

Rotation (Midpoint-esque) Presentation

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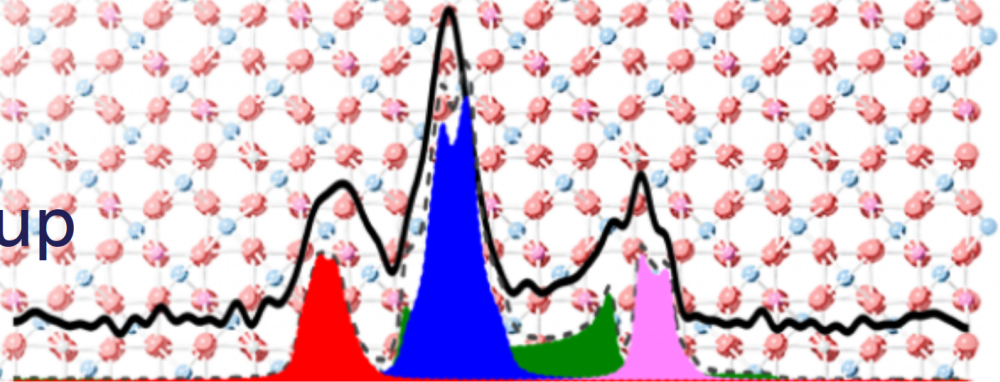
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WEIZMANN INSTITUTE OF SCIENCE

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Magnetic Resonance in Materials



Direct Detection of Lithium Exchange across the Solid Electrolyte Interphase by ^7Li Chemical Exchange Saturation Transfer

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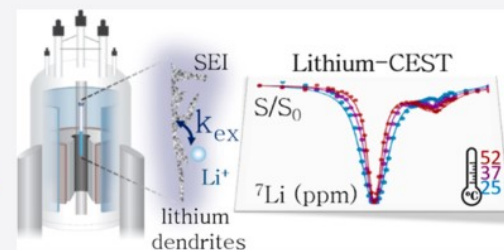


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Supporting Information

ABSTRACT: Lithium metal anodes offer a huge leap in the energy density of batteries, yet their implementation is limited by solid electrolyte interphase (SEI) formation and dendrite deposition. A key challenge in developing electrolytes leading to the SEI with beneficial properties is the lack of experimental approaches for directly probing the ionic permeability of the SEI. Here, we introduce lithium chemical exchange saturation transfer (Li-CEST) as an efficient nuclear magnetic resonance (NMR) approach for detecting the otherwise invisible process of Li exchange across the metal–SEI interface. In Li-CEST, the properties of the undetectable SEI are encoded in the NMR signal of the metal resonance through their exchange process. We benefit from the high surface area of lithium dendrites and are able, for the first time, to detect exchange across solid phases through CEST. Analytical Bloch-McConnell models allow us to compare the SEI permeability formed in different electrolytes, making the presented Li-CEST approach a powerful tool for designing electrolytes for metal-based batteries.



- What is CEST?
- The typical continuous wave (CW) CEST experiment
- Bloch-McConnell equations
- Numerical vs. Analytical solution
- MATLAB simulation of exchange between multiple spin populations.

- CEST fitting
- Frequentist or Bayesian approach?
- Monte Carlo simulation and Metropolis-Hastings algorithm
- Diagnostics, analysis & problems with the algorithm
- Hamiltonian Monte Carlo & Stan to the rescue
- Results so far (please help)

