Chemical Exchange Saturation Transfer MRI

Contrast and Quantification

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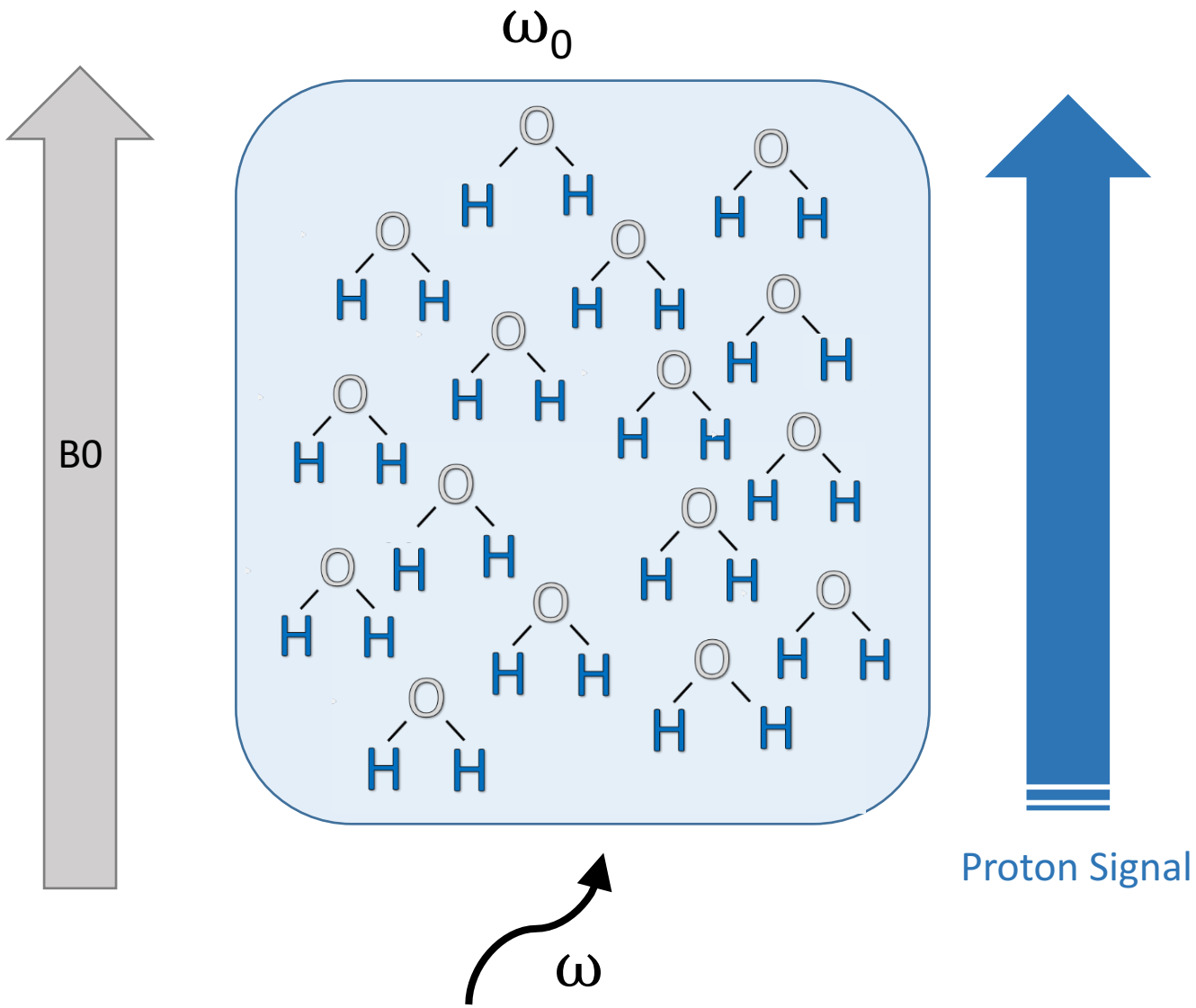
CEST MRI: The Basics

- Chemical Exchange Saturation Transfer MRI
- Molecular imaging technique
- Detect low concentration of metabolites that have exchangeable protons
  - Amides
  - Amines
  - Hydroxyls
  - Creatine

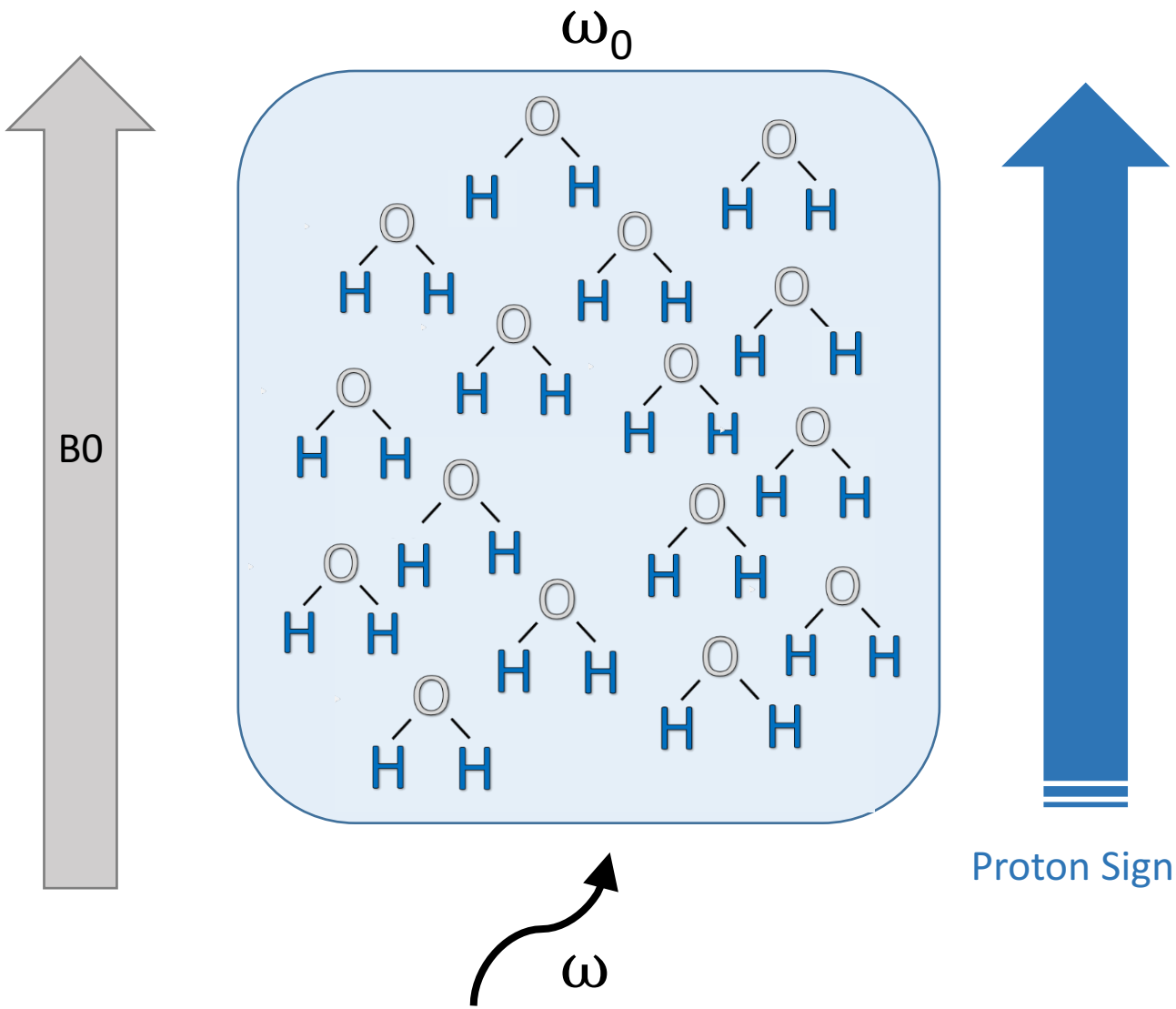
Why CEST?

