Rotation (Midpoint-esque) Presentation

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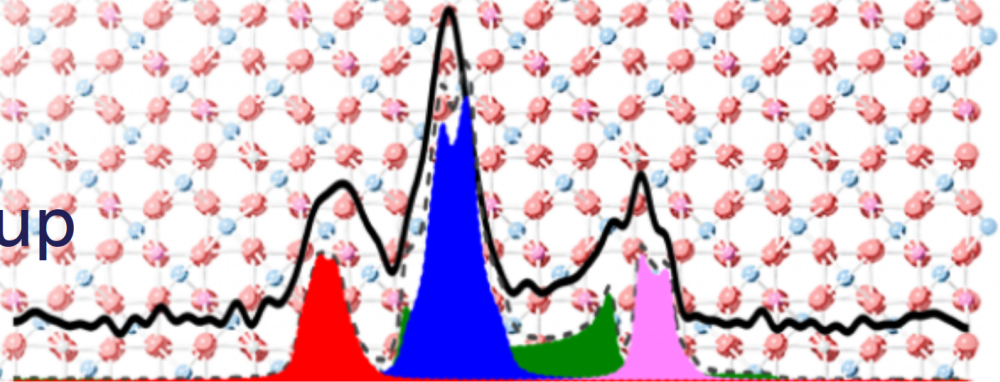
Direct Detection of Lithium Exchange across the Solid Electrolyte Interphase by ^{7}Li Chemical Exchange Saturation Transfer

David Columbus, Vaishali Arunachalam, Felix Glang, Liat Avram, Shira Haber, Arava Zohar, Moritz Zaiss, and Michal Leskes*

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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.
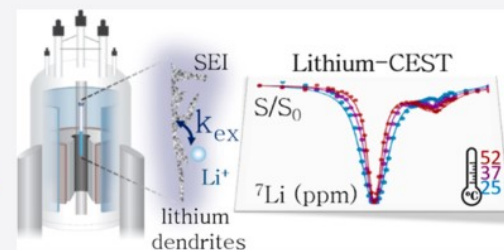
- What is CEST?

- 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)

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- 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.

Pool B   Pool A
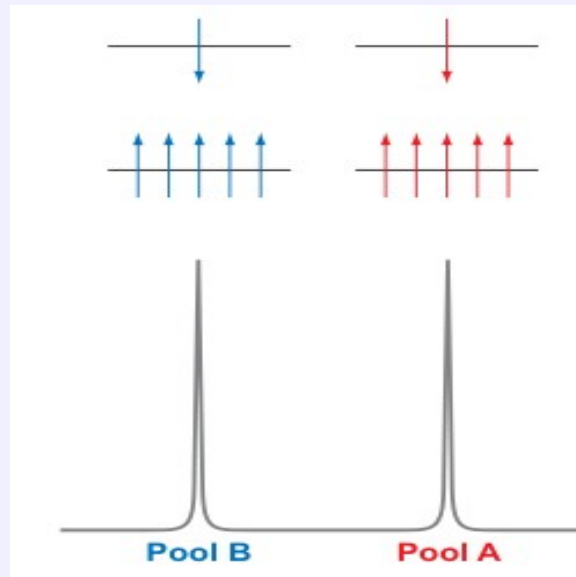
- Using a low-intensity magnetic field B_1, Pool B is irradiated at its resonance frequency until the net magnetization reaches zero (saturation) .
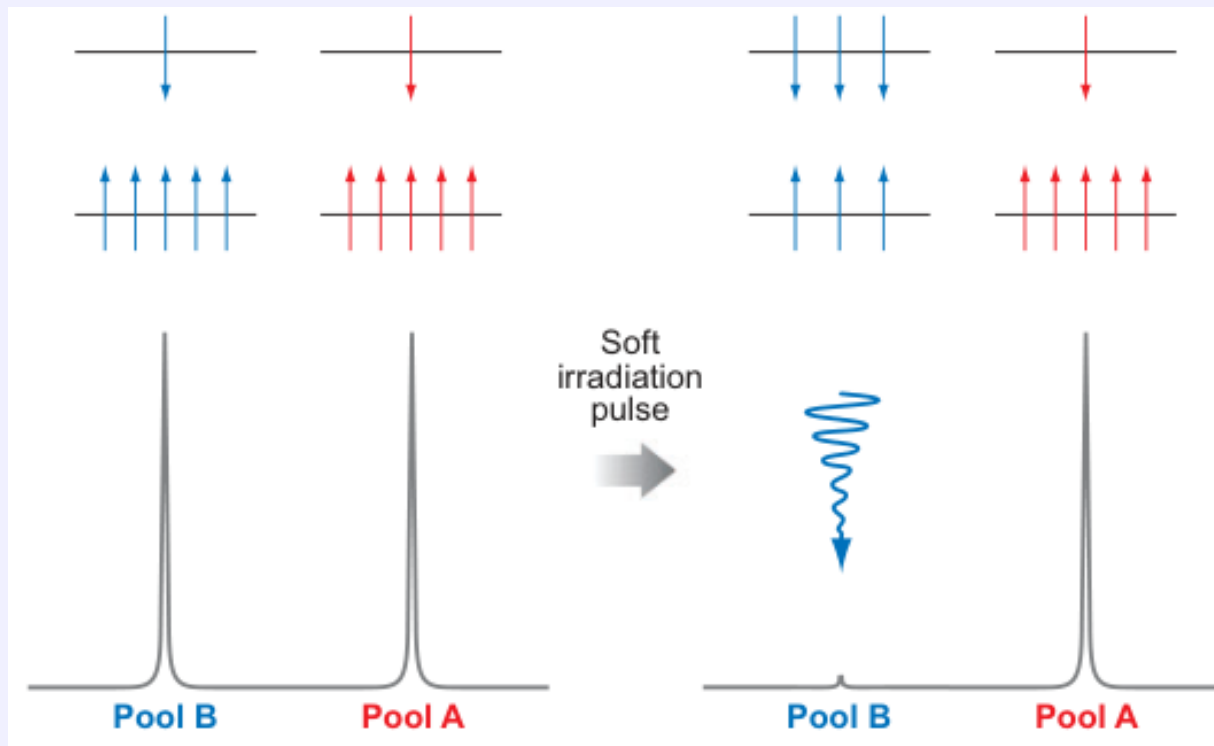
- Nuclei in pool B and pool A are in exchange throughout the process:

- Spins from pool B that are aligned against B_0 are transfered to pool A.

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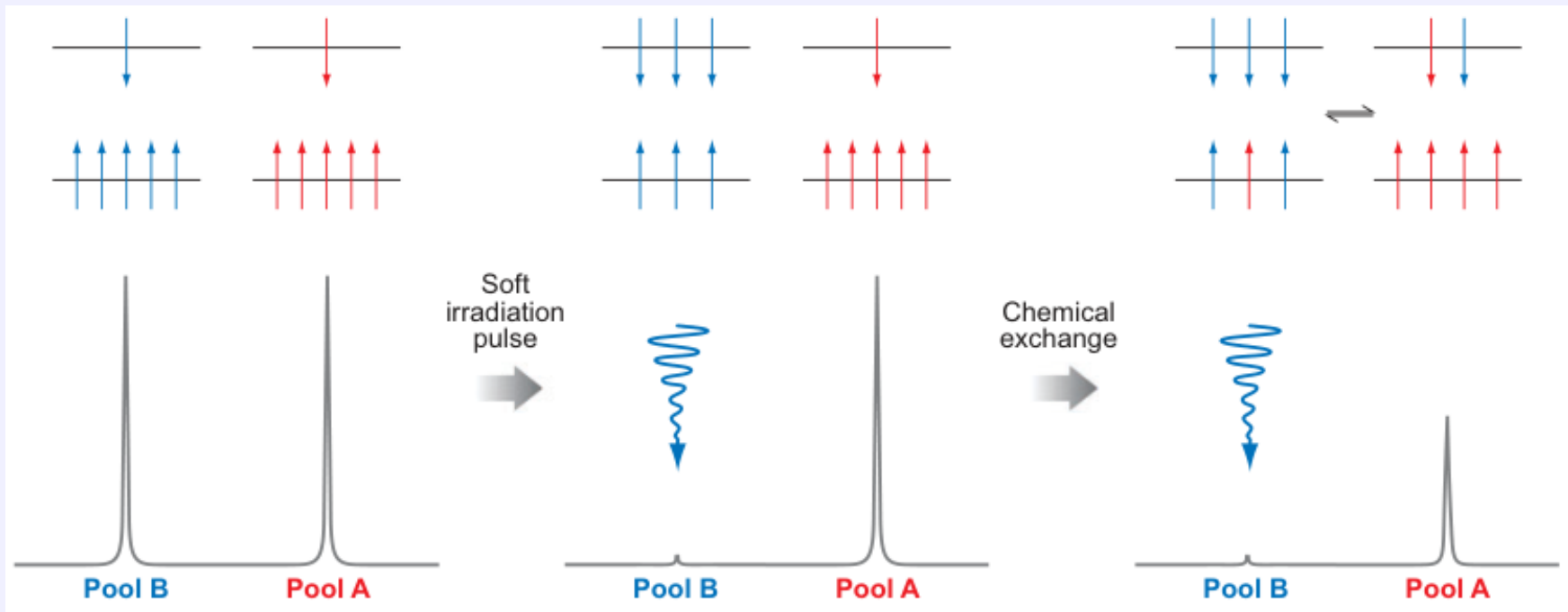
- We wish to **quantify** the exchange between pool A and pool B.