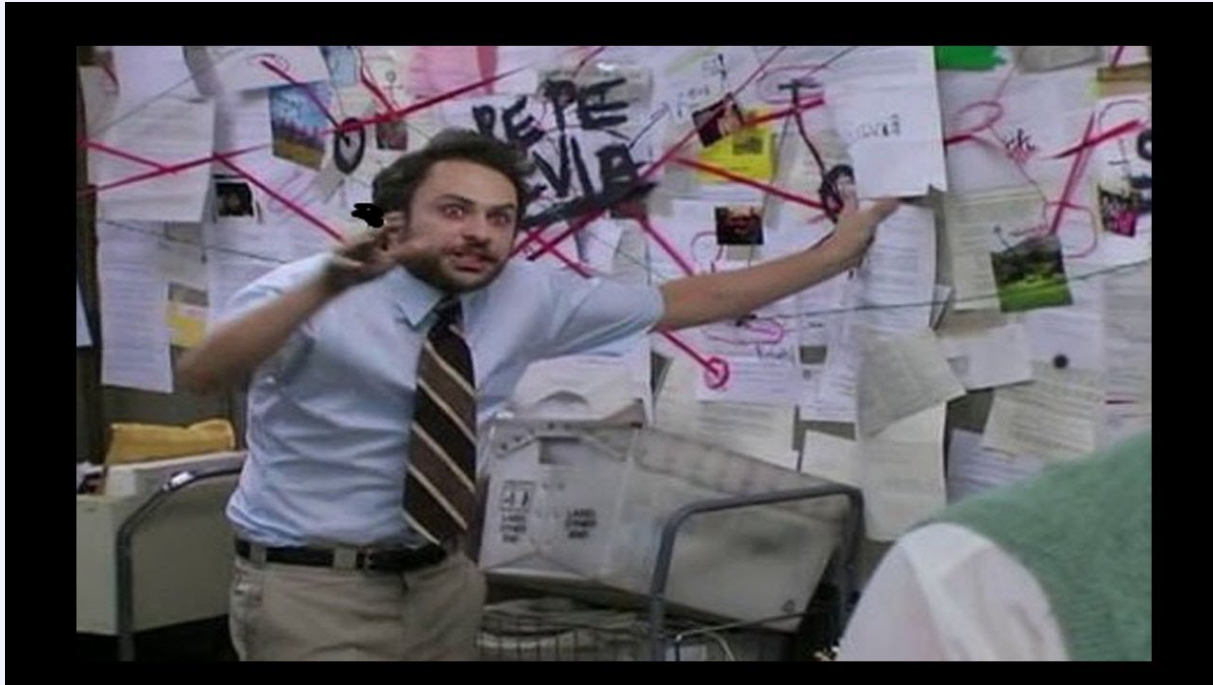
A Word of Caution

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A Word of Caution

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- Method mainly used in MRI, where generation of images with minimal concentration of contrast agents is critical. (As to avoid perturbation of the physiological environment to minimize toxicity.)

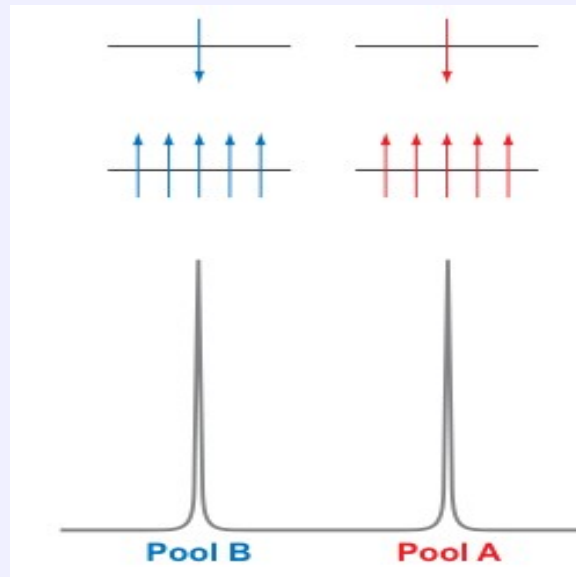
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- NMR being NMRTM, the hydrogen is barely detectable in the ^1H spectrum.

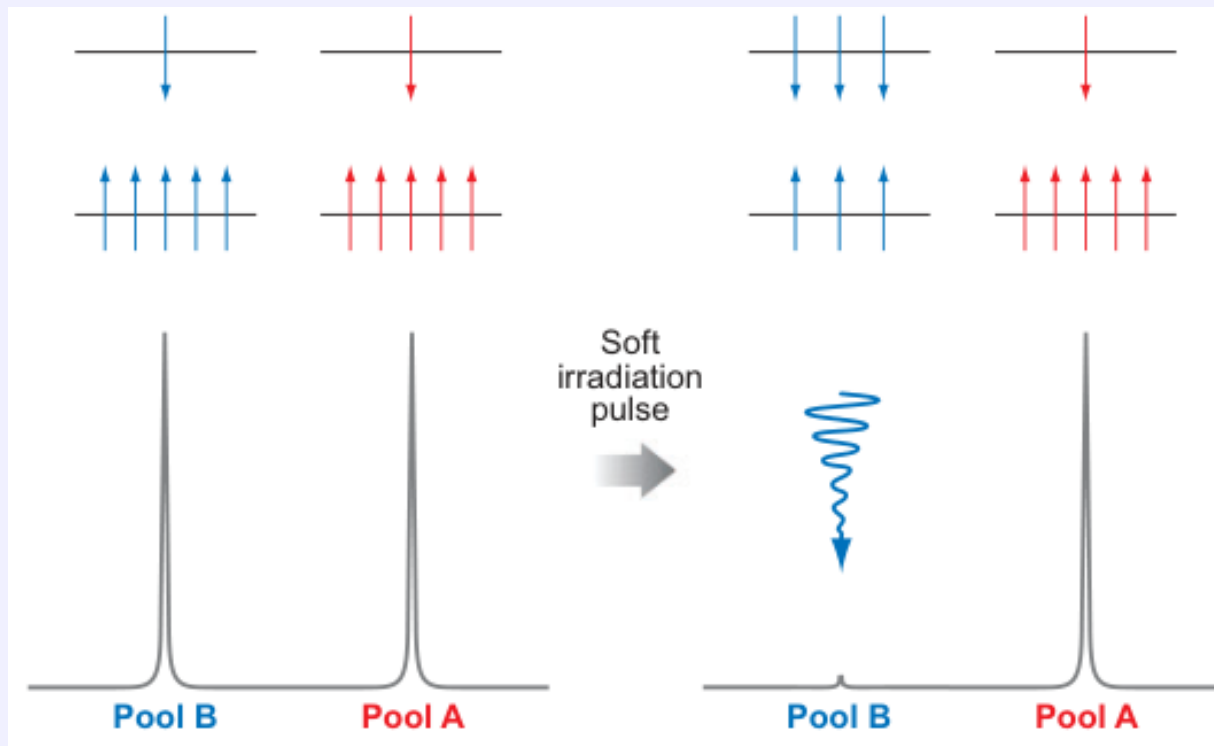
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- NMR being NMRTM, the hydrogen is barely detectable in the ^1H spectrum.
- However, irradiating the dilute population to saturation can have a detectable effect on the NMR signal of the bulk water hydrogen population!

