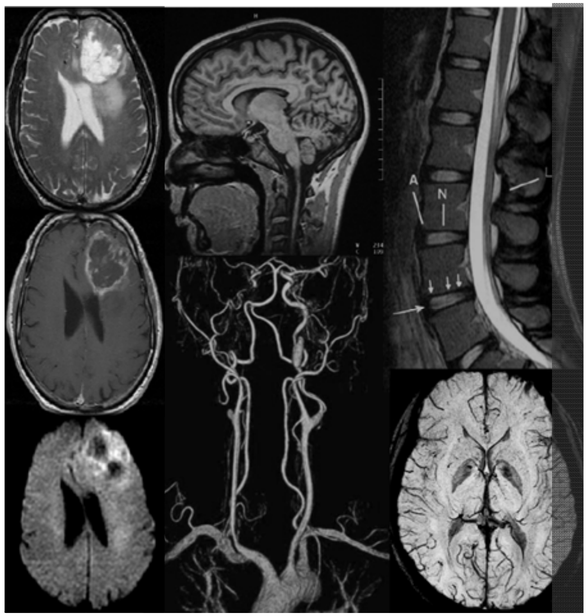

醫用磁振學MRM

Chemical Exchange Saturation Transfer - CEST

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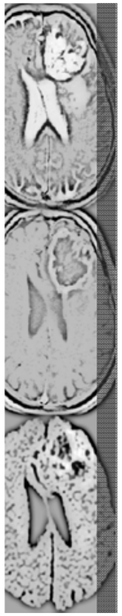


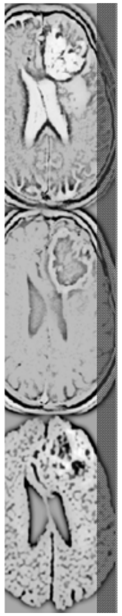
本週課程內容 http://www.ym.edu.tw/~cflu

- 化學交換飽和轉移Chemical exchange saturation transfer (CEST)

- CEST: from basic principles to applications, challenges and opportunities - E. Vinogradov, A. Sherry, R. Lenkinski, J Magn Reson., (2013) 229: 155.
- Chemical Exchange Saturation Transfer: What is in a Name and What Isn't? - Peter C. M. van Zijl and Nirbhay N. Yadav, Magnetic Resonance in Medicine, (2011) 65:927-948.

化學交換飽和轉移原理

Principles of CEST



Why CEST-MRI?

- Conventional MRI gives T1, T2, and proton density weighted images.
- The most common contrast agent, Gd-chelate, shortens the relaxation time of the free water protons.
  - These agents are not selective, and distribute uniformly throughout the extracellular space after intravenous injection.
  - These agents are often toxic.

CEST provides a molecule-specific contrast for MRI.

Principles of CEST

- *A slowly exchanging MR-active nucleus, typically a proton, possessing a chemical shift distinct from water is selectively saturated and the saturated spin is transferred to the bulk water via chemical exchange.*

→ New contrast with the normal T1-relaxation time

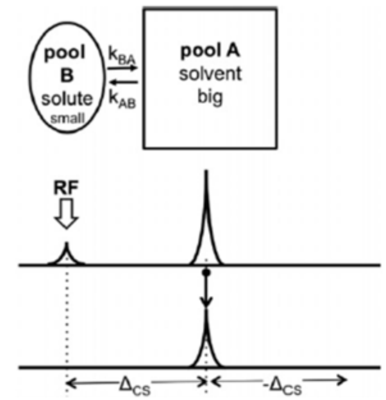
→ Indirect measurement of (metabolic) exchange-processes

Introduced by Balaban and co-workers as a new class of MRI contrast in 2000.

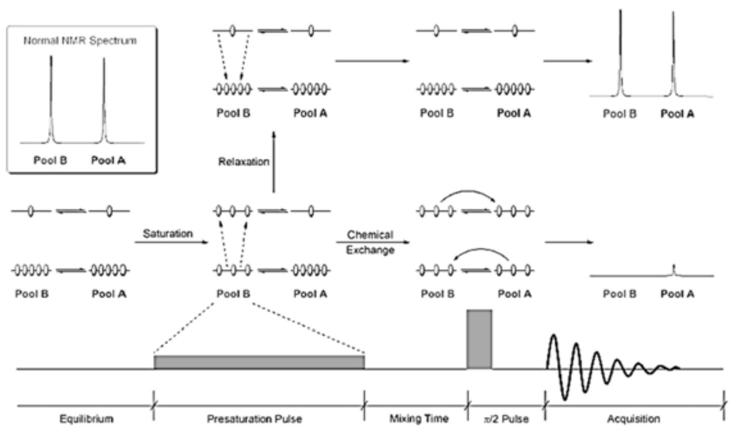
Schematic of CEST

Solute:
µM to mM range.

