Department of Medical Physics and Biomedical Engineering
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Self-supervised deep learning to improve quantification of blood-brain barrier permeability from MRI data

Friday 22nd March 2024
Photo adapted from D koi on Unsplash[1]

Background motivation

- **Blood-brain barrier (BBB)**
  - Selectively permeable barrier [1] [2]
  - Maintains homeostasis in brain and CNS [3]

[1] The 'barrier' is a description given to the microvasulature

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  - Selectively permeable barrier [1] [2]
  - Maintains homeostasis in brain and CNS [3]
- **Dysfunction:** Pathogens and toxins leak from blood to brain [2]
  - Stroke
  - Multiple sclerosis
  - Tumours
  - Can occur early in disease
- **Biomarker**

[1] The 'barrier' is a description given to the microvasulature

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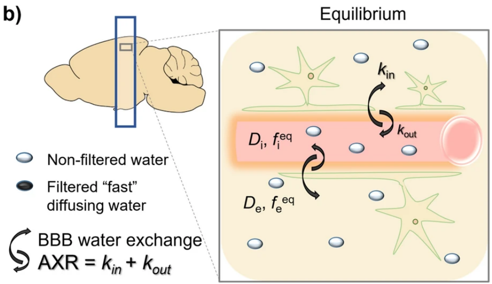

Figure: Adapted from [4]

- **FEXI** (Filtered exchange imaging) - dMRI (Diffusion MRI) technique
  - Originally used to track water exchange across cell membranes
  - Can be used to track water exchange across the BBB

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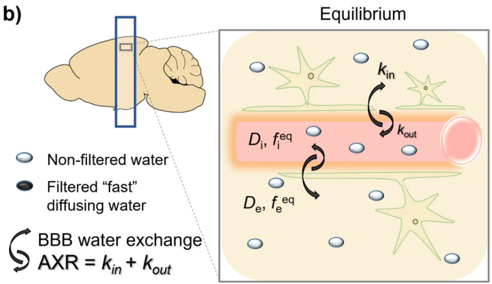

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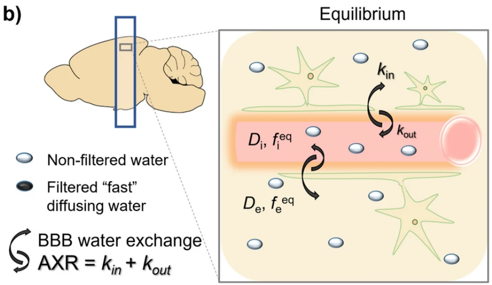

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  - Originally used to track water exchange across cell membranes
  - Can be used to track water exchange across the BBB
- **Existing method:** Non-linear least squares fit (NLLS)
  - Suffers from bias and noise.
- **New method:** Neural networks (NN) show promise in other dMRI methods
  - ssVERDICT - A model of Prostate tumours
  - Reduced bias compared to existing NLLS method [5]
  - Side effect: Slow to train but quicker once implemented
    - 10s of minutes for NLLS
    - Fractions of a second

Aims and objectives

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Objectives:

- Simulate the MRI signal in Python using NumPy.
- Implement a baseline Non-linear least squares (NLLS) estimation to FEXI.
    - Previously made in MATLAB
- Create a self supervised deep learning model in PyTorch to estimate FEXI parameters.

FEXI theory

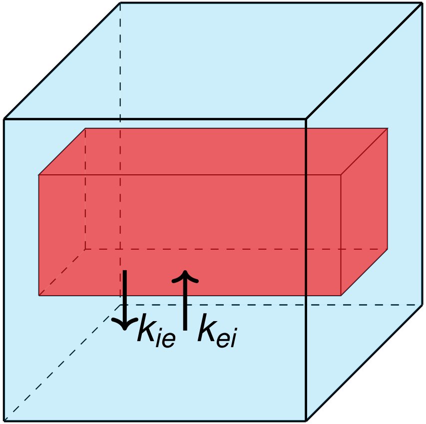

Figure: A FEXI voxel, extra-vascular compartment in blue and intra-vascular compartment in red.

- FEXI assumes a 2 compartment model in every voxel (Volume Element)
- FEXI tracks the water in each compartment. (Blood-water in the intra-vascular compartment)
- The main parameter of interest is the apparent exchange rate $AXR = k_{ie} + k_{ei}$ between the compartments.