Consider the following NMR experiment:

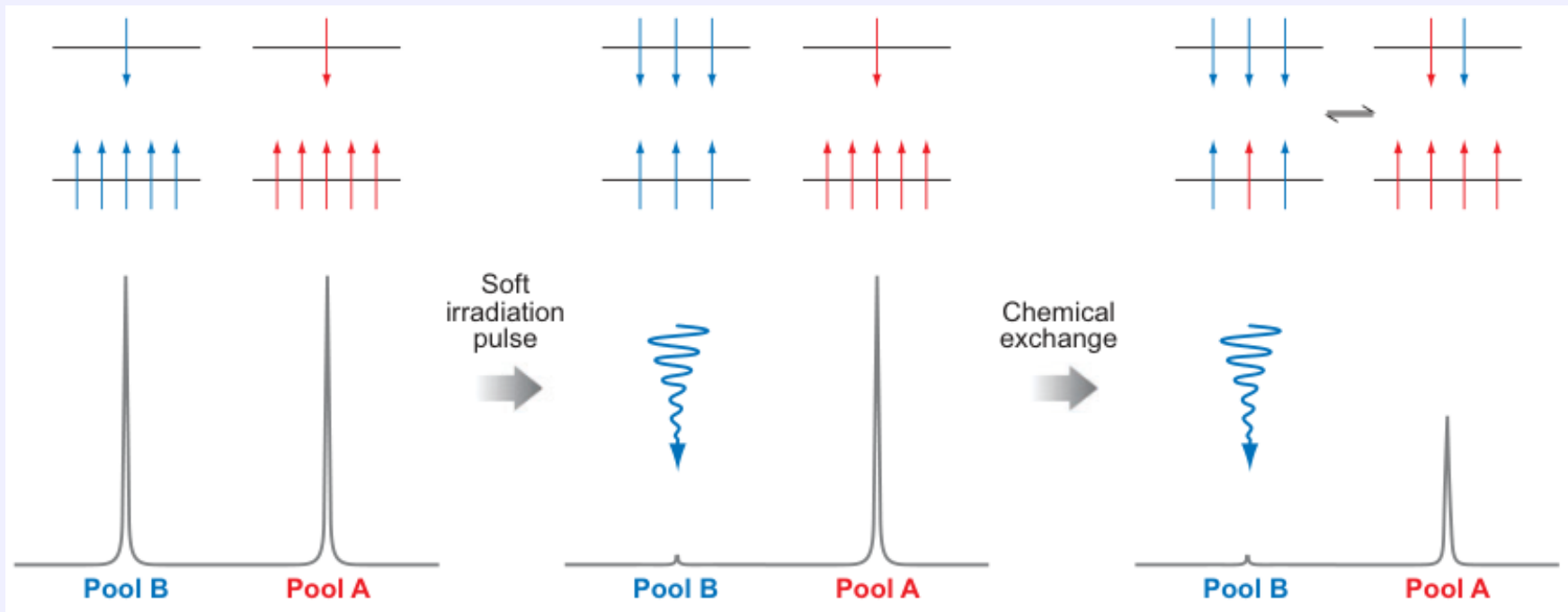
- Two nuclei ensembles **A** and **B** exposed to different chemical environments are placed in an external magnetic field B_0 (e.g. 7.4T)
- Using a low intensity magnetic field, a $\frac{\pi}{2}$ pulse is applied to both ensembles to initiate free induction decay.



- Using a low-intensity magnetic field B_1 , Pool B is irradiated at its resonance frequency until the net magnetization reaches zero (saturation).