- Pool A (solvent) is in exchange with pool B (solute).
- Pools A and B have distinct chemical shifts, with the difference of Δ_{CS}.
- RF is applied on-resonance with pool B resulting in saturation transfer and signal decrease of pool A.



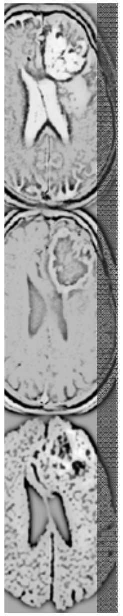
Scheme of CEST



M Woods, Chem Soc Rev 2006, 35(6): 500-511.

Essentials for CEST

- A pool with target protons that will exchange to water
- Frequency-specific RF Pulse to saturate the protons
- Mathematical processing of the data

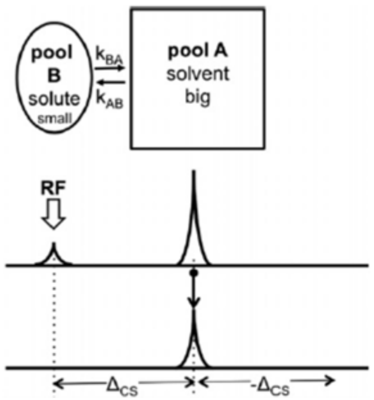


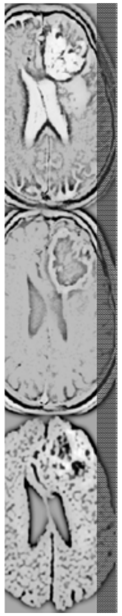
Exchangeable Protons

- Must posses exchangeable protons or molecules.
- The exchange rate k_{ex} must be sufficiently fast
- the chemical shift Δ_{cs} has to be big enough $\Delta_{cs} > k_{ex}$

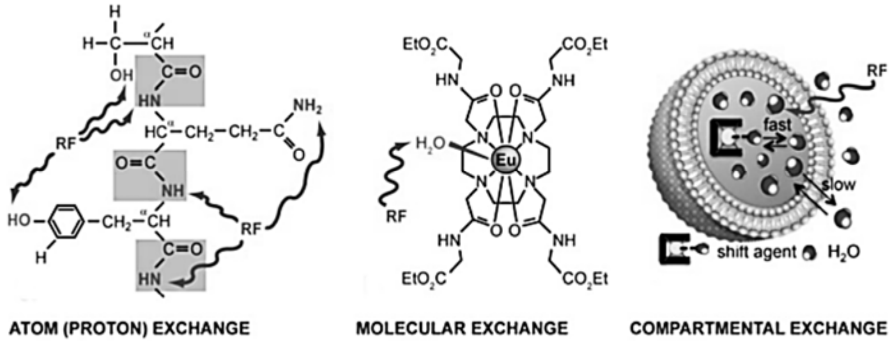
The exchange rate:

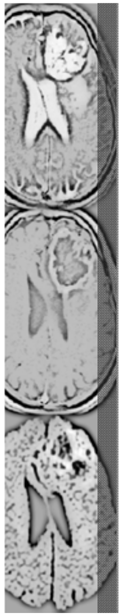
$$k_{ex} = k_{BA} + k_{AB}$$





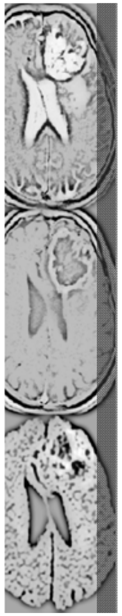
Types of CEST Agents





Types of CEST Agents

- Proton exchange
  - Endogenous and exogenous diamagnetic CEST (diaCEST)
  - Some paramagnetic CEST (paraCEST)
- Molecular exchange
  - paraCEST
  - Hyper-polarized gases (**hyperCEST**)
- Compartmental exchange
  - Liposomes (lipoCEST) and hyperCEST



diaCEST

- The chemical types of proton exchange groups are largely confined to
  - -NH
  - $-NH_2$
  - -OH
- The chemical shift of the diaCEST agents is typically within 5 ppm (relatively small shift) from water.
  - In the environment of 9.4T, only the exchange rates of 2×10^3 s^{-1} or slower are needed for CEST.
- Increase the number of the exchanging groups per agent can increase the CEST effect → polymers or dendrimers.