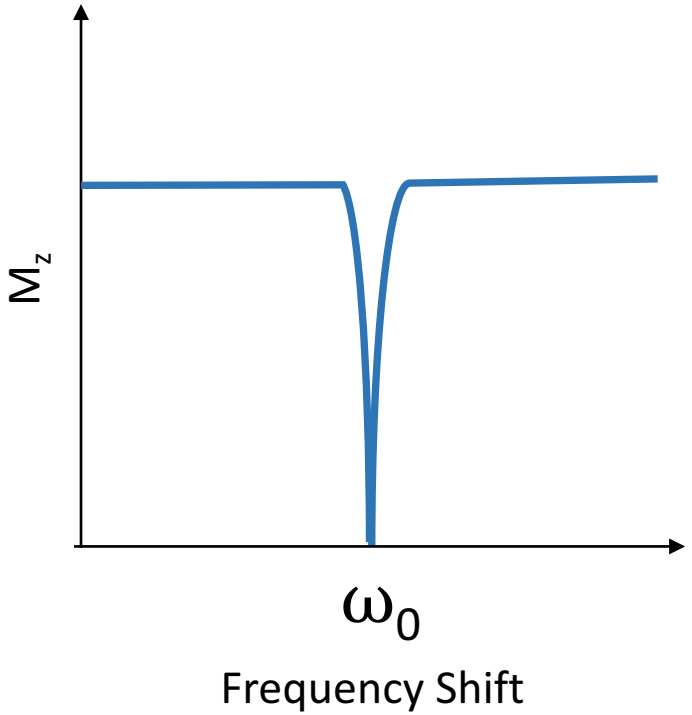
- Means of enhancing the sensitivity of MRI to broad range of solute molecules.
- Non-invasive means to measure biophysical and physiological properties.
- Clinically feasible and increasing evidence of clinical role.
- Broad range of CEST MRI depending on application.
  - Endogenous (e.g. APT CEST)
  - Exogenous (e.g. GlucoseCEST)

A Typical MRI Experiment

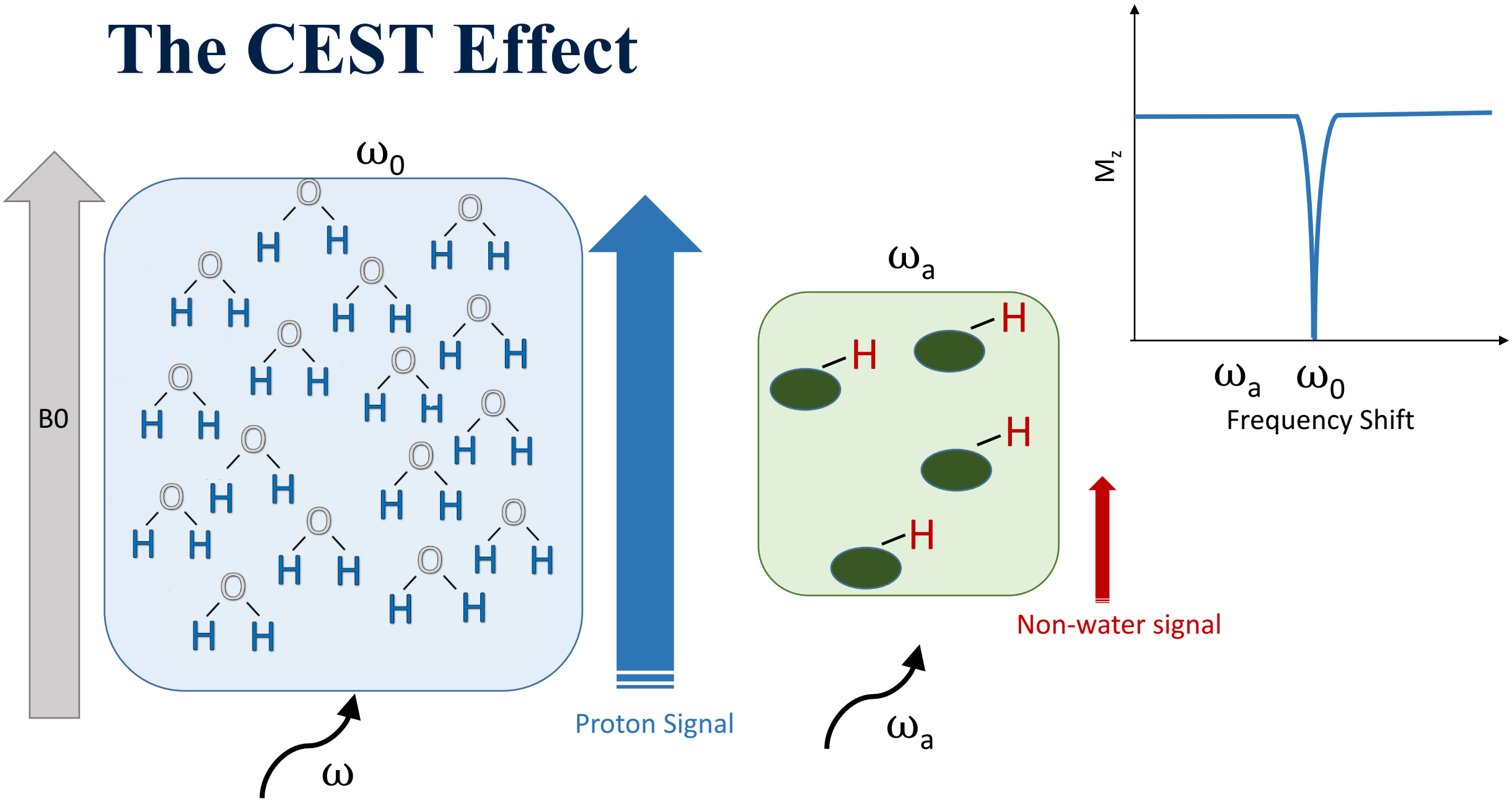


A Typical MRI Experiment: Saturation

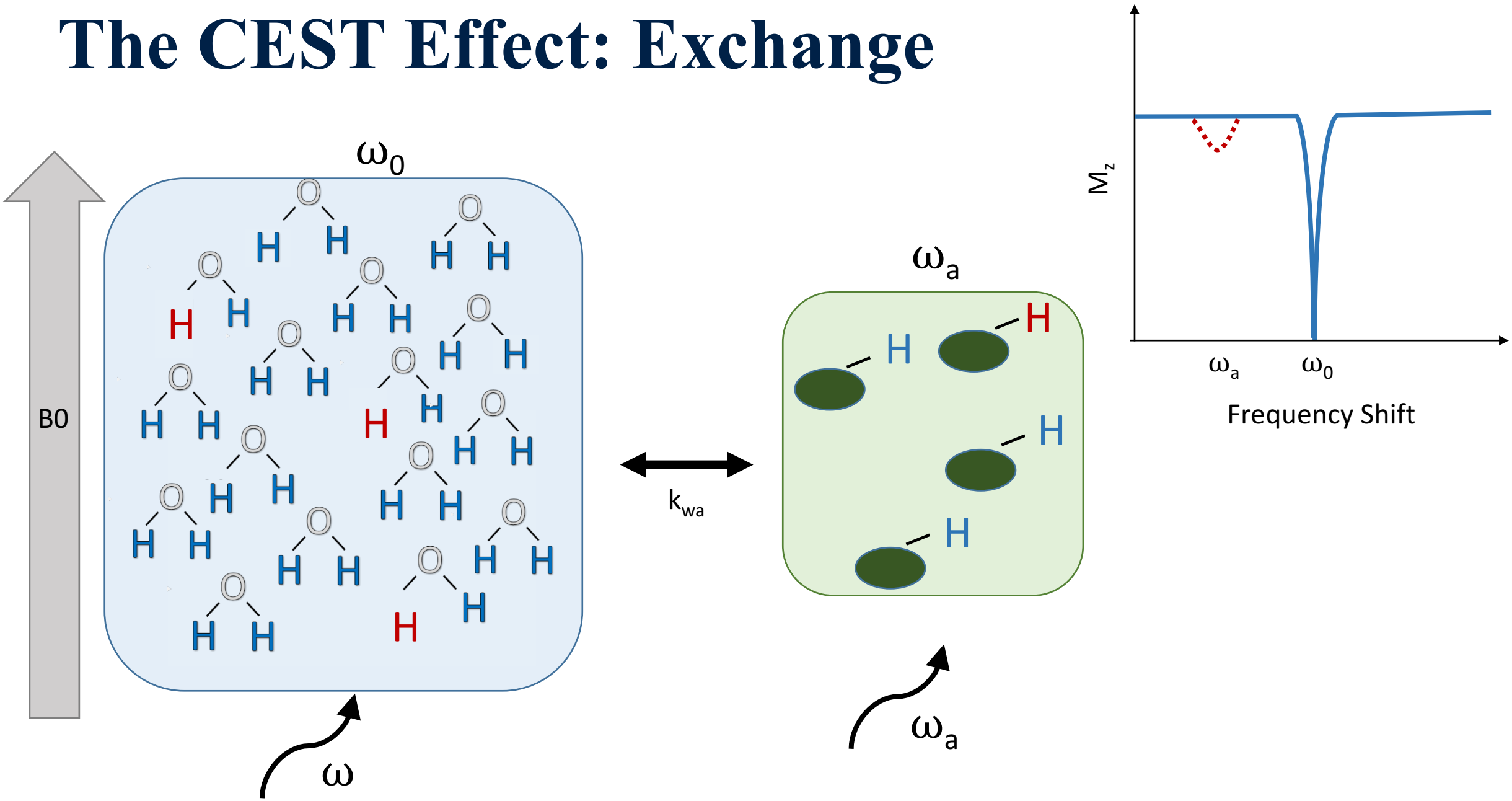




The CEST Effect



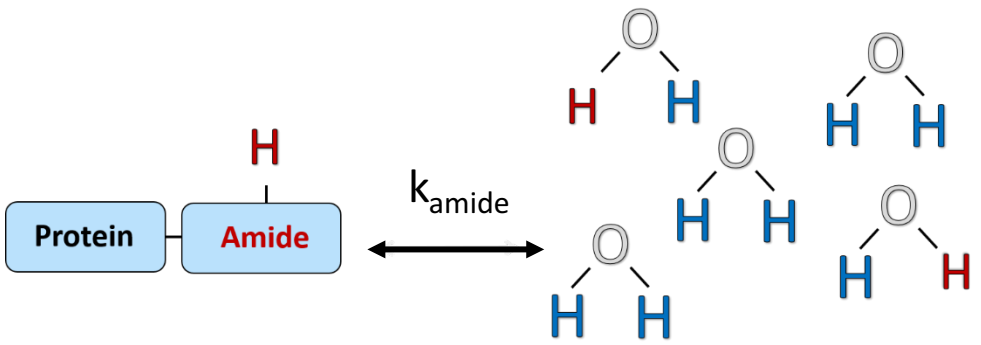
The CEST Effect: Exchange



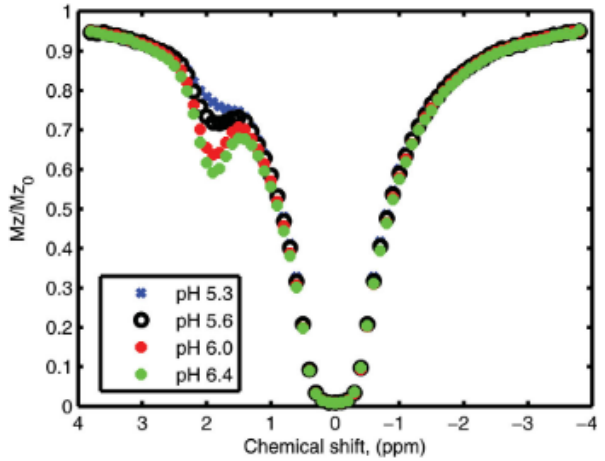
APT CEST MRI

What are we trying to measure?