- 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.

- The saturated pool A signal is usually reported against the saturation frequency and centered at the resonance frequency of pool A, and is termed the **Z-spectrum**.
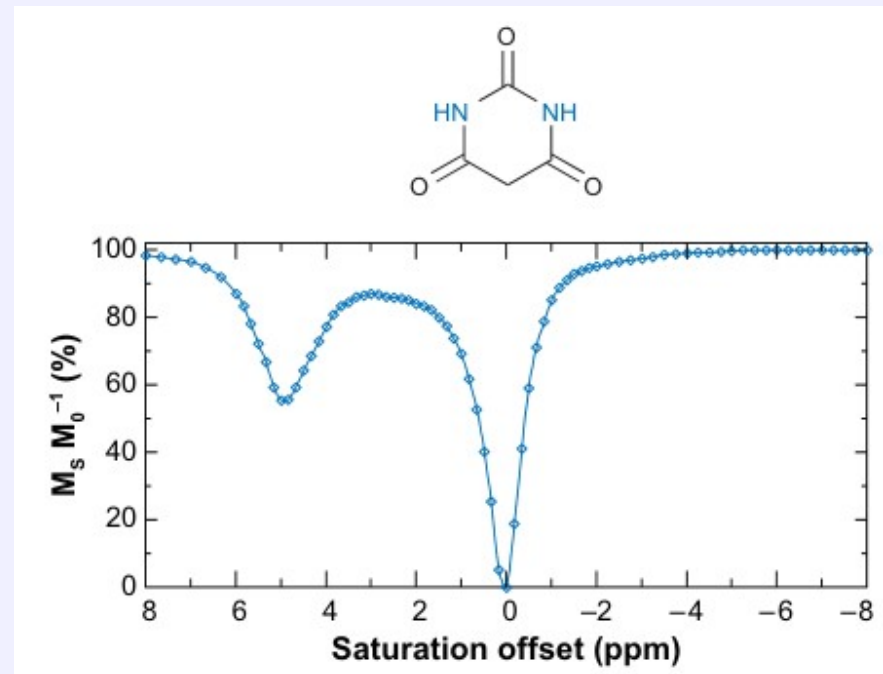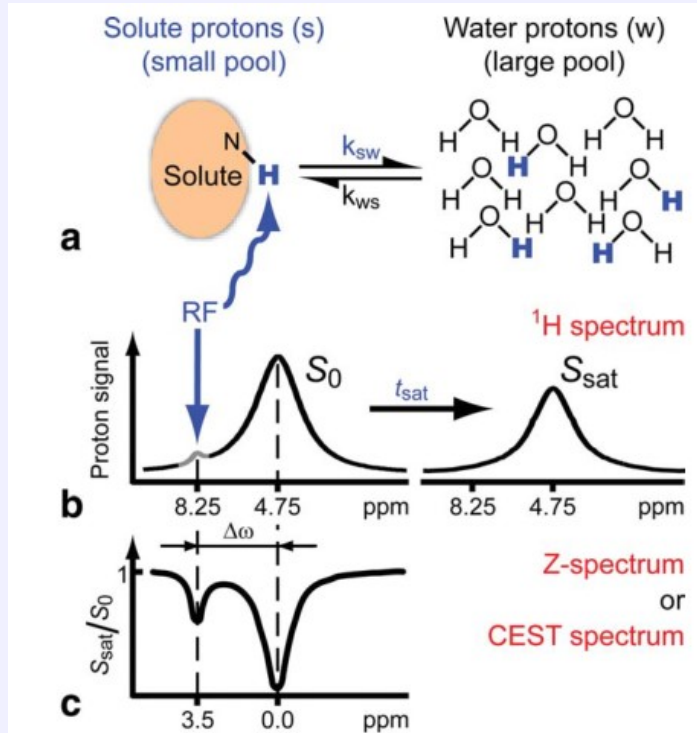
Generally, The CEST effect is influenced by the following parameters:

- The relaxation times of each pool, $T_{1i}, T_{2i}, \quad i \in A, B$

- The back and forward exchange rate of nuclei (spins), $k_{A \to B}, k_{B \to A}$

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

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

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

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:

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

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

The Bloch equations in the rotating frame are:

$$\begin{aligned}
\frac{\mathrm{d}M_x}{\mathrm{d}t} &= -\frac{1}{T_2}\, M_x + \Delta\omega\, M_y \\[1ex]
\frac{\mathrm{d}M_y}{\mathrm{d}t} &= -\Delta\omega\, M_x - \frac{1}{T_2}\, M_y + \omega_1\, M_z \\[1ex]
\frac{\mathrm{d}M_z}{\mathrm{d}t} &= -\omega_1\, M_y - \frac{1}{T_1}\, M_z + \frac{M_0}{T_1}
\end{aligned}$$

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 transfered between the pools according to the exchange rate.

$$\frac{\mathrm{d}M_x^A}{\mathrm{d}t} = -\frac{M_x^A}{T_{1A}} + \Delta\omega_A\, M_y^A - k_{\mathrm{AB}}\, M_x^A + k_{\mathrm{BA}}\, M_x^B$$

$$\frac{\mathrm{d}M_y^A}{\mathrm{d}t} = -\frac{M_y^A}{T_{2A}} - \Delta\omega_A\, M_x^A + \omega_1\, M_z^A - k_{\mathrm{AB}}\, M_y^A + k_{\mathrm{BA}}\, M_y^B$$

$$\frac{\mathrm{d}M_z^A}{\mathrm{d}t} = -\frac{M_z^A - M_0^A}{T_{1A}} - \omega_1\, M_y^A - k_{\mathrm{AB}}\, M_z^A + k_{\mathrm{BA}}\, M_z^B$$

$$\frac{\mathrm{d}M_x^B}{\mathrm{d}t} = -\frac{M_x^B}{T_{2B}} + \Delta\omega_B\, M_y^B - k_{\mathrm{BA}}\, M_x^B + k_{\mathrm{AB}}\, M_x^A$$

$$\frac{\mathrm{d}M_y^B}{\mathrm{d}t} = -\frac{M_y^B}{T_{2B}} - \Delta\omega_B\, M_x^B + \omega_1\, M_z^B - k_{\mathrm{BA}}\, M_y^B + k_{\mathrm{AB}}\, M_y^A$$

$$\frac{\mathrm{d}M_z^B}{\mathrm{d}t} = -\frac{M_z^B - M_0^B}{T_{1B}} - \omega_1\, M_y^B - k_{\mathrm{BA}}\, M_z^B + k_{\mathrm{AB}}\, M_z^A$$

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

$$\frac{\mathrm{d}\vec{M}}{\mathrm{d}t} = A\,\vec{M} + \vec{b}$$

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

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

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

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

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

Using the definition for the integral of a matrix exponential:

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

we get:

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

- 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 computationaly expensive.
- Simulation of a Z-spectrum with N data point requires performing N matrix 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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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 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 μs).

- Also, extracting all parameters may require repetitions of the experiment.

- Least squares fitting is equivalent to **maximum likelihood estimation**, which is **Frequentist** by nature.

- It assumes that the data is independently and identically distributed, thus treated as a *random variable*, while the model parameters are *fixed*.

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- An alternative approach to fit a model to data is via **Bayesian inference**.

- It treats data as a fixed variable and the parameters as random variables, which are given *probability distributions*.

- The advantage of using Bayesian inference is that **prior information** can be incorporated in the fitting procedure, while **likelihood** is still taken into account.