diaCEST

- Involves both endogenous and exogenous proton exchange types.
- Exogenous injection of the agent
  - Glucose imaging (glucoCEST)
  - pH imaging using iopamidol

paraCEST

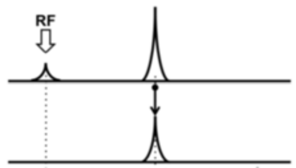
- Exogenous paramagnetic lanthanide (III) complexes that exhibit large hyperfine shifts (on the order of 50–700 ppm).
- Pre-saturated targets
  - The highly shifted bound water protons
  - The ligand's amide
  - Hydroxyl protons
- Usages in reporting biological indices
  - pH, temperature, lactate, glucose concentration, enzyme activity, cell-labeling.

paraCEST

- Larger chemical shift allows a wide range of exchange rates.
- The fast exchange rates should allow detection of much lower concentrations of paraCEST agents in comparison with diaCEST.
- The selective RF pulse is applied far from the free water resonance frequency, which reduces direct RF saturation.

The Pre-saturation Pulse

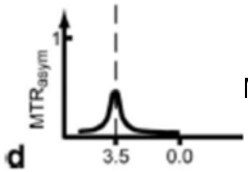
- Saturate exchangeable protons with RF-pulse
- → the protons exchange with water-protons and the water signal gets lower.
- → if t_{sat} longer than the exchange, the water-signal gets lowered visibly because the saturation builds up



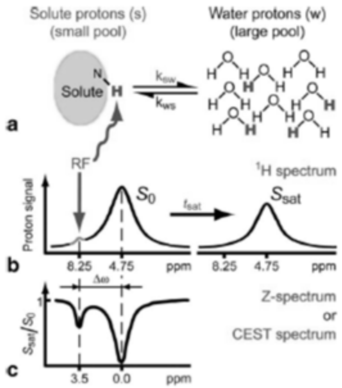
Z-Spectrum

- Normalized water Spectrum (S_{sat}/S_0)
- Magnetization transfer asymmetry

  $MTR_{asym} = \{S_{sat}(-\Delta\omega)-S_{sat}(\Delta\omega)\}/S_0$



MTR_{asym} Spectrum



Two-Pool Model

- Assume CEST contrast = proton transfer ratio (PTR)
- Analytical solution:

$$\mathrm{PTR} = x_s \cdot \alpha \cdot k_{sw} \cdot T_{1w}\left(1 - e^{-t_{sat}/T_{1w}}\right),$$

$$x_s = \frac{[\text{exchangeable proton}]}{[\text{water proton}]} = \frac{k_{ws}}{k_{sw}}.$$

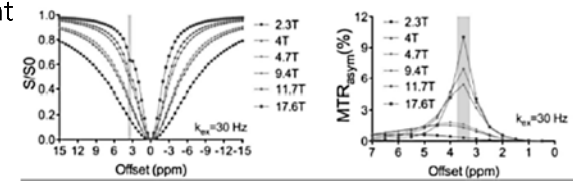
k_{sw} = exchangerate saturation-pool $\rightarrow$ water
α = saturation efficiency
T_{1w} = T_1 of water
t_{sat} = saturation time

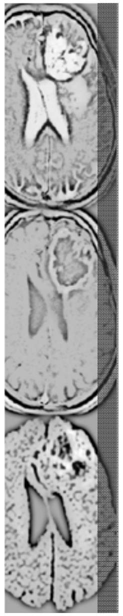
Factors of CEST

- The magnetic fields
- The Pulse-Sequences
- Imaging issue
- Different Z-Spectra of molecules