- Amide Proton Transfer (APT) CEST MRI



- In simplest terms, we just want to know what the effect size is at 3.5 ppm in relation to water



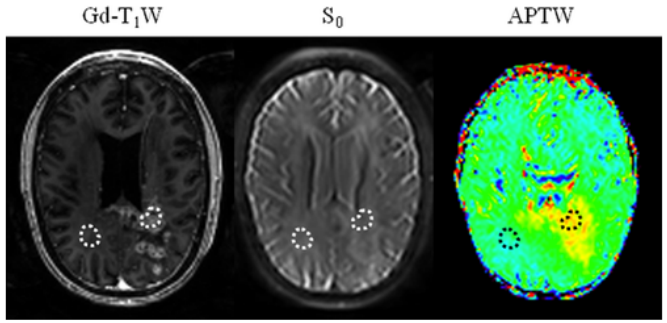
- A key appeal of the amide pool is that the exchange rate (k_{amide}) is base-catalysed
  - pH measurement

- Broad range of clinical applications

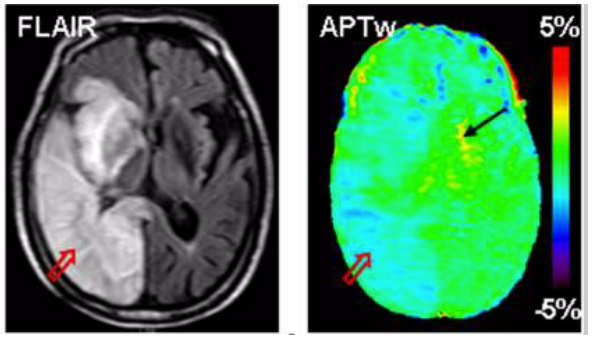
Chappell et al., MRM, 2013

Measuring the APT Effect

- Asymmetry Analysis



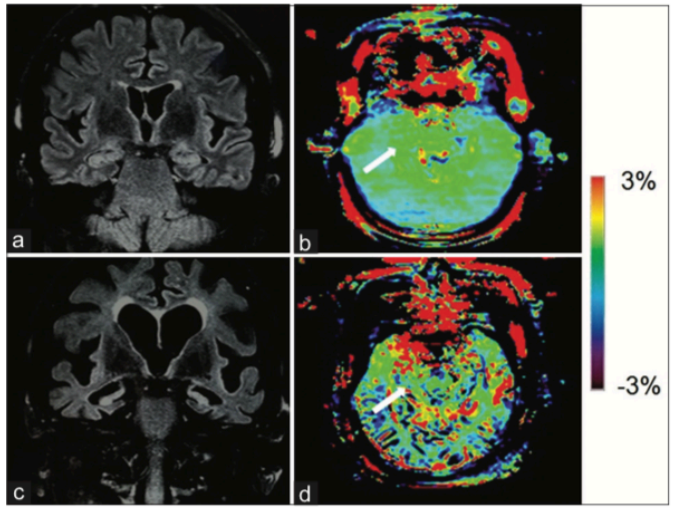
$$MTR_{asym}(\Delta) = \frac{S(-\Delta) - S(\Delta)}{S_0}$$

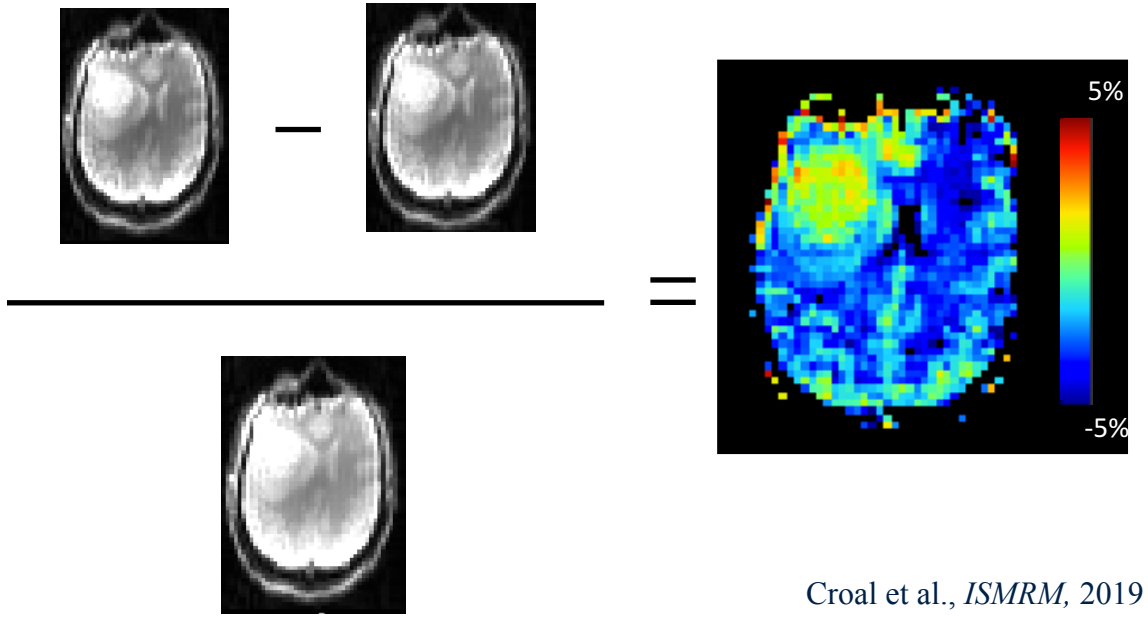


Ma et al., JMRI, 2016

Zhao et al, MRM, 2012

Wang et al., Chin Med J, 2015





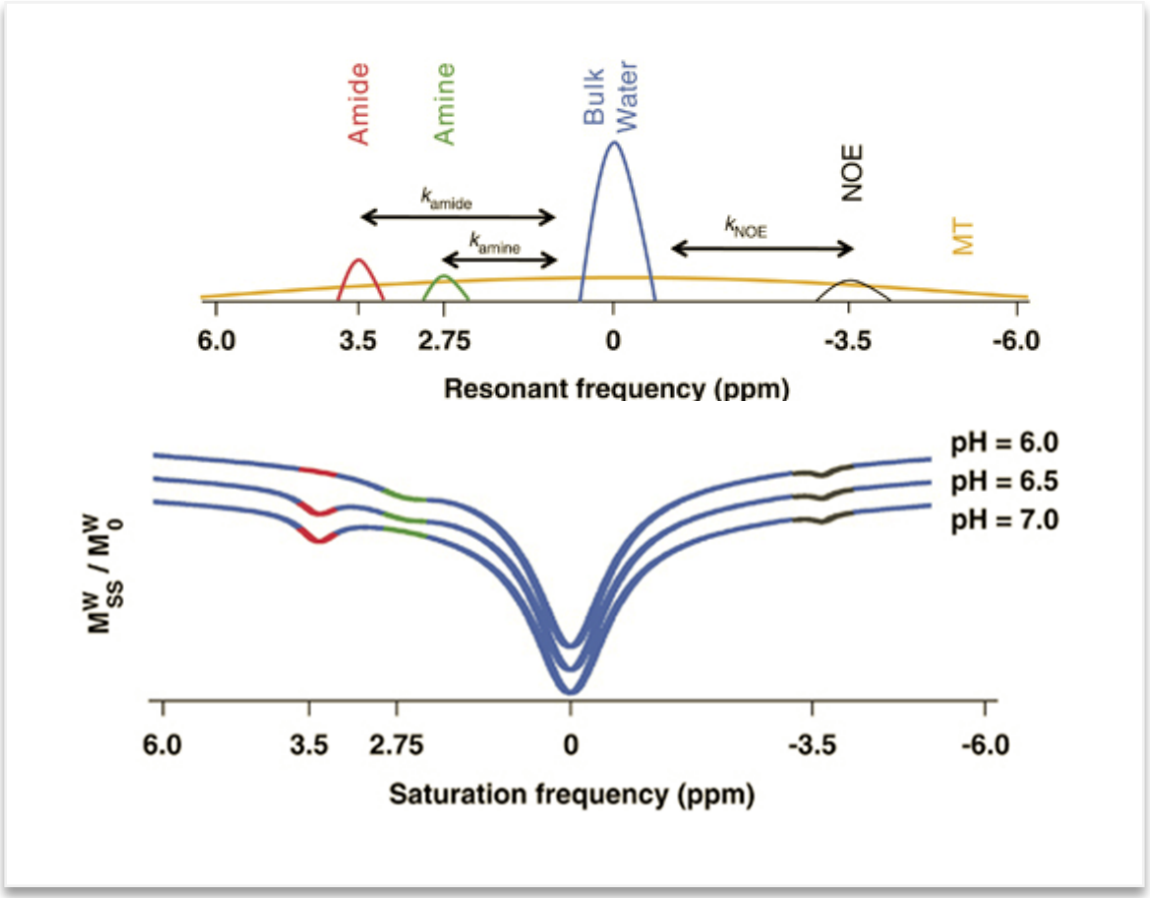
Croal et al., *ISMRM,* 2019

Is it really that simple?