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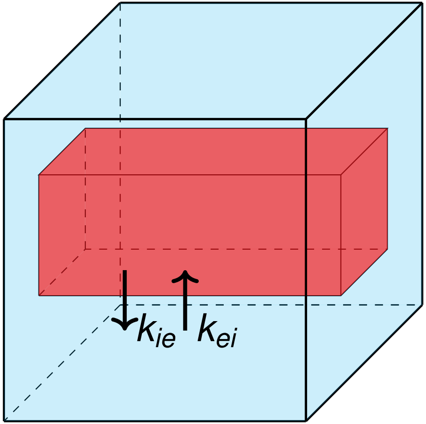

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- Other estimated parameters:
  - Apparent diffusion coefficient ADC
  - Filter efficiency σ

FEXI Theory

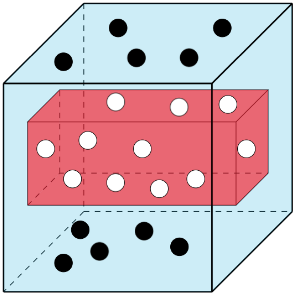
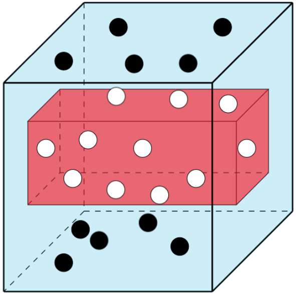


Figure: Exchange of water between intra- and extra-vascular compartments during mixing time

- The FEXI MRI sequence contains a mixing time
- There is water exchange between the 2 compartments during this time
- This is what *AXR* measures

FEXI Theory



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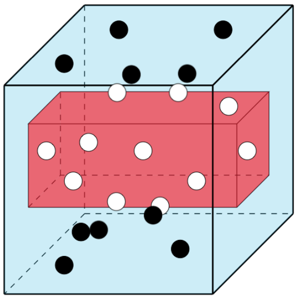

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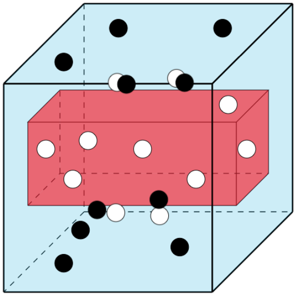

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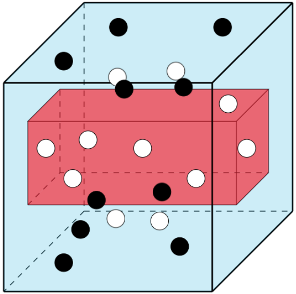

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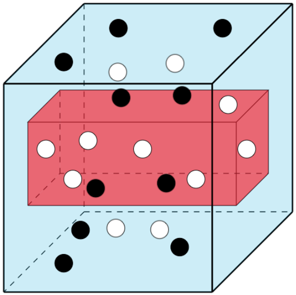

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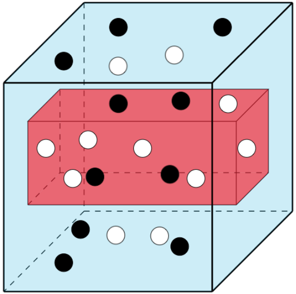

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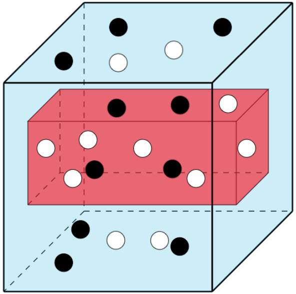

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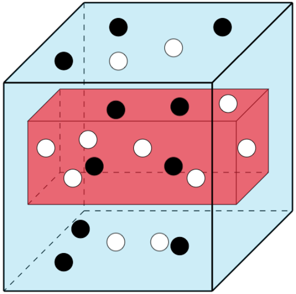

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Methods

- **Simulations**
  - Simulate 10,000 voxels
    - Random distribution of underlying model parameters *ADC*, σ and *AXR*
  - Calculate the signal produced by each voxel
  - Add rician noise[2] (SNR=50) to the signals
    - The ground truth

[2] "Rician is the thermal noise found in MRI due to the thermal agitation of electrons."[6]

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- **Simulations**
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    - Random distribution of underlying model parameters ADC, σ and AXR
  - Calculate the signal produced by each voxel
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    - The ground truth
- **NLLS and Neural network**
  - Input noisy MRI signal
  - Estimate underlying model parameters ADC, σ and AXR
  - Calculate the mean squared error between the estimated signal and the ground truth (with noise added).
  - Iterate

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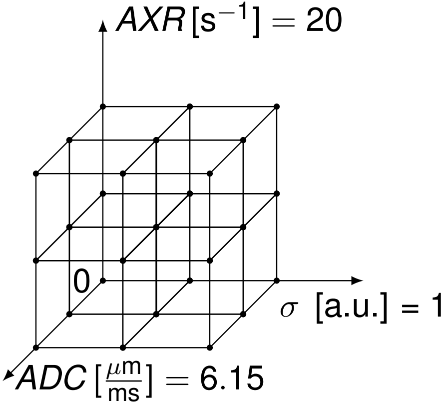
Non-linear Least squares theory

- The scipy.optimize.minimize() function [7] within Python was used to make the estimations. [3]
  - Minimising the sum of squares error between the estimated signal and the noisy ground truth signal.