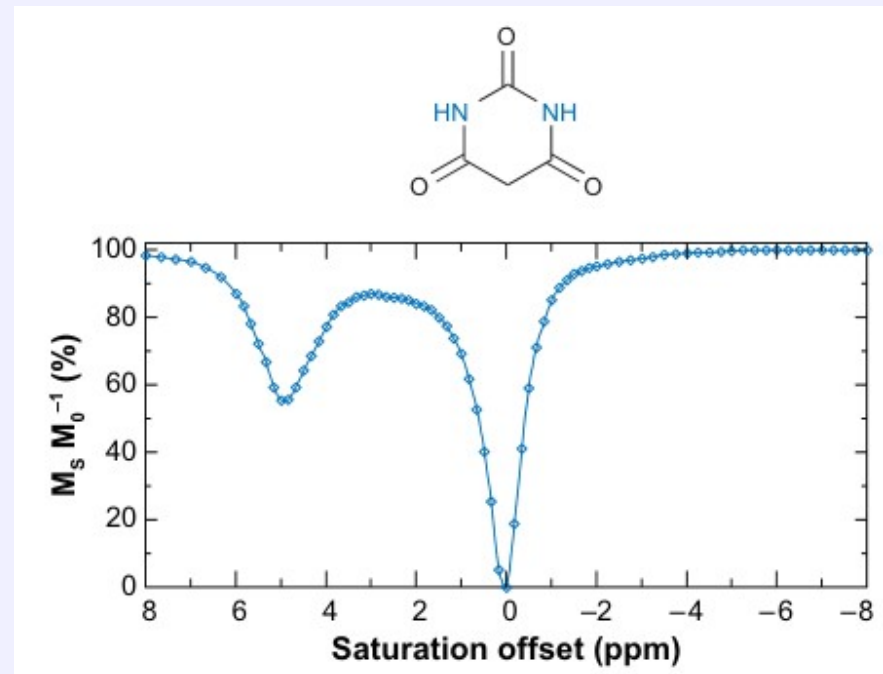
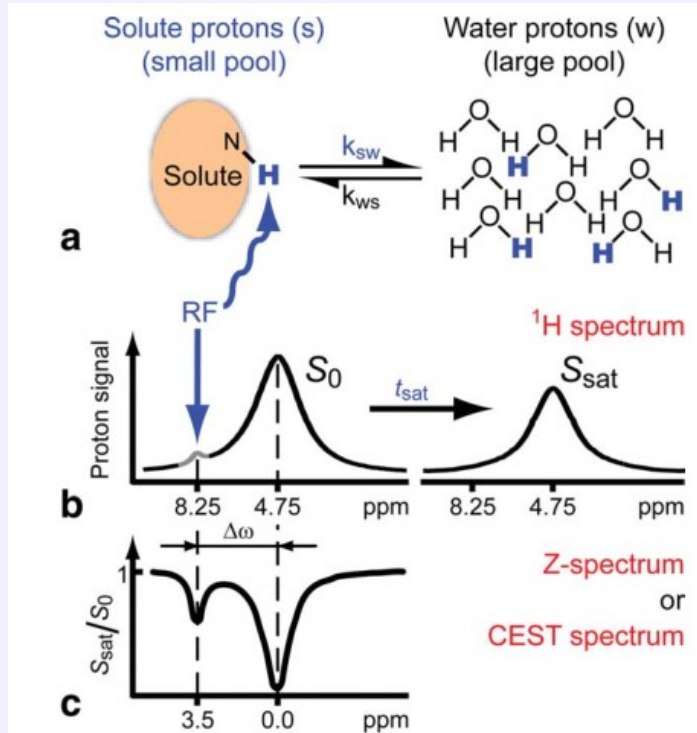
- Nuclei in pool **B** and pool **A** are in exchange throughout the process:
- Spins from pool **B** that are aligned against B_0 are transferred to pool **A**.
- Spins from pool **A** that are aligned with B_0 are transferred to pool **B**.



- How would the CEST effect be influenced by changing the saturation irradiation frequency?
 - Straying away from the resonance frequency of pool **B** results in less effective saturation of its population, which in turn makes the chemical exchange less effective in attenuating pool **A** NMR signal.
 - *However*, Approaching the resonance frequency of pool **A** results in **direct saturation** and thus much more effective reduction of the signal.
- A typical CEST experiment involves swiping the saturation frequency and measuring the attenuation of the signal of pool **A**, to get a **Z-spectrum**.

A typical 2-pool Z-spectrum

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Generally, The CEST effect is influenced by the following parameters:

- The relaxation times of each pool, T_{1i}, T_{2i} , $i \in A, B$
- The back and forward exchange rate of nuclei (spins), $k_{A \rightarrow B}, k_{B \rightarrow A}$
- The fraction of pool B in solution (relative to pool A), $f_B = M_B^0 / M_A^0$
- The saturation field intensity and frequency, $B_1, \Delta\omega$
- The offset between the resonance frequency of the pools, $\Delta\omega_B$
- The saturation irradiation duration t_{sat}

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How do these parameters govern the CEST effect?

Bloch-McConnell equations!

In 1946, Felix Bloch proposed a set of 3 differential equations that describe the time evolution of nuclear magnetization under the influence of a constant, z -aligned field B_0 and a field B_1 aligned on the x -axis and alternating at frequency ω .



Define: $\vec{B}_1(t) = \mathbf{i} (2B_1 \cos \omega t)$, $\vec{B}_0 = \mathbf{k} B_0$.

If $\vec{M} = \mathbf{i} M_x + \mathbf{j} M_y + \mathbf{k} M_z$, then:

$$\frac{d\vec{M}}{dt} = \vec{M} \times \gamma [\vec{B}_0 + \vec{B}_1(t)] + \left(-\frac{M_x}{T_2} \mathbf{i} - \frac{M_y}{T_2} \mathbf{j} + \frac{M_z - M_0}{T_1} \mathbf{k} \right)$$

The second summand in the equation refers to **relaxation terms**.

The time dependence of $\vec{B}_1(t)$ can be eliminated by moving to a *rotating frame* rotating at frequency ω . The equation is then transformed:

$$\frac{d\vec{M}}{dt} = \vec{M} \times [\gamma B_1 \mathbf{i} + (\gamma B_0 - \omega) \mathbf{k}] + \left(-\frac{M_x}{T_2} \mathbf{i} - \frac{M_y}{T_2} \mathbf{j} + \frac{M_z - M_0}{T_1} \mathbf{k} \right)$$

Define $\Delta\omega = \gamma B_0 - \omega$ and $\gamma B_1 = \omega_1$.

The Bloch equations in the rotating frame are:

$$\begin{aligned} \frac{dM_x}{dt} &= -\frac{1}{T_2} M_x + \Delta\omega M_y \\ \frac{dM_y}{dt} &= -\Delta\omega M_x - \frac{1}{T_2} M_y + \omega_1 M_z \\ \frac{dM_z}{dt} &= -\omega_1 M_y - \frac{1}{T_1} M_z + \frac{M_0}{T_1} \end{aligned}$$

In 1957, Harden M. McConnell modified the Bloch equations to permit chemical exchange and RF saturation.