- The Z-spectra is actually made up from a range of signal contributions

- Direct water saturation
- Multiple pools
- Macromolecular Effects (non-symmetrical)

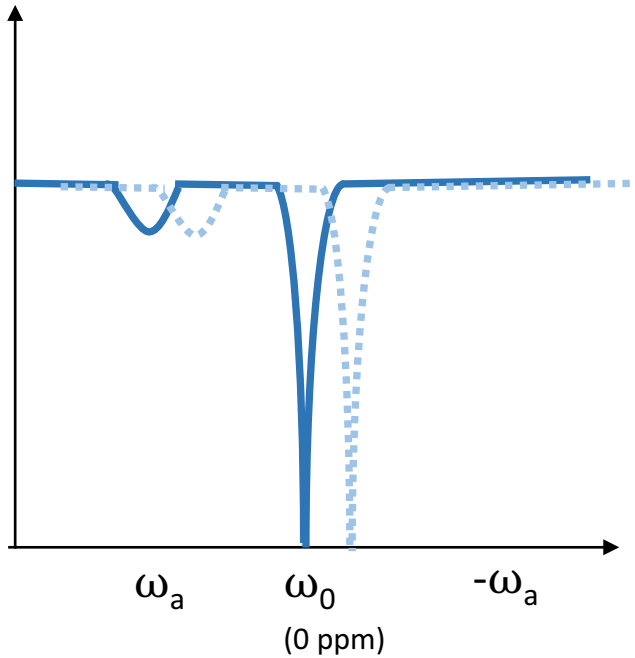
- B_0 offsets
- T_1/T_2 effects
- Acquisition parameters

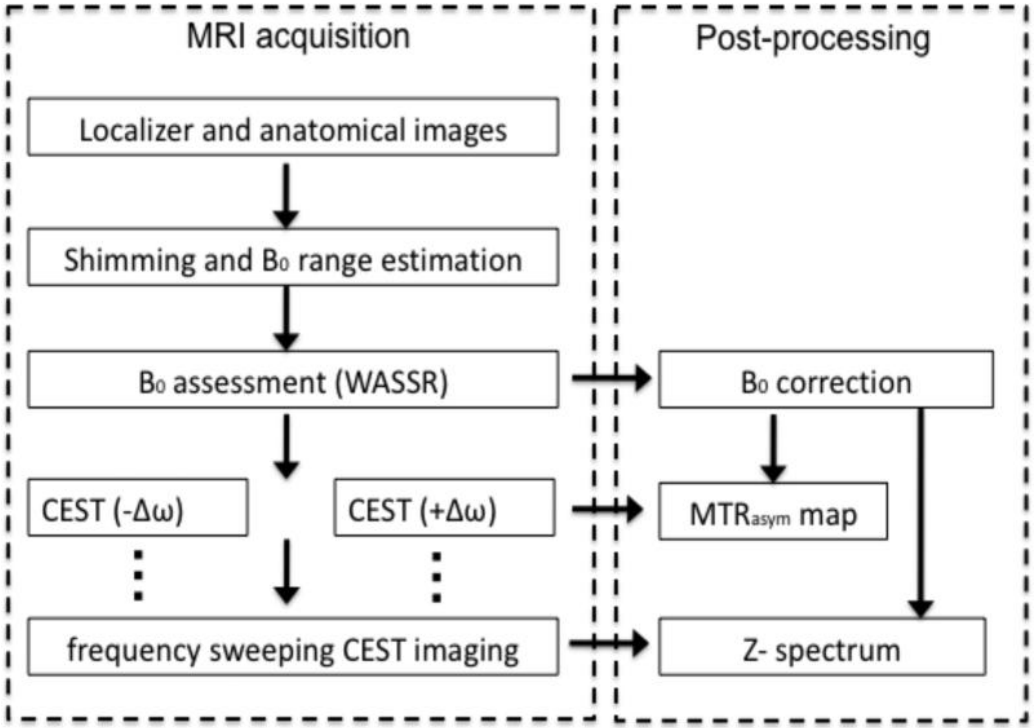


McVicar et al., 2014, JCBFM, 34: 690-698

Correcting for B_0 Effects

- Magnetic field inhomogeneities can result in a shifting of the spectra
- Rather problematic if left uncorrected
- Solution is to estimate your field shift and sample spectrum accordingly

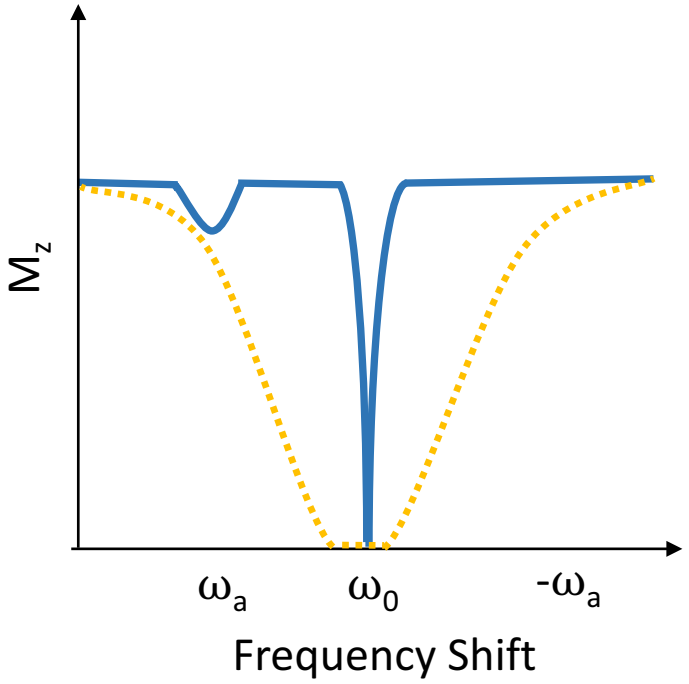


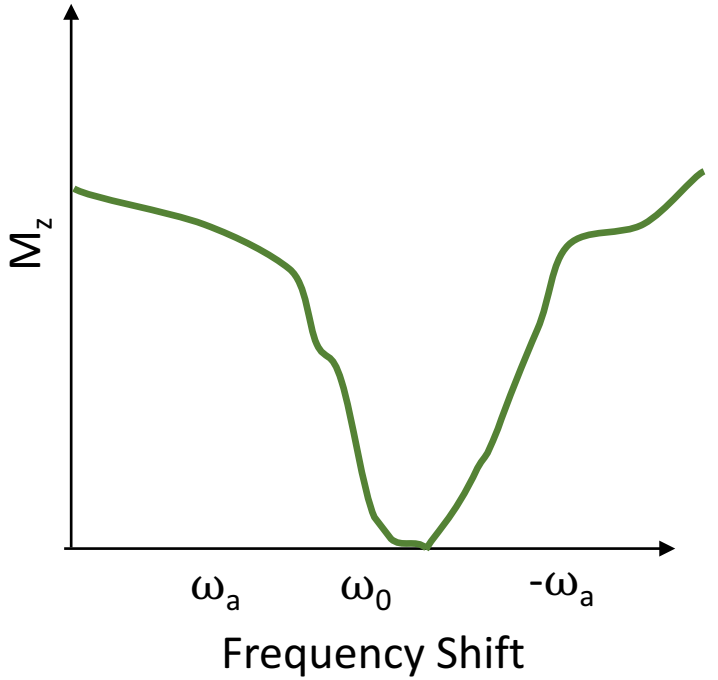


Kim et al., *MRM, 2009,* Liu et al, *Methods Mol Biol*. 2011;

Macromolecular effects

- You can ignore the fact that they are asymmetrical…
  - Proceed with asymmetry analysis
- You could try and incorporate them into your analysis.
  - Both model-free and model-based options