[3] Using the Limited-memory Broyden-Fletcher-Goldfarb-Shanno with Bounds algorithm

Non-linear Least squares theory

- The scipy.optimize.minimize() function [7] within Python was used to make the estimations. [3]
    - Minimising the sum of squares error between the estimated signal and the noisy ground truth signal.
- The function requires an initial value
    - 3 equally spaced initial values for each parameter (*ADC*, σ and *AXR*) were used, producing $3^3 = 27$ initial starting points.
    - The best estimation from these 27 starting points was used
- Each parameter is bounded within the simulation range.



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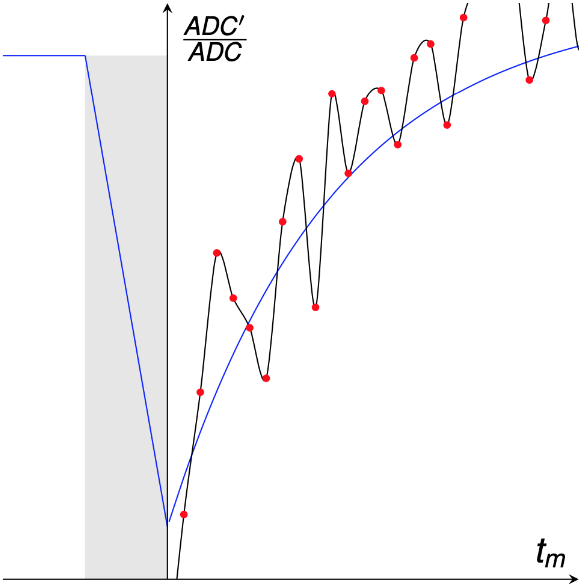
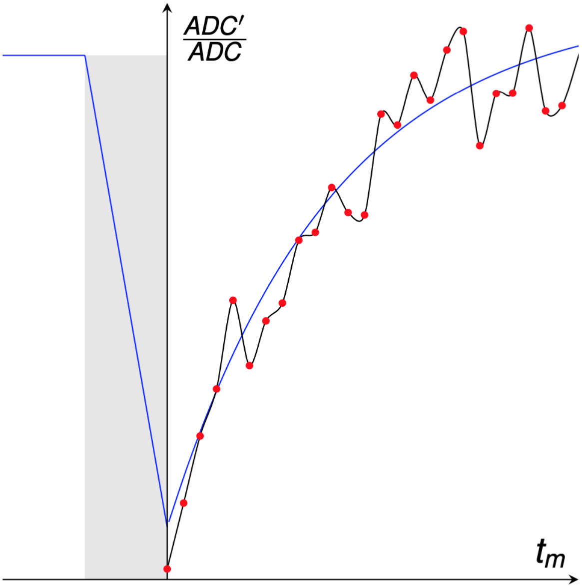


- Here is an example of fitting the curve using a NLLS fit

Non-linear Least squares theory



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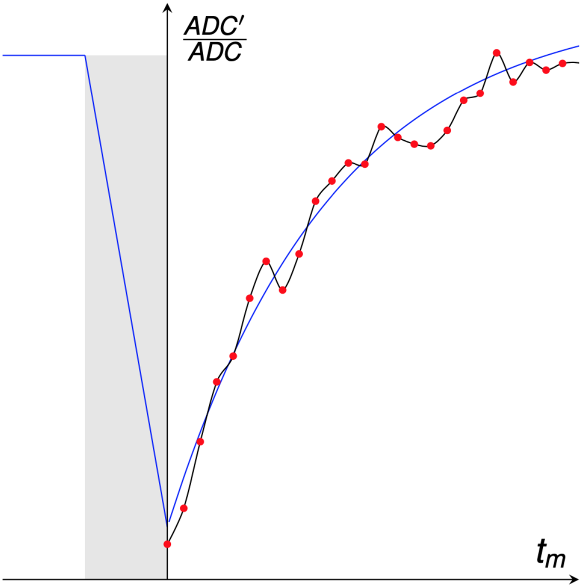