Given two pools, A and B, that undergo nuclei exchange under constant RF irradiation at frequency ω , the time-evolution of their spacial magnetization follows **Bloch-McConnell equations**:



- Each pool's x , y and z -magnetization develop “independently” according to Bloch equations.
- Each pool's x , y and z -magnetization is transferred between the pools according to the exchange rate.

$$\frac{dM_x^A}{dt} = -\frac{M_x^A}{T_{1A}} + \Delta\omega_A M_y^A - k_{AB} M_x^A + k_{BA} M_x^B$$

$$\frac{dM_y^A}{dt} = -\frac{M_y^A}{T_{2A}} - \Delta\omega_A M_x^A + \omega_1 M_z^A - k_{AB} M_y^A + k_{BA} M_y^B$$

$$\frac{dM_z^A}{dt} = -\frac{M_z^A - M_0^A}{T_{1A}} - \omega_1 M_y^A - k_{AB} M_z^A + k_{BA} M_z^B$$

$$\frac{dM_x^B}{dt} = -\frac{M_x^B}{T_{2B}} + \Delta\omega_B M_y^B - k_{BA} M_x^B + k_{AB} M_x^A$$

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$$\frac{dM_z^B}{dt} = -\frac{M_z^B - M_0^B}{T_{1B}} - \omega_1 M_y^B - k_{BA} M_z^B + k_{AB} M_z^A$$

Let $\vec{M} = [M_x^A, M_y^A, M_z^A, M_x^B, M_y^B, M_z^B]^T$. Then:

$$\frac{d\vec{M}}{dt} = A \vec{M} + \vec{b}$$

$$A = \begin{bmatrix} -\left(\frac{1}{T_{2A}} + k_{AB}\right) & \Delta\omega_A & 0 & k_{BA} & 0 & 0 \\ -\Delta\omega_A & -\left(\frac{1}{T_{2A}} + k_{AB}\right) & \omega_1 & 0 & k_{BA} & 0 \\ 0 & -\omega_1 & -\left(\frac{1}{T_{1A}} + k_{AB}\right) & 0 & 0 & k_{BA} \\ k_{AB} & 0 & 0 & -\left(\frac{1}{T_{2B}} + k_{BA}\right) & \Delta\omega_B & 0 \\ -\Delta\omega_B & k_{AB} & 0 & -\Delta\omega_B & -\left(\frac{1}{T_{2B}} + k_{BA}\right) & \omega_1 \\ 0 & 0 & k_{AB} & 0 & -\omega_1 & -\left(\frac{1}{T_{1B}} + k_{BA}\right) \end{bmatrix}$$

$$\vec{b} = \left[0, 0, \frac{M_0^A}{T_{1A}}, 0, 0, \frac{M_0^B}{T_{1B}} \right]^T$$

As this is a system of linear ODEs with a constant coefficient matrix, it can be solved numerically using matrix exponentials.

Given $\frac{d\vec{M}}{dt} = A \vec{M} + \vec{b}$, by variation of parameters,

$$\begin{aligned}\vec{M}(t) &= e^{tA} \vec{M}(0) + \int_0^t e^{(t-s)A} \vec{b} \, ds \\ &= e^{tA} \vec{M}(0) + e^{tA} \left(\int_0^t e^{-sA} \, ds \right) \vec{b}\end{aligned}$$

Using the definition for the integral of a matrix exponential:

$$\int_0^t e^{-sA} \, ds = (I - e^{-tA}) A^{-1}$$

we get:

$$\vec{M}(t) = e^{tA} (\vec{M}(0) + A^{-1} \vec{b}) - A^{-1} \vec{b}$$

- By calculating $\vec{M}(t)$ for t_{sat} , we get $M_z^A(t_{\text{sat}})$ — the saturated signal of pool A after irradiation at $\Delta\omega_A$!
- By solving Bloch-McConnell equations for different saturation frequencies we can simulate a CEST experiment and plot the Z-spectrum.
- Fitting a Z-spectrum according to Bloch-McConnell equations is a powerful tool to characterize the dilute pool and extract its relaxation times, exchange rate with the large pool, and its fraction in the solution.

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Why isn't this method frequently implemented in fitting?

Why resort to analytical solutions with approximations?

- Matrix exponential calculation is (in principle) very computationally expensive.
- Simulation of a Z-spectrum with N data point requires performing N matrix exponential calculations.

4. The four horsemen of incomputability

This wisdom took decades to crystallise – from the point of view of numerical computing, some operations in magnetic resonance are in the whole separate category of horrible. **Every time you use them, a kitten dies. A kitten with big eyes (Fig. 2).**

1. **Diagonalisation.** We were all brought up with energy level diagrams – get the Hamiltonian, solve the secular equation... this works for a two-spin system. With more spins, two nasty properties of the diagonalisation operation manifest themselves:

- (a) Spin Hamiltonians are always sparse, but their eigenvectors are not – memory and bandwidth will be needed store and move every single one of those $16 \cdot 2^N$ bytes.