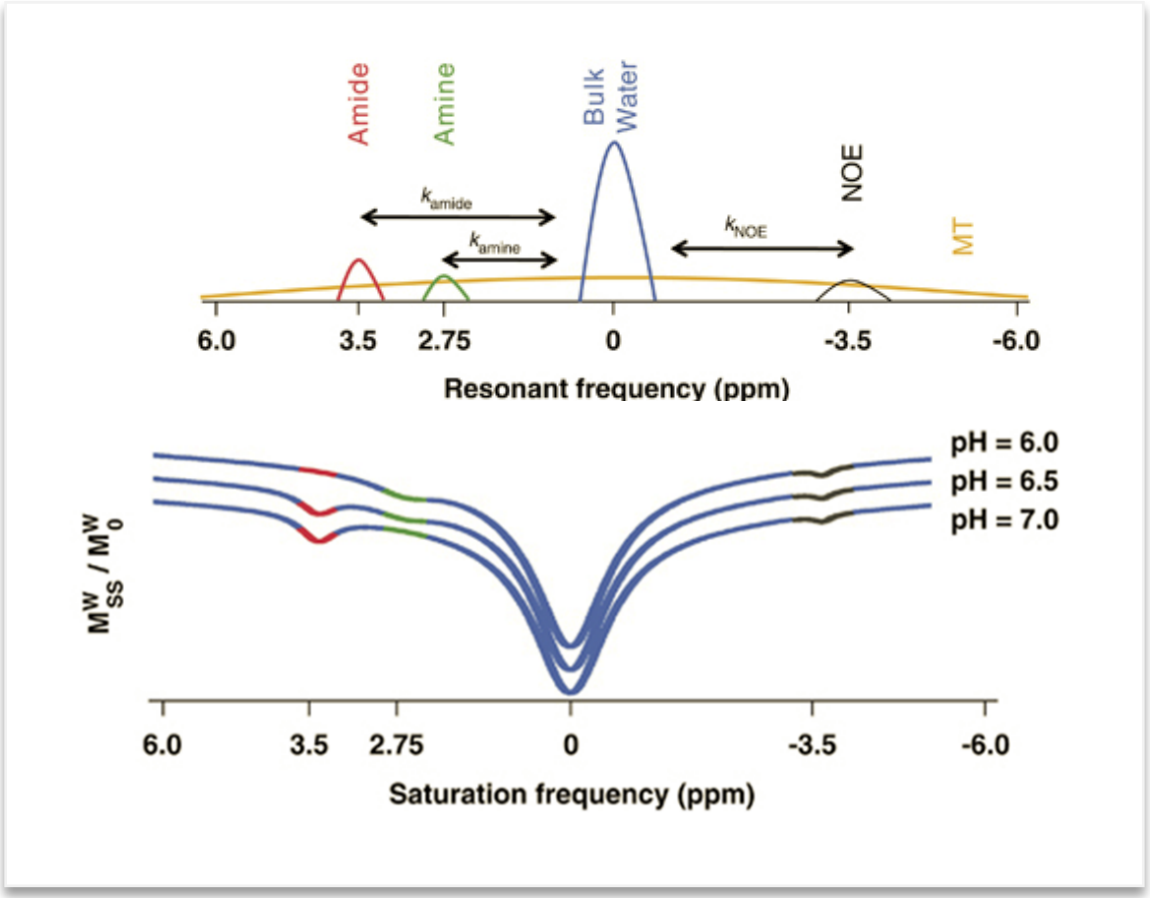


Accounting for Multiple Pools

- The advantage of incorporating macromolecular effects into your analysis, is that you can also use this approach to account for additional pools.

- The challenge is how best to characterise pool(s) of interest, while accounting for confounding pools.

- Your pool of interest will depend on what physiological parameter you are trying to measure.



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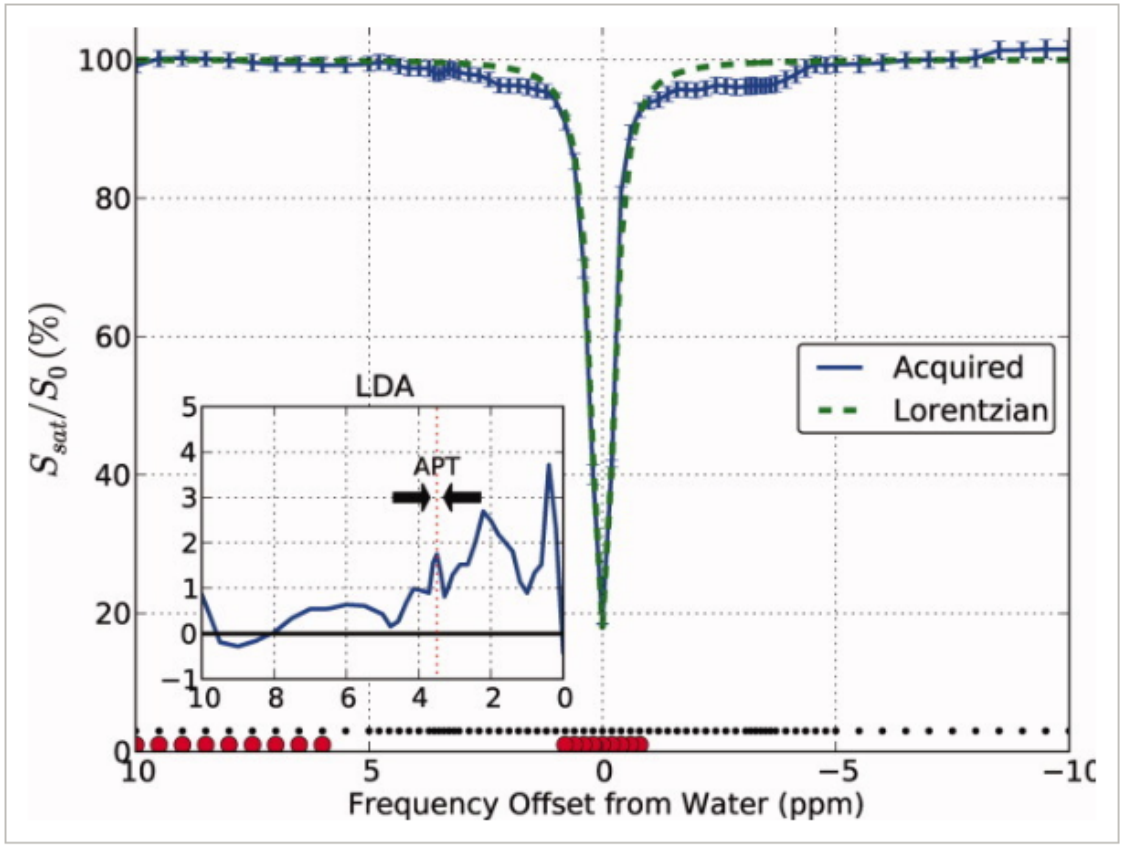
Lorentzian Difference Analysis



Overview:

- Z-spectrum described assumed to be:
  - Water pool (Lorentzian)
  - Solute pools of interest
- Exploratory
- Doesn't require a whole z-spectra.

Challenges:

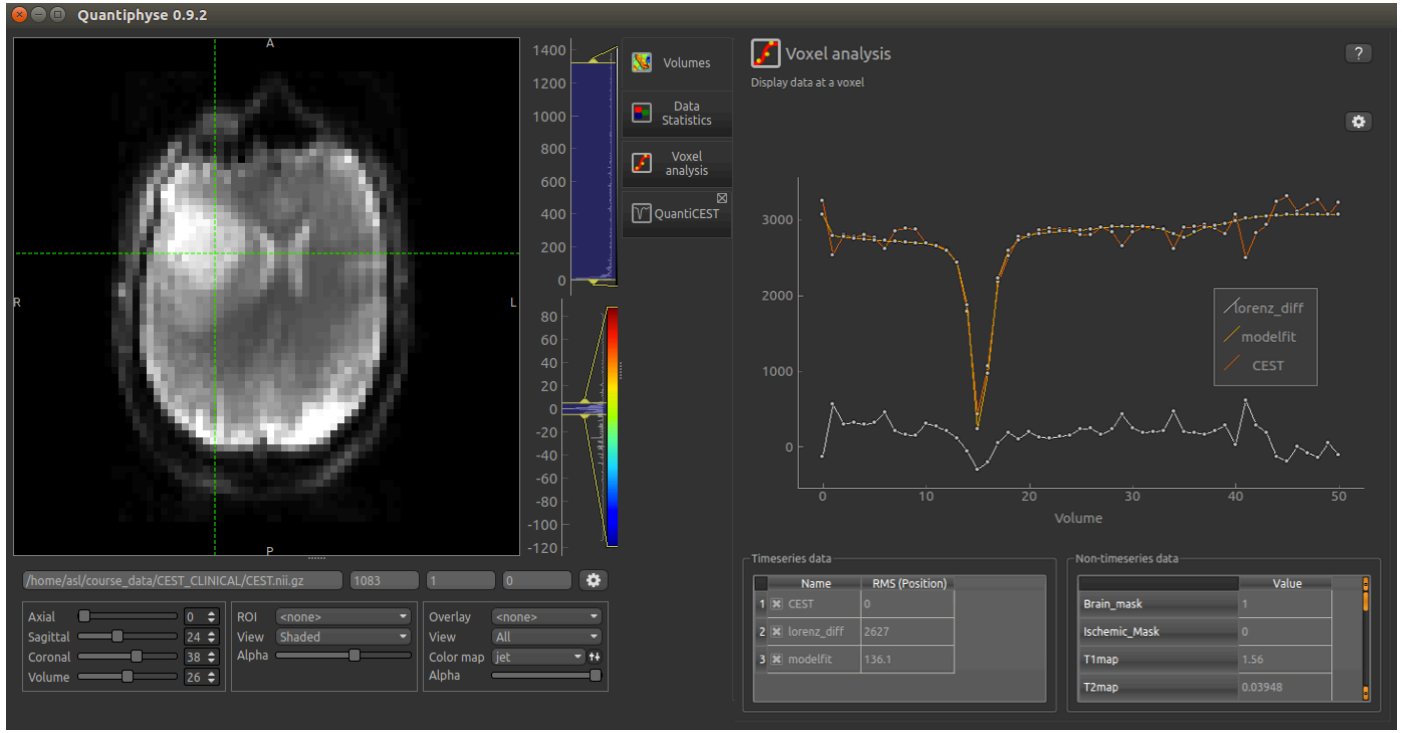
- MT affects need to be well-accounted for.
- No T_1 correction.
- Non-quantitative in physiological terms.