The Magnetic Fields

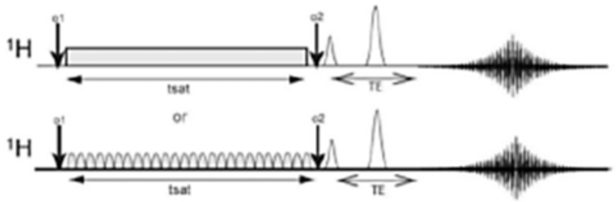
- From experiments: B0 ↑ → T1 ↑ & T2 ↓
- Δ_{CS} is proportional to strength of the main-field
- higher Δ_{CS} allows agents with faster exchange rate
- long T1 means slower recovery from saturation → larger CEST-contrast
- Increase B0 increases the sensitivity → CEST is suitable for the high-field measurement

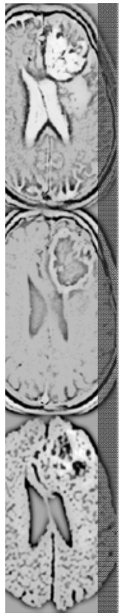




The Pulse-Sequences

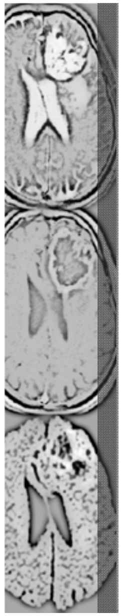
- One saturation-pulse before the T1-image sequence
  - one long saturation pulse
  - repetition of many short pulses
- To minimize the recovery of from the saturation → shorter pulse and dephasing after every taken slice



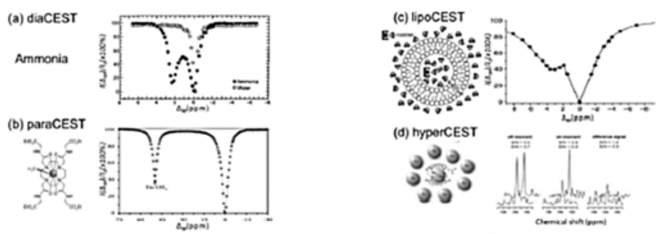


Imaging Issues

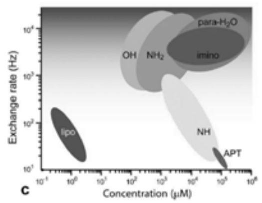
- Problems while taking CEST-MRI:
- Time: t_{sat} > 2 sec → time for measurement > 9min per saturation (need more for imaging).
- For faster measurement
  - limited offset sampling
  - reduce sampling points in k-space
- Desaturation: Spins flip back from saturation and signal gets lower.
- Solutions:
  - shorter pulse and dephasing after every taken slice
  - reduce taken time for measurement

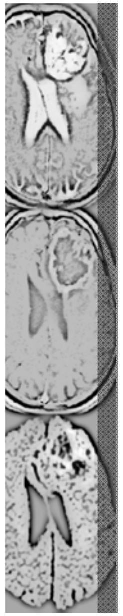


Different Z-Spectra of molecules



- a) Ammonia (black) and water (white)
- b) Glycerin ethyl esther
- c) Liposome filled with agent
- d) free Xe (blue), coated Xe (green)





Summary

- CEST-MRI measures indirect exchange of protons/molecules → (indirect) measurement of processes in the tissue
- Suitable for high-field measurements, 7T or 9.4T
- Further development with more exchange-mechanism and further contrasts arise

Applications of CEST

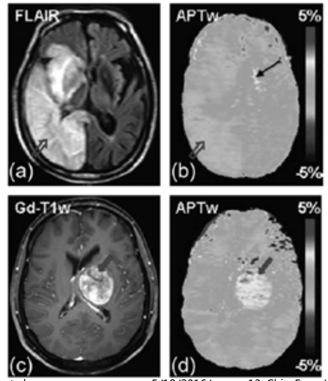
- The CEST effect can be used to image important physiological parameters, such as pH and metabolite levels.
- The technique can be applied for variety of ailments and metabolic disorders
  - cancer,
  - ischemia,
  - cartilage degeneration

Amide Proton Transfer (APT)

- The maximum APT effect is observed at 3.5 ppm from water
- pH=9.4+log[APTR/5.73]

Stroke

Lung metastasis



THE END

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