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I. Kuprov / Journal of Magnetic I

vector multiplications, meaning that the cost is negligible relative to the other mathematics that is going on. The sage advice here: *avoid operations that cost more than a few matrix-vector products.*

4. **Matrix exponential.** We have yet to vanquish this one. There are places in magnetic resonance where it is unavoidable,

Ilya Kuprov — Defeating the matrix, 2019

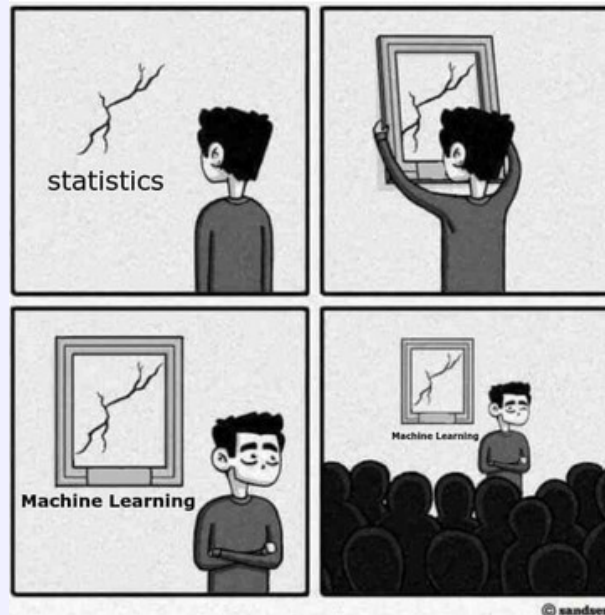


- Applying a fitting algorithm to a solution of a set of ODEs is difficult.
- Conventional fitting procedures (e.g. non-linear least squares) rely heavily on the initial estimate of the fitting parameters and on the sensitivity of the design matrix (A in BM equations) to noise in the data.

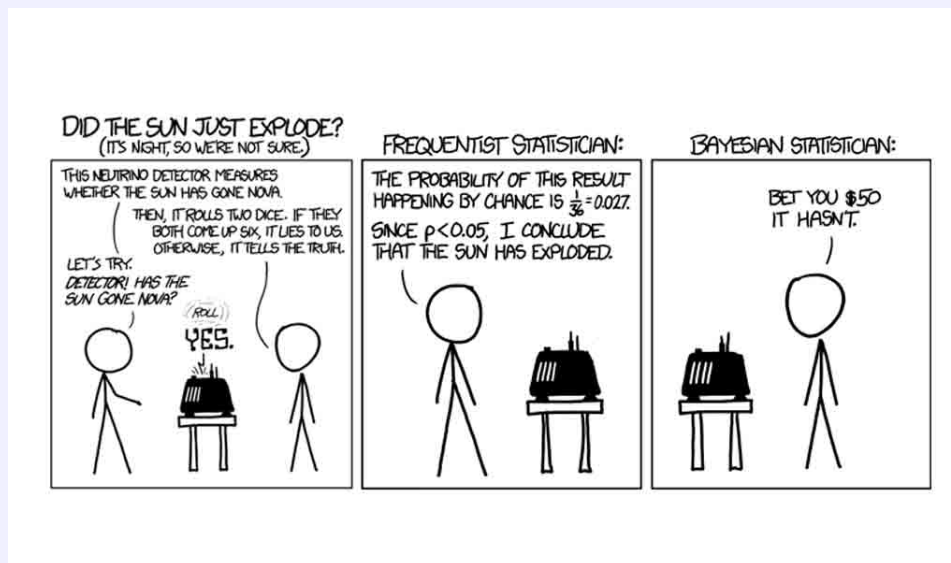
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- Analytic approaches provide a formula for the Z-spectrum and are much more easy to implement.
- *However*, approximations do not always hold in Li-CEST, where transverse relaxation times are very short (ms to μ s).
- Also, extracting all parameters may require repetitions of the experiment.

Everything considered, in Li-CEST the **numerical** approach seems most reliable.
Which means that probability theory statistics must be applied rigorously.

(Call it Machine Learning to make it sound better)

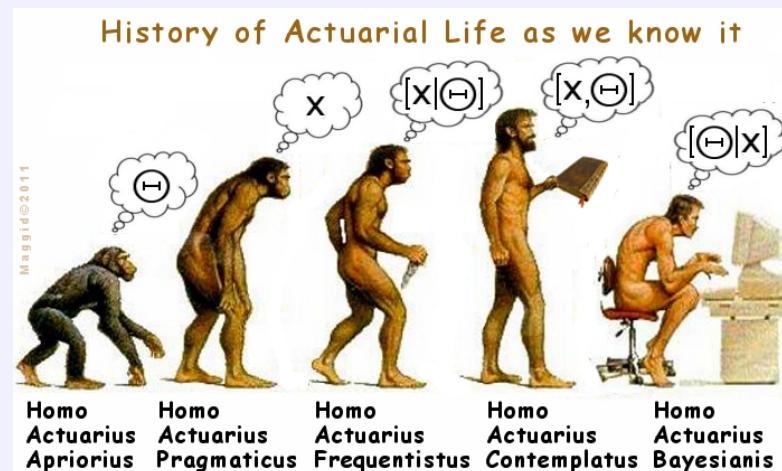


- Least squares fitting is equivalent to **maximum likelihood estimation**, which is conventionally **Frequentist** by nature.
- **Frequentism:**
 - Unknown model parameters are *fixed*. The model is *deterministic*.
 - Optimal parameters recreate the system's response with the *highest frequency*.



- **Bayesianism:**

- Unknown model parameters are *randomly distributed*.
- Parameters are given **prior distributions** according to belief/information
- Evidence from data *updates* our belief.
- Optimal parameters are taken from the **posterior distribution**.