Jones et al., *MRM,* 2011

Lorentzian Difference Analysis: Tools

Quantiphyse

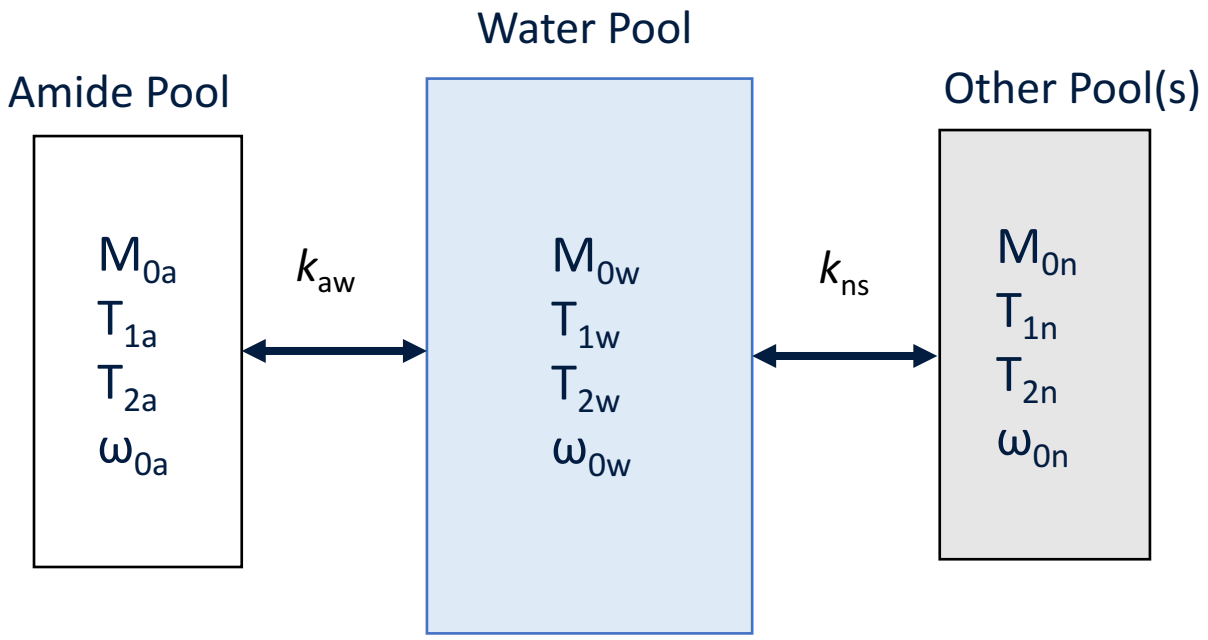
- Visualisation and quantification software
- Freely available for research purposes
- www.quantiphyse.org



Bayesian Model-based Analysis

- The Bloch-McConnell equations allow us to characterise both the MR signal characteristics of water, as well as the exchange of protons between pools of interest and water.

- The user has control over the number of pools modelled; initialising parameters such as T_1, T_2, proton concentration (M_0), and exchange rate (k) to literature or experimental values.



Utilising a Bayesian model allows us to incorporate image priors, and attach degree of certainty

Chappell et al., 2013, *MRM*, 70:556-67

Bayesian Model-based Analysis

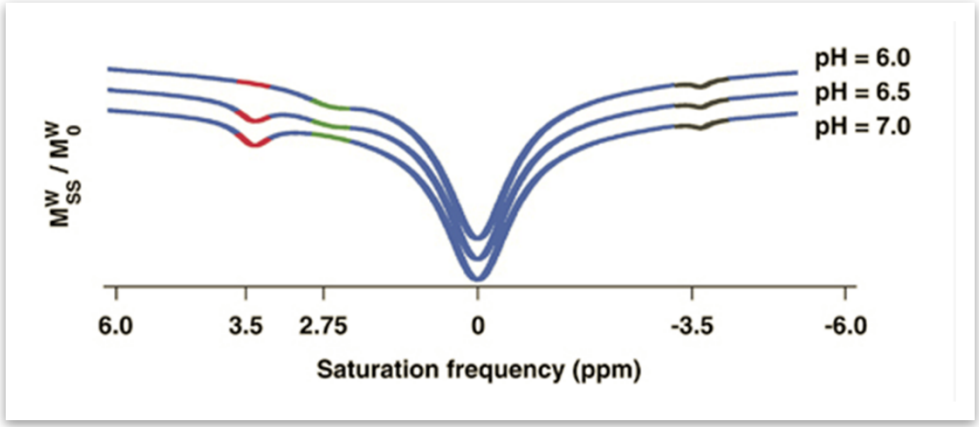
Measure CEST MRI data (Z-spectrum)

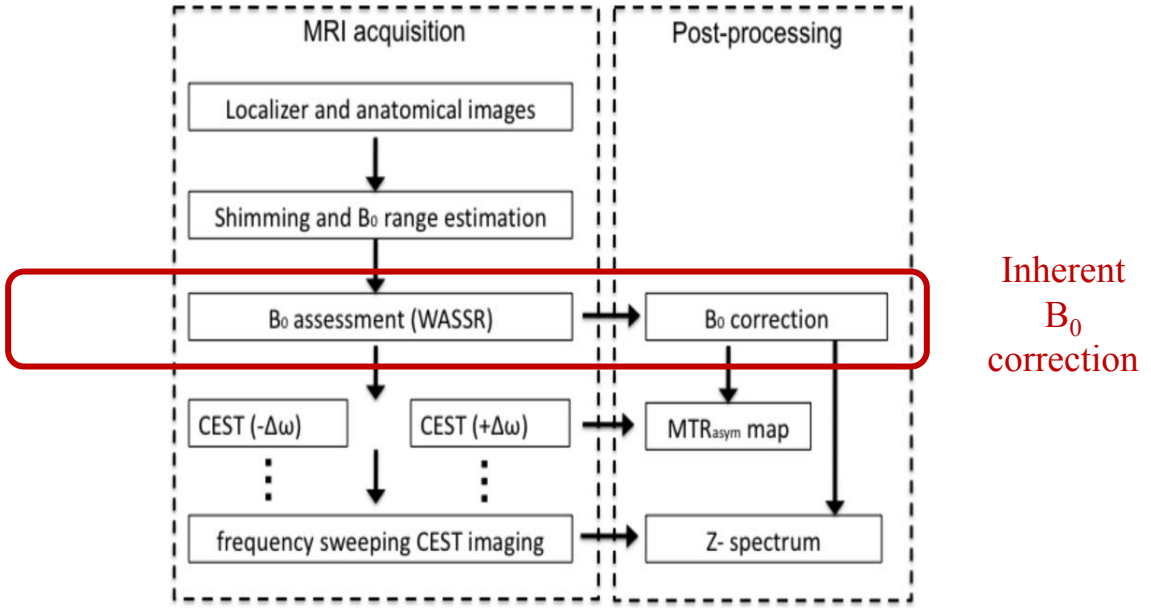
Fit Bloch-McConnell Equations to measured data using Bayesian algorithm

Extract fitted Exchange Rate and Concentration values for amide pool

Simulate idealised 2-pool system with these amide pool properties

CESTR* is difference between 1-pool and 2-pool systems





Inherent B_0 correction

$$CESTR^* = \frac{S_{Water}(\Delta\omega) - S_{water+pool\ of\ interest}(\Delta\omega)}{M_0}$$