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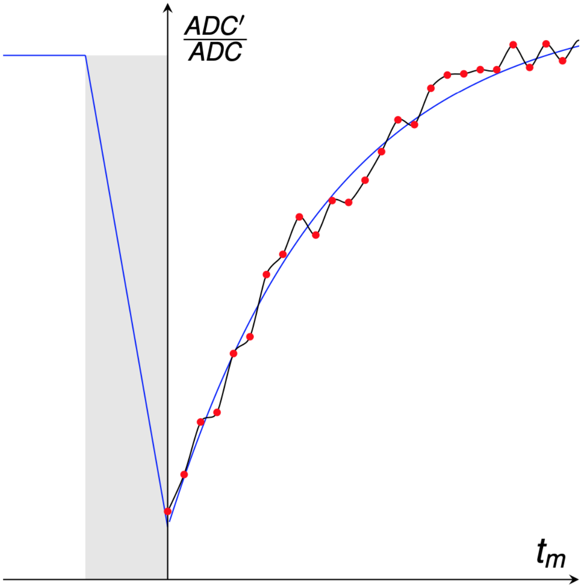

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Neural network theory

- Input: 8 image volumes
- Passed through the weights of each layer
- 3 outputs: *ADC*, σ and *AXR*. (Known as the forward model)
- Each parameter is bounded by the same bounds as the simulation.
- Mean squared error calculated between the ground truth noisy signals and estimated signals

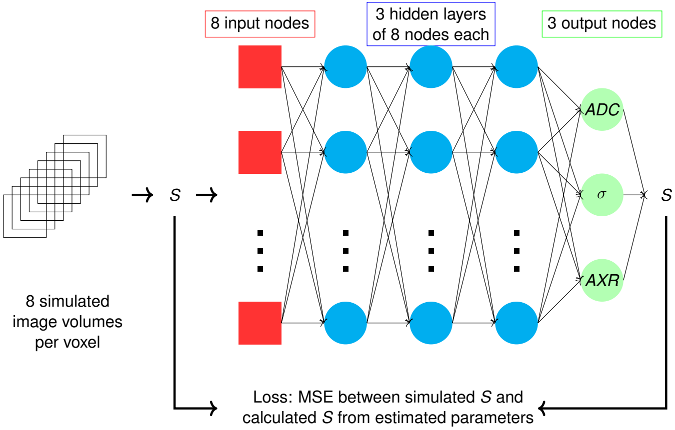
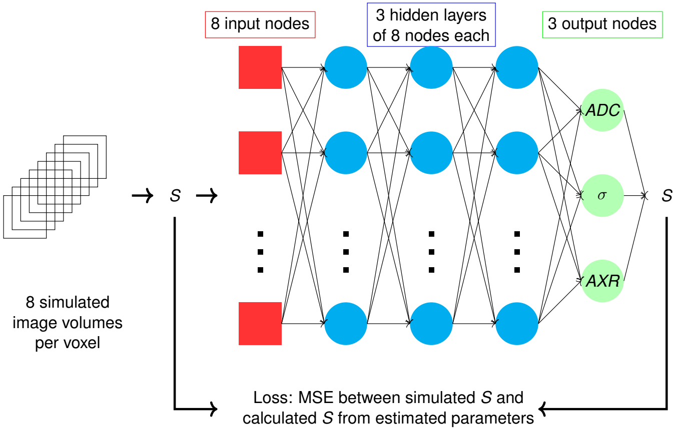


Figure: Neural network

- The gradients of the weights are calculated.
- If error improves, then the weights in the model are updated, with gradients giving the most efficient change (Known as backpropagation)
- This process (one epoch) is repeated, and stops after 100 epochs in a row where there is no improvement to the loss.