Bayes theorem states that given a data set (\mathbf{x}, \mathbf{y}) and model f with parameters $\boldsymbol{\theta}$,

$$P(\boldsymbol{\theta}|\mathbf{y}) \propto P(\mathbf{y}|\boldsymbol{\theta}) \cdot P(\boldsymbol{\theta})$$

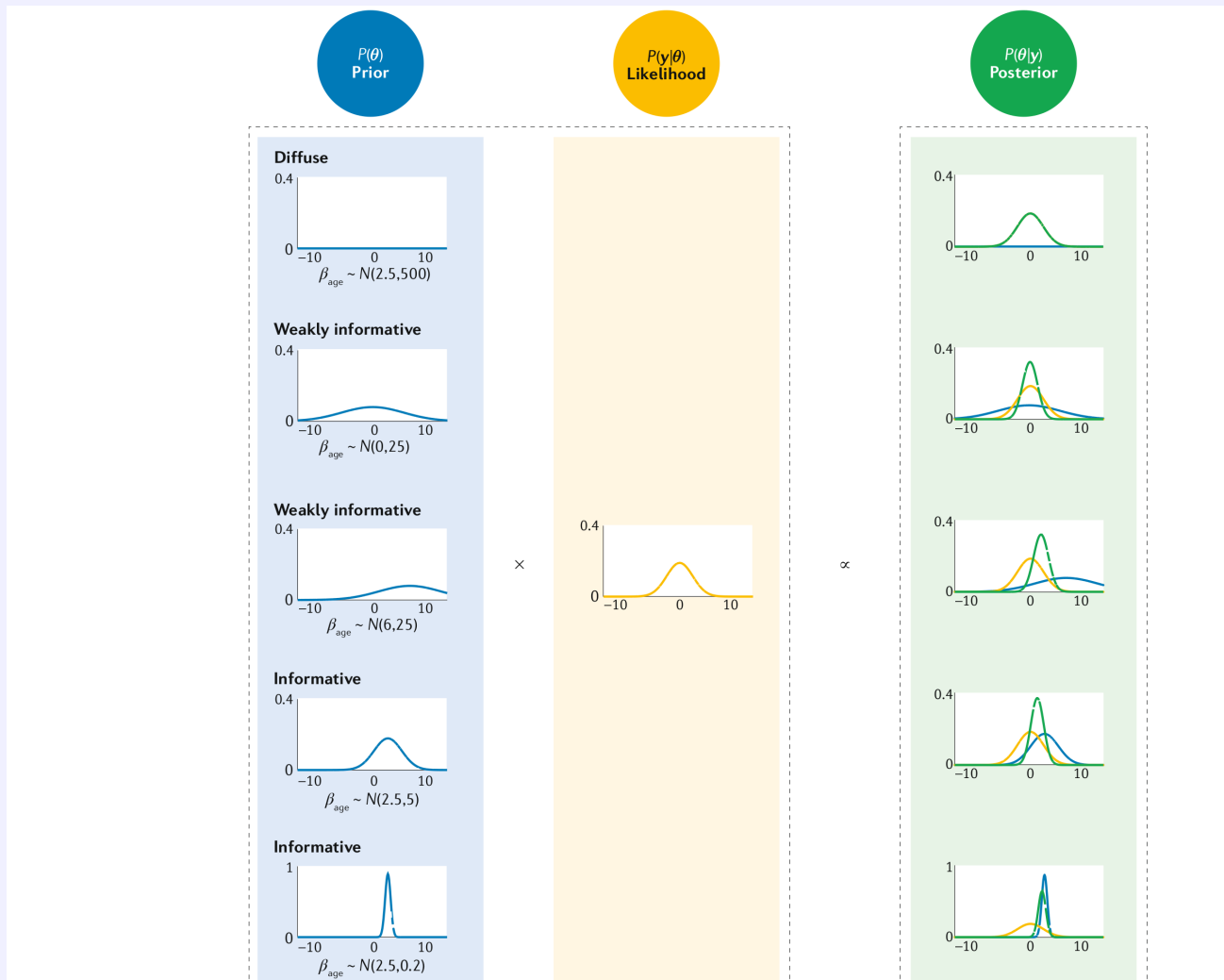
- $P(\boldsymbol{\theta})$ — Encodes information **prior** to measurement.
- $P(\mathbf{y}|\boldsymbol{\theta})$ — **Likelihood** of the model to recreate the data.
- $P(\boldsymbol{\theta}|\mathbf{y})$ — Encodes all information **a posteriori** to measurement.

The minimum mean-squared error estimation of a model parameter θ^i is its **expected value** — an **integral**.

$$\theta_{\text{MMSE}}^i = \mathbb{E}(\theta^i|\mathbf{y}) = \int \theta^i P(\theta^i|\mathbf{y}) \, d\theta^i$$

Bayes Theorem In Action

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- Performing expectation operations on the posterior retrieves optimal parameters.
- *However*, the posterior is **multi-dimensional**!
 - How can we sample from such a complex distribution/function?
 - How can we calculate complex multi-dimensional integrals?

Care for a game of chance?