Chappell et al., 2013, *MRM*, 70:556-67

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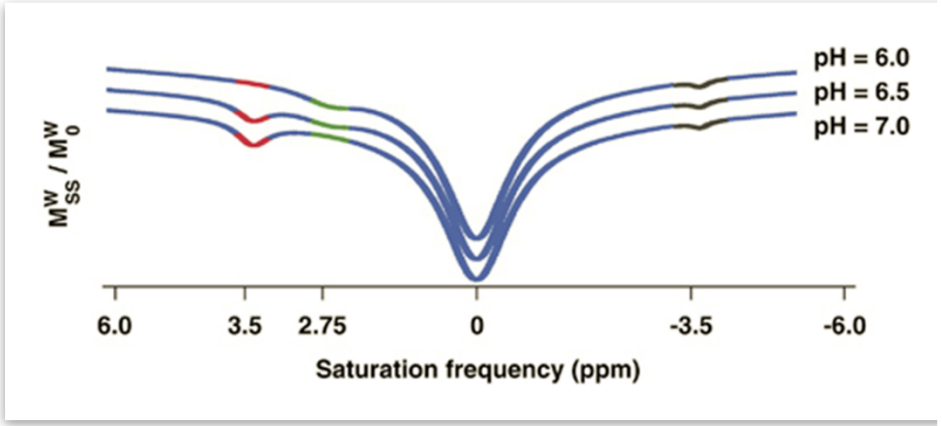
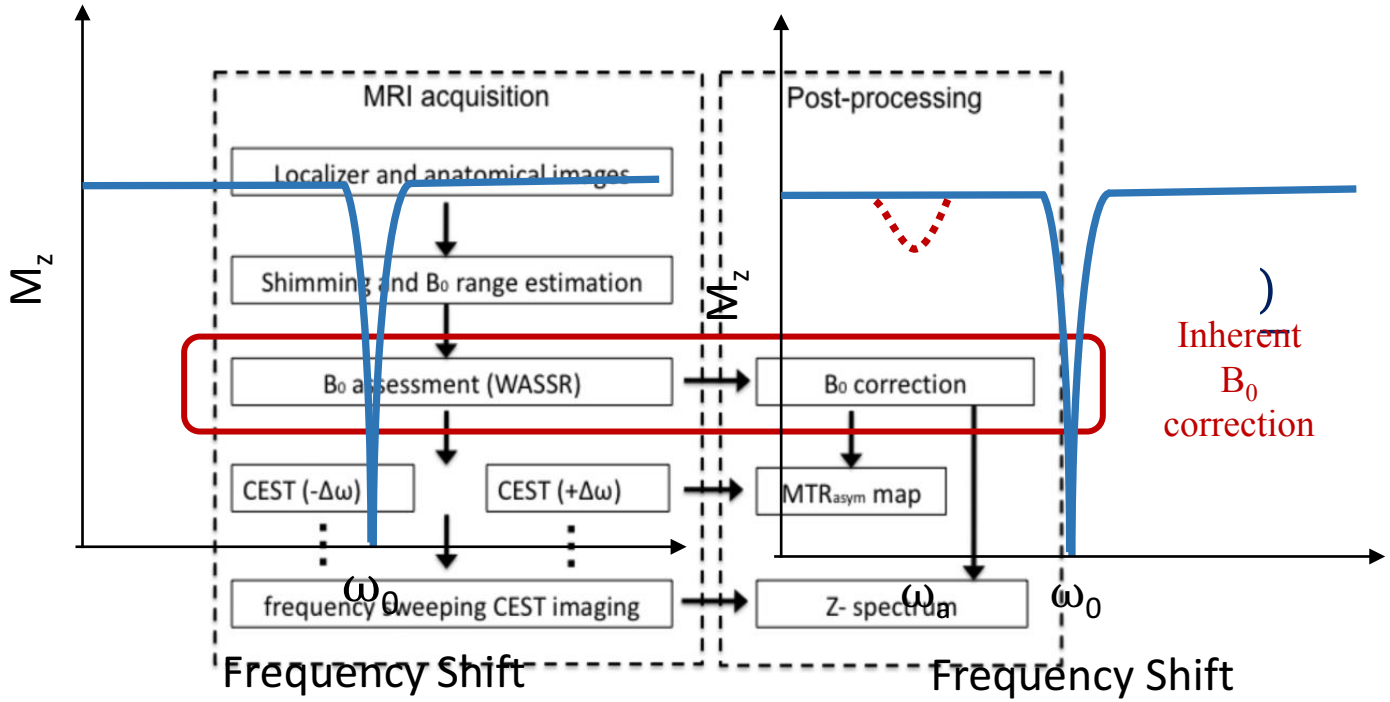


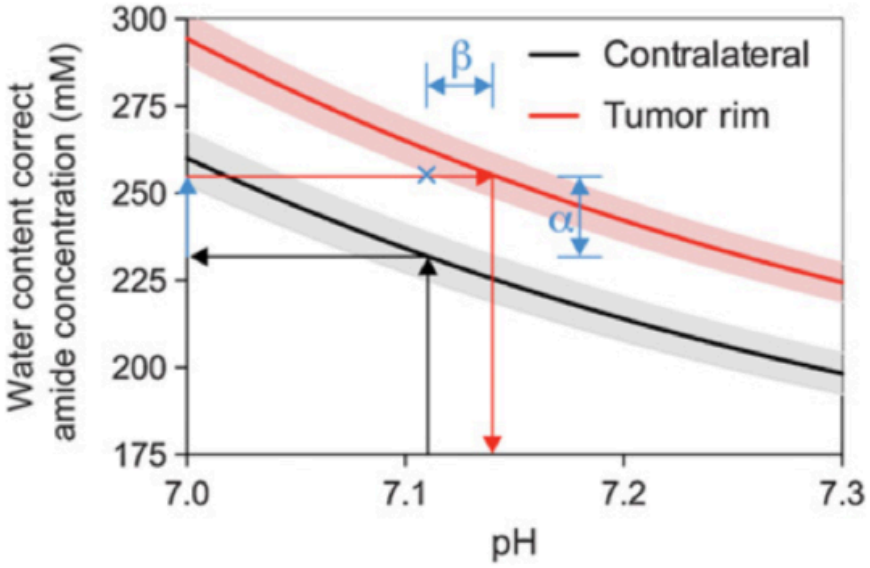


Chappell et al., 2013, *MRM*, 70:556-67

Bayesian Model-Based Analysis: CESTR*

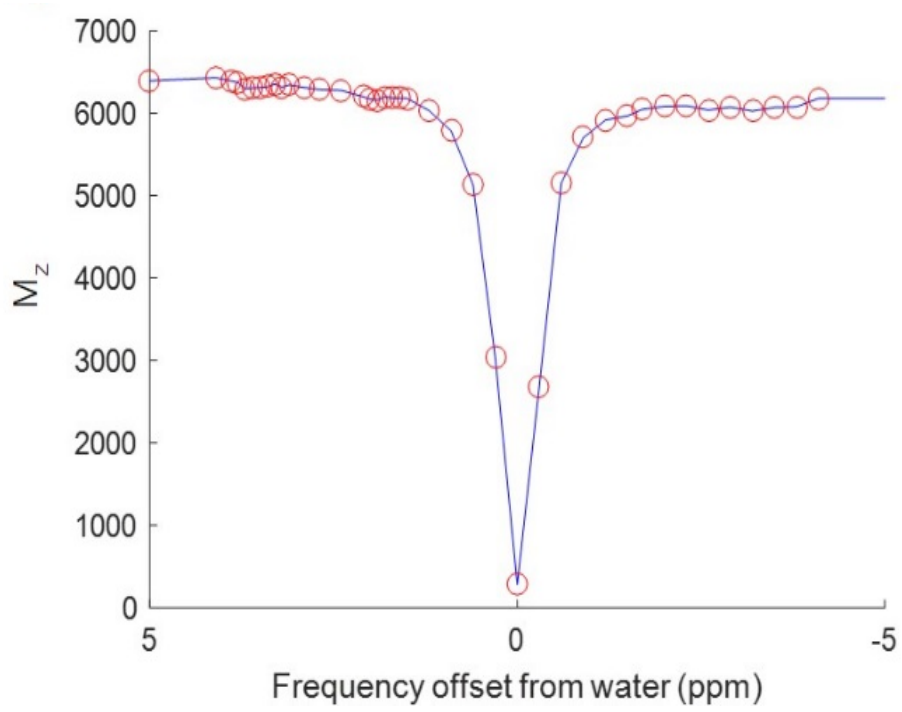
$$CESTR^* = \frac{S_{Water}(\Delta\omega) - S_{water+pool\ of\ interest}(\Delta\omega)}{M_0}$$

- Model-based measures of exchange rate and concentration are not independent.
- Current approach is to combine into a ratio metric
  - Serves as an internal reference point
  - Comparable across subjects
  - Quantitative, yet comparable to MTR_{asym}
- Shown to be more robust than "conventional" metrics
- However, a solution would be to acquire at multiple powers



Chappell et al., 2013, *MRM*, 70:556-67
Ray et al., *Cancer Res.* 2019

Bayesian Model-based Analysis



Overview:

- Pools initialised to literature and/or experimental values
- BM Equations used to model full Z-spectra
- 'Pure' CEST effect than characterised by CESTR*