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

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

- $P(\boldsymbol{\theta})$ is called the **prior (joint) distribution**
- $P(\boldsymbol{y}|\boldsymbol{\theta})$ is the **likelihood function/distribution**
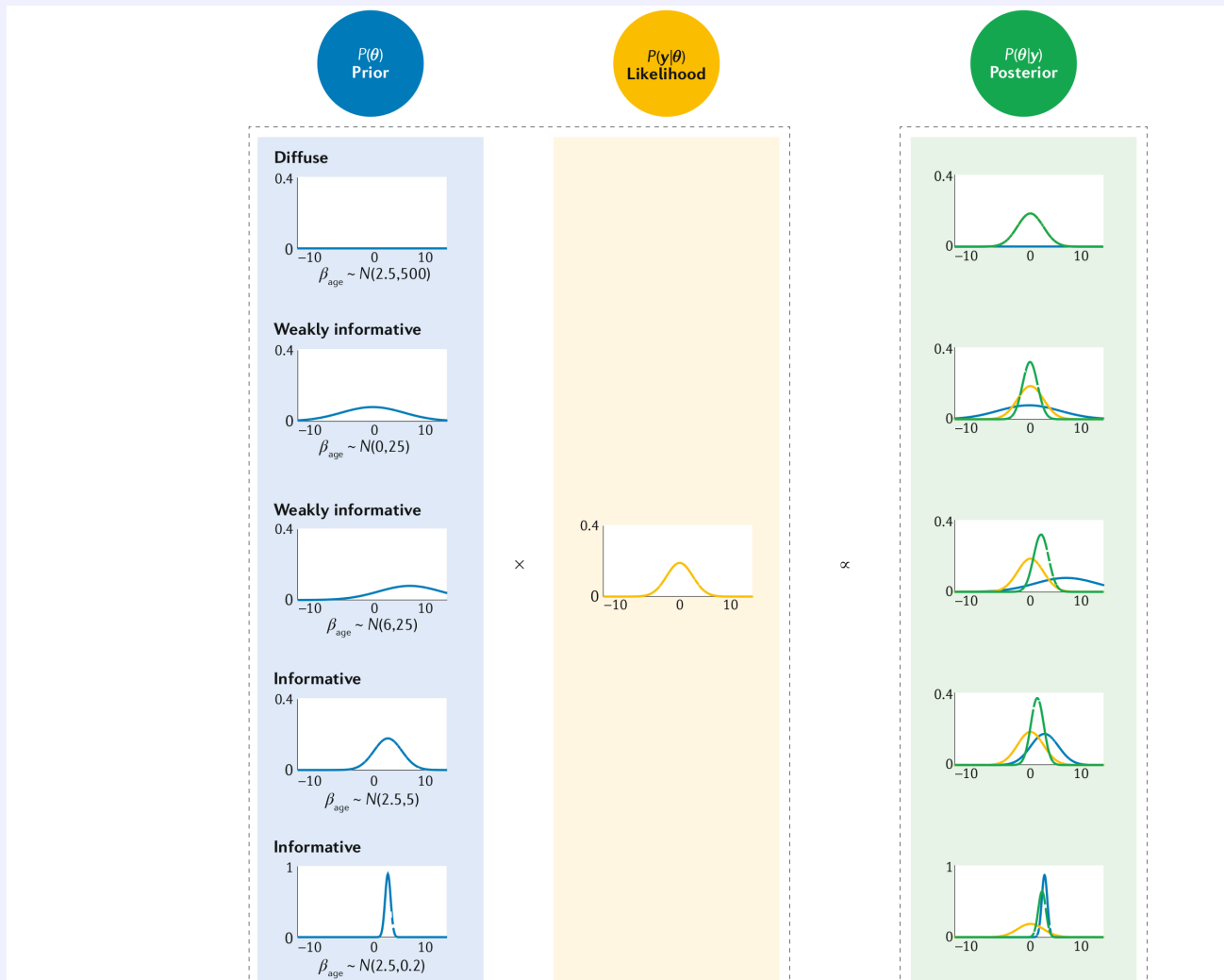- $P(\boldsymbol{\theta}|\boldsymbol{y})$ is called the **posterior (joint) distribution** — Our desired quantity

Assuming data is identically, independently, and normally distributed:

$$P(\boldsymbol{\theta}) = \prod_{i=1}^{n} P(\theta_i)$$

$$P(\boldsymbol{y}|\boldsymbol{\theta}) = \prod_{i=1}^{n} \frac{1}{\sigma\sqrt{2\pi}}\, \mathrm{e}^{-\frac{(y_i - f(\boldsymbol{\theta}, x_i))^2}{2\sigma^2}}$$

- As stated, the joint posterior distribution may be used to infer how the model parameters are (individually) distributed, and what are their most probable values.

- *However*, the posterior is **multi-dimensional**! How can we sample from such a complex distribution/function?

Care for a game of chance?

- A Monte Carlo simulation is about **sampling** and **scoring**.

- Sampling is done from the target posterior distribution.

- Scoring is book-keeping of samples that passed a certain test criterion.

- Averaging over successful scoring histories provides an estimate of the parameters.

- A popular and powerful tool to generate samples from the posterior destribution utilizes **random walk** and construction of a **Markov chain** that converges to the target distribution at steady state.