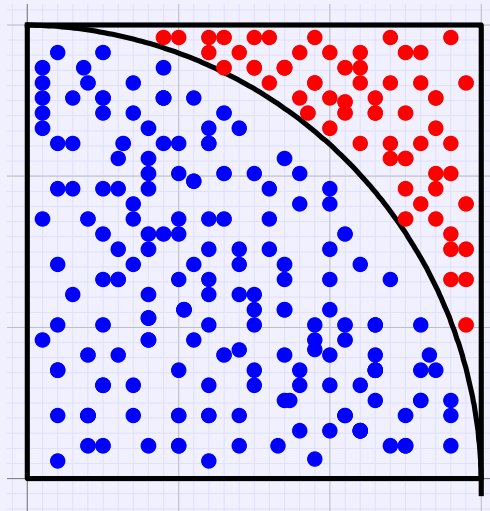
- Monte Carlo simulation is about **sampling** and **scoring**.
- Sampling is done randomly from some distribution.
- Scoring is book-keeping of samples that passed a certain test criterion.

Averaging over successful scoring histories provides an estimate of the integral.

Goal: Estimate π by the ratio of the area under a quadrant.

- Draw a square and a quadrant
- **Sample** points randomly within the square
- **Score** points within the quadrant (distance from origin less than 1)
- **Estimate integral:** Ratio of inside count to total sample count is $\frac{\pi}{4}$.

Multiply by 4 to estimate π



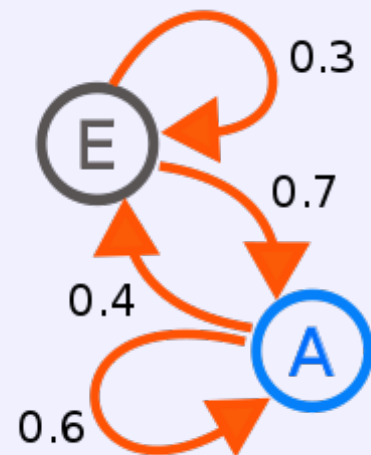
- **Markov chains** may be used to generate samples from complex distributions.
- A Markov chain is a sequence of random samples \mathbf{x}_i for which the value \mathbf{x}_{i+1} depends only on the previous state \mathbf{x}_i .

Suppose the system can move between states E and A .

Each transition $i \rightarrow j$ has a certain probability T_{ij} .

the matrix \mathbf{T} encodes chances for the **next** transition:

$$\mathbf{T} = \begin{bmatrix} T_{AA} & T_{EA} \\ T_{AE} & T_{EE} \end{bmatrix} = \begin{bmatrix} 0.6 & 0.7 \\ 0.4 & 0.3 \end{bmatrix}$$



If $\boldsymbol{\pi} = [\pi_1, \dots, \pi_n]$ lists the probabilities of being in states $\boldsymbol{x} = [x_1, \dots, x_n]$, then

$$\boldsymbol{\pi}^{(n+1)} = \boldsymbol{\pi}^{(n)} \boldsymbol{T}$$

By induction,

$$\boldsymbol{\pi}^{(n)} = \boldsymbol{\pi}^{(0)} \boldsymbol{T}^n$$

As n becomes large enough, $\boldsymbol{\pi}^{(n)}$ represents the **steady-state** of the system, or the **stationary probability distribution**.

The local weather may be “sunny” ($x_1 = \text{s}$), “cloudy” ($x_2 = \text{c}$) or “rainy” ($x_3 = \text{r}$).

The transition matrix is:

$$\mathbf{T} = \begin{bmatrix} T_{\text{ss}} & T_{\text{sc}} & T_{\text{sr}} \\ T_{\text{cs}} & T_{\text{cc}} & T_{\text{cr}} \\ T_{\text{rs}} & T_{\text{rc}} & T_{\text{rr}} \end{bmatrix} = \begin{bmatrix} 0.3 & 0.4 & 0.3 \\ 0.3 & 0.2 & 0.5 \\ 0.4 & 0.1 & 0.5 \end{bmatrix}$$

Today is a cloudy day. Out of the next three days, on which day is it least likely to rain?

Method: Compare $T_{\text{cr}}^{(n)}$ for $n = 1, 2, 3$.

From \mathbf{T} , the probability of rain tomorrow is 50.0%.

$$\mathbf{T}^2 = \begin{bmatrix} 0.33 & 0.23 & 0.44 \\ 0.35 & 0.21 & 0.44 \\ 0.35 & 0.23 & 0.42 \end{bmatrix}, \mathbf{T}^3 = \begin{bmatrix} 0.3434 & 0.2254 & 0.4312 \\ 0.3430 & 0.2258 & 0.4312 \\ 0.3430 & 0.2254 & 0.4316 \end{bmatrix}$$

From \mathbf{T}^2 , the probability of rain on the second day is 44.0%.

From \mathbf{T}^3 , the probability of rain on the third day is 43.12%.

$$\mathbf{T}^4 = \begin{bmatrix} 0.343137 & 0.225490 & 0.431372 \\ 0.343137 & 0.225490 & 0.431372 \\ 0.343137 & 0.225490 & 0.431373 \end{bmatrix}$$

Note: $\mathbf{T}^{(4)}$ gives the **stationary probability density** to five decimal places.

The unique property of Markov chains is that it is impossible to predict the next state of the system, as the transition is random.

However, once enough transitions occur the system approaches a steady state and the statistical properties of the equilibrium distribution are revealed.

In **Markov Chain Monte Carlo**, a Markov chain is constructed with the **posterior** as the equilibrium distribution of the chain.

Then, once the chain has converged to steady state, any further steps of the chain are effectively samples from the target posterior distribution!