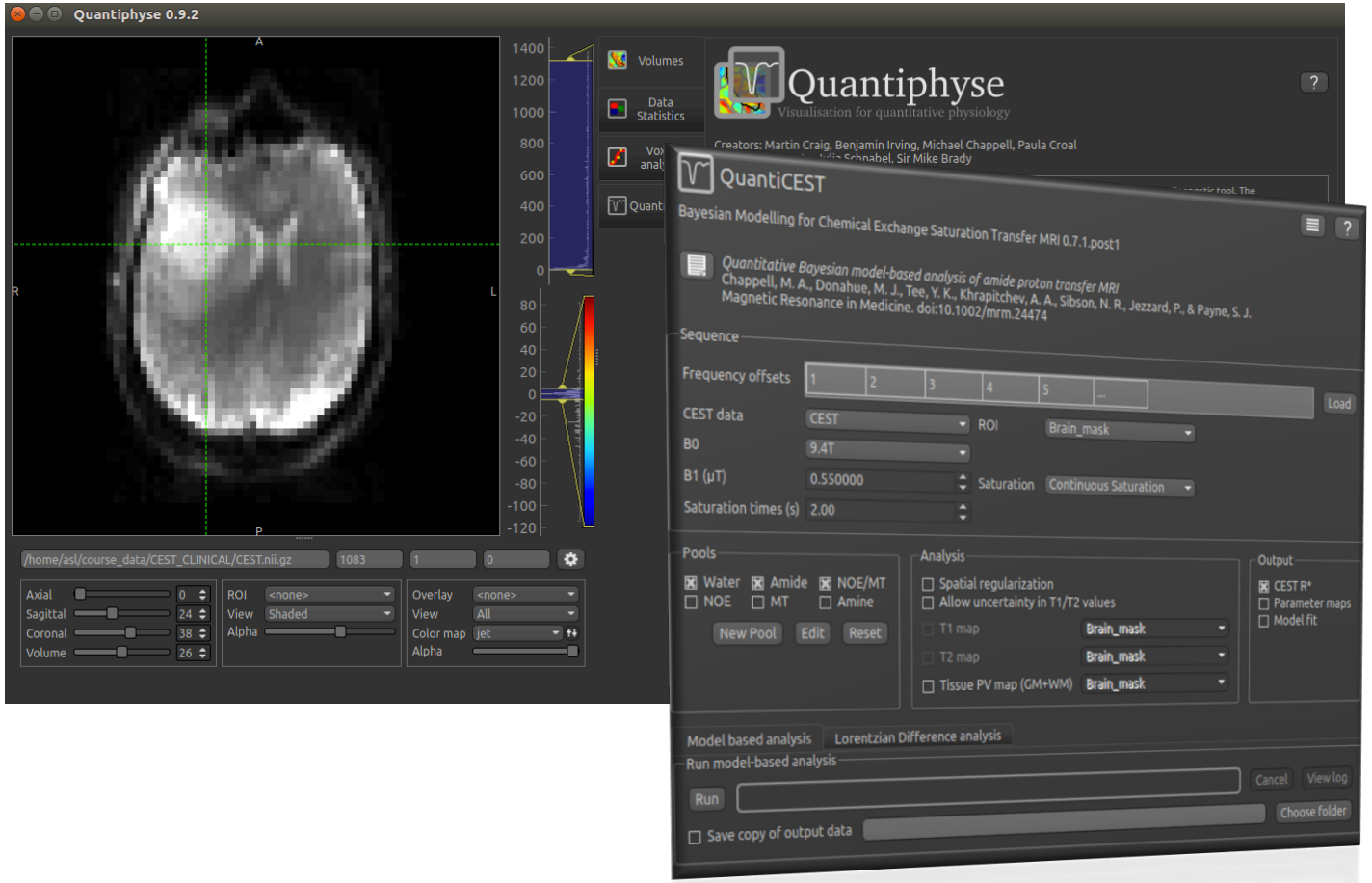
Challenges:

- Relatively large time requirement
  - Acquisition
  - Analysis
- Challenging to implement (**Quantiphyse**)
- Reliance on metrics?

Bayesian Model-Based Analysis : Tools

Quantiphyse

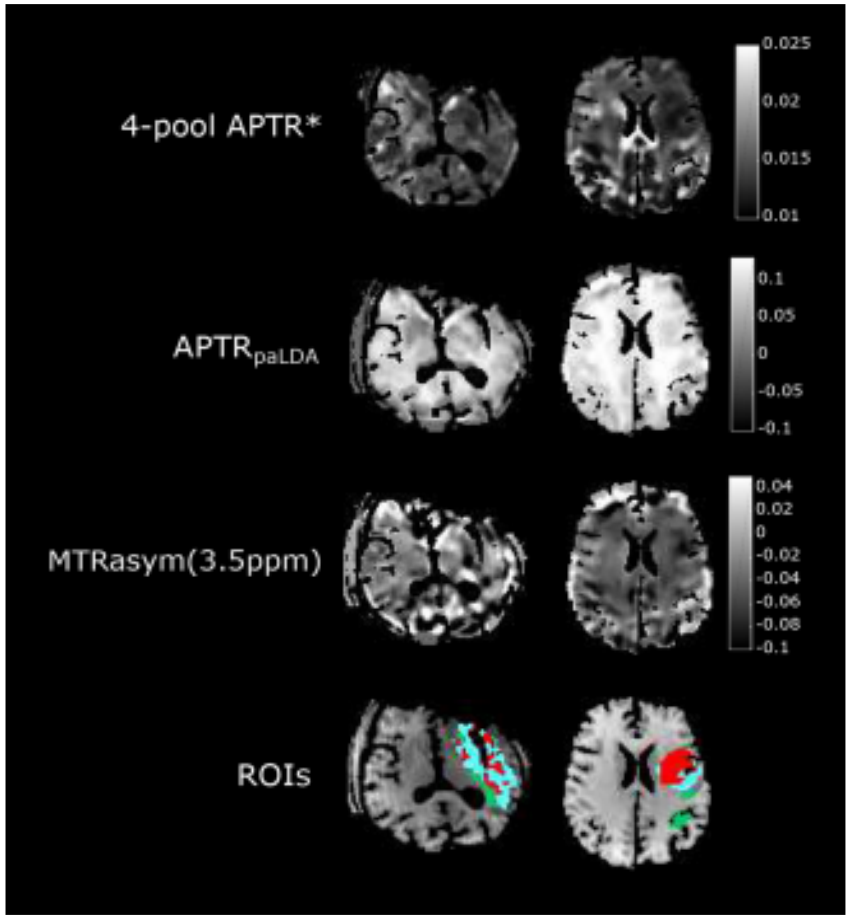
- Visualisation and quantification software
- Freely available for research purposes
- www.quantiphyse.org

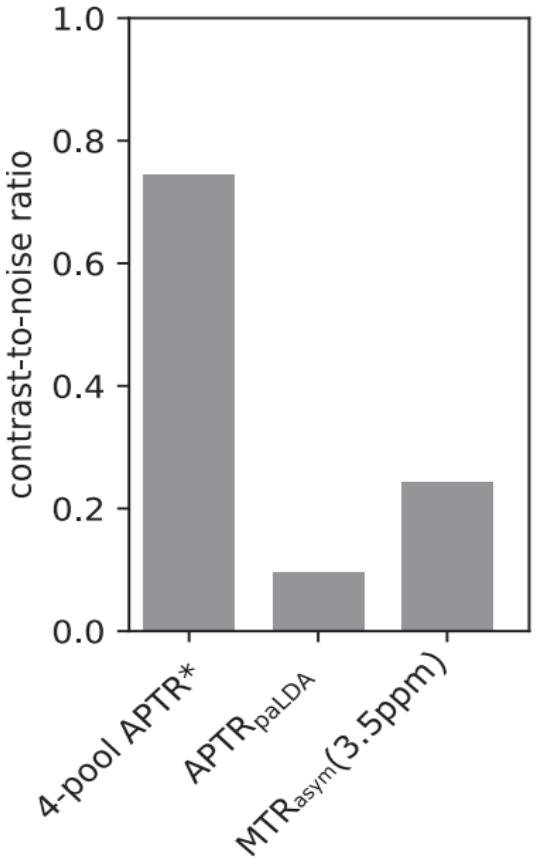


Croal et al., *ISMRM,* 2018

Does Analysis Method Really Matter?

- There are a vast array of CEST metrics available to use.
- Your choice will likely be influenced by a variety of factors.
  - Experimental design
  - Clinical population
  - Availability of resources
- However, choice of metric may significantly impact interpretation.

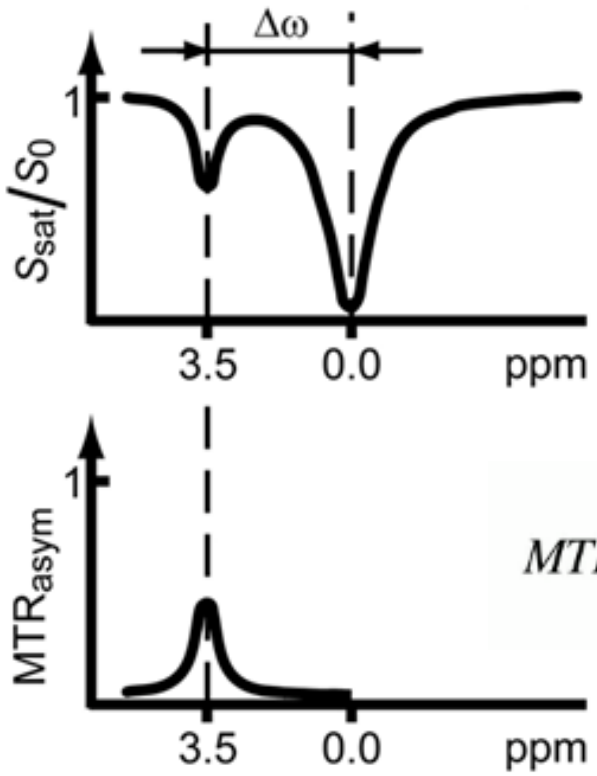




Adapted from Mysaib et al., *Neuroimage*, 2019

Is it Really That Simple?

Revisiting Asymmetry Analysis



$$MTR_{asym}(\Delta) = \frac{S(-\Delta) - S(\Delta)}{S_0}$$

Overview:

- Aims to isolate CEST contrast.
- Only requires 3 frequency offsets.
- Straightforward analysis.
- Broad range of applications.

Challenges:

- Pools on both sides.
- Asymmetric MT effects.
- No T_1 correction.

Van zijl et al., *2011, MRM,* 65(4): 927-948

Conclusions:

- As with many imaging techniques, there is no consensus on how best to quantify parameters of interest.
- General trend to use “metrics”, however there are a large number available.
  - Choice of metric may impact interpretation
- Model-based analysis likely offers a robust approach.
  - Bayesian model-based (CESTR*)
    - Inherent B0 correction
    - Ability to incorporate “image priors”
    - May be particularly important in pathology

Online Materials

https://quantiphyse.readthedocs.io/en/latest/cest/cest.html

- General user guide
- Tutorials: Preclinical and clinical

Practical Session: Quantiphyse

- Model-based analysis of APT CEST MRI
- Choice of preclinical ischemia or clinical brain tumour
- Run from virtual machine

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