. "19F Magnetic resonance imaging of perfluorooctanoic acid encapsulated in liposome for biodistribution measurement." *Magnetic Resonance Imaging* 22 (2004): 855-860.

The ^{19}F NMR spectra in the female mouse stomach and liver were measured 0.4 and 2.7 h after the administration of the PFOA-liposome solution, respectively.

- **Chemical shift between -CF_3 group and other -CF_2 groups > 35 ppm (10 times that of fat and water ^{1}H) → frequency difference ~14 kHz**
- **Chemical shift selection was able to eliminate chemical shift artifacts.**
- **Only -CF_3 signal was excited → no the signal intensity modulation by J-coupling caused by adjacent ^{19}F atoms**

^{19}F Relaxation Times

In vivo and in vitro relaxation times of the CF_3 signal of PFOA

Standard deviations in parentheses	PFOA	
	T_1 (ms)	T_2 (ms)
In vivo	140 (20)	6.3 (2.2)
In excised liver	300 (30)	15.7 (1.5)
In PFOA-liposome	400 (40)	2.3 (1.4)
In ethanol	1900 (100)	1300 (80)

- **T1 by Inversion Recovery → double dynamic range**
- **T2 by Carr-Purcell-Meiboom-Gill (CPMG) → refocusing pulse error corrected at even echoes**
- **T2 of water ^1H ~ several tens to hundreds of ms; T2 of -CF_3 group of PFOA < 10 ms *in vivo***

  Short T2 in liposome probably due to high solution viscosity
- **Both T1 and T2 of -CF_3 of PFOA were shortened *in vivo***

  Molecular motion of PFOA restricted, especially the -CF_3 group

In Vitro ^{19}F-MRI of PFOA-Liposome Solution – Parameter Optimization for *In Vivo* ^{19}F-MRI

ETL = 2 in (b) more effective than ETL = 4 in (c)

- **[PFOA] = 5.4 mM; Effective TE = 1 ms**
- **For ETL = 4, last two echoes at 3, 4 ms**
- **T2 of -CF_3 of PFOA in solution = 2.3 ms**

Maximum TE value constrained by T2, increase ETL to reduce effective TE

- **More 180° RF pulses per TR**
- **Requires strong and rapidly switching gradients**
- **Under instrumental constraints, ETL = 2 was used as the optimal value for *in vivo* ^{19}F-MRI.**

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In Vivo ^{19}F-MRI

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1 mL PFOA-liposome solution orally administered to mice with fasting for 4 hr

9.4T (376.2 MHz); Chemical shift selection: Gaussian pulse, 9kHz band width; TR = 0.15 s; Effective TE = 1 ms; ETL = 2; 64 x 16 data points; FOV = 8cm x 4cm; No slice selection; Acquisition time = 12min

PFOA initially in the mouse stomach → at 1 hr, began to distribute into the liver → at 2.7 hr, PFOA mostly transferred to the liver

PFOA Tissue Distribution Quantification by ^{19}F-NMR

Tissue	Concentration (μmol/g tissue)	Percent dose (%/g tissue)
Liver	1.74 (± 0.41)	32.0 (± 8.6)
Plasma	0.74 (± 0.01)	13.6 (± 0.2)
Stomach	0.30 (± 0.05)	5.5 (± 0.9)
Lung	0.27 (± 0.02)	5.0 (± 0.4)
Intestine	0.25 (± 0.08)	4.6 (± 1.5)
Kidney	0.15 (± 0.03)	2.8 (± 0.6)
Spleen	0.14 (± 0.01)	2.5 (± 0.2)

Mice were sacrificed after ^{19}F-MRI and the organs were excised and cut into pieces for ^{19}F-NMR.

^{19}F-NMR signal intensity of -CF_3 of PFOA from different organs was measured and calibrated by signal from benzene solution of trifluoroactamide (CF_3CONH_2) for quantification.

The lowest concentration of PFOA that ^{19}F-MRI was able to visualize was estimated from the images → ~ 1 μmol PFOA / g tissue

Assume tissue density = 1g/mL → ~1 mM of PFOA << ~100M of water ^{1}H

Conclusions

- **Tissue distribution of PFOA was successfully traced by ^{1}H and ^{19}F -MRI, the latter of which used chemical shift selected fast spin-echo method.**
- **It was necessary to administer PFOA at high concentration of 100 mg (0.19 mmol)/kg body weight, corresponding to 20 times the dose using radiolabel method. → major challenge for ^{19}F-MRI is SNR**
- **Contrast agents that elongate T2 and shorten T1 are desirable.**

Questions?

- **Would you use ETL = 3 or 4 for *in vivo* ^{19}F-MRI since T2 = 6.3ms instead of 2.3ms?**
- **If the acquisition time is 12 min (0.2 hr) and PFOA is moving, what actual states do the images at 0.4, 0.6, 1.0 hr … represent?**
- **Is FSE is the optimal sequence for ^{19}F-MRI?**
- **How to make use of all the ^{19}F nuclei in PFOA instead of -CF_3 only since the concentration of PFOA is the limiting factor?**