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Results

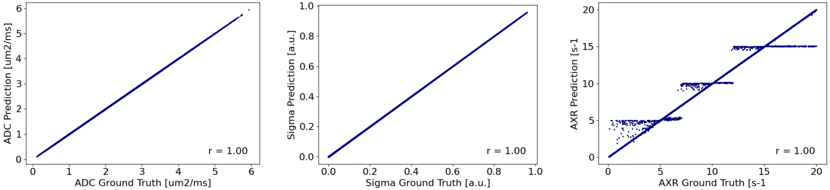

Figure: NLLS estimations

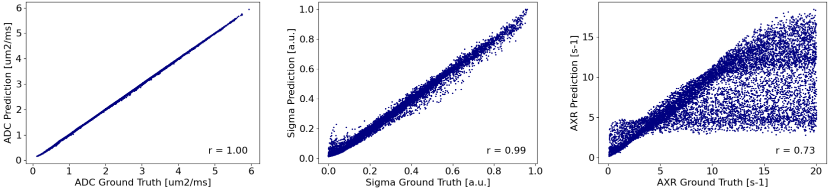

Figure: NN estimations

Results continued

MSE			
Method	*ADC*	σ	*AXR*
NLLS	$\mathbf{1.75 \times 10^{-7}}$	$\mathbf{1.03 \times 10^{-8}}$	**0.331**
NN	2.53	0.104	56.3
Bias			
Method	*ADC*	σ	*AXR*
NLLS	$\mathbf{-3.02 \times 10^{-5}}$	$\mathbf{-6.70 \times 10^{-6}}$	$\mathbf{3.33 \times 10^{-3}}$
NN	3.57×10^{-3}	$- 3.09 \times 10^{-3}$	-2.52
Variance			
Method	*ADC*	σ	*AXR*
NLLS	1.27	5.27×10^{2}	32.2
NN	**1.26**	$\mathbf{5.07 \times 10^{2}}$	**23.3**

Table: Comparing NLLS to NN (Best results are bolded)

$$\text{MSE} = \frac{1}{N}\sum_{i=0}^{N}(O_i - E_i)^2$$

$$\text{Bias} = \frac{1}{N}\sum_{i=0}^{N}(O_i - E_i)$$

$$\text{Varience} = \frac{1}{N}\sum_{i=0}^{N}(O_i - \overline{O})$$

Where O is ground truth parameter value, E is estimated value, and N is number of samples.

Discussion

- NLLS fit outperforms NN in MSE and Bias for all parameters
- NN outperforms NLLS in variance for all parameters
- AXR is hardest parameter to estimate in both methods
  - *ADC* and σ have a linear relationship to the signal, but *AXR* has a exponential relationship.
- **Future work**
  - Use other variations hyper-parameters of NN.
  - Calculate the loss on a per parameter basis.
  - Physics informed network - Calculate AXR from other parameters rather than estimating in NN
  - Apply to in-vivo data

Thank you for listening

[1] Unsplash. *Photo by D koi on Unsplash*. 2022-06-29. URL: https://unsplash.com/photos/a-white-and-grey-striped-surface-GU_nNLVna_4 (visited on 2024-03-15).

[2] Richard Daneman and Alexandre Prat. "The Blood–Brain Barrier". In: *Cold Spring Harbor Perspectives in Biology* 7.1 (2015-01), a020412. ISSN: 1943-0264. DOI: 10.1101/cshperspect.a020412. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4292164/ (visited on 2024-03-14).

[3] Gerard J. Tortora and Bryan H. Derrickson. *Introduction to the Human Body*. 11th ed. Wiley, 2017-12-15. ISBN: 978-1-119-39273-6. URL: https://bibliu.com/app/#/view/books/9781119392736/epub/OPS/c10.html#page_393 (visited on 2024-03-07).

[4] Yolanda Ohene et al. “Filter exchange imaging with crusher gradient modelling detects increased blood–brain barrier water permeability in response to mild lung infection”. In: *Fluids and Barriers of the CNS* 20.1 (2023-04-03), p. 25. ISSN: 2045-8118. DOI: 10.1186/s12987-023-00422-7. URL: https://doi.org/10.1186/s12987-023-00422-7 (visited on 2024-03-21).

[5] Snigdha Sen et al. *ssVERDICT: Self-Supervised VERDICT-MRI for Enhanced Prostate Tumour Characterisation*. 2023-09-27. DOI: 10.48550/arXiv.2309.06268. arXiv: 2309.06268[cs,eess]. URL: http://arxiv.org/abs/2309.06268 (visited on 2024-03-21).

[6] Divya Pankaj, Govind D., and Narayanankutty K.a. “A novel method for removing Rician noise from MRI based on variational mode decomposition”. In: *Biomedical Signal Processing and Control* 69 (2021-08-01), p. 102737. ISSN: 1746-8094. DOI: 10.1016/j.bspc.2021.102737. URL: https://www.sciencedirect.com/science/article/pii/S1746809421003347 (visited on 2024-03-22).

[7] *scipy.optimize.minimize — SciPy v1.12.0 Manual*. URL: https://docs.scipy.org/doc/scipy/reference/generated/scipy.optimize.minimize.html (visited on 2024-03-14).

Thank you for listening!
Any questions?

Appendix equations

$$S(b_f, t_m, b) = S_0(b_f, t_m)e^{-b \cdot ADC'(t_m)} \tag{1}$$

where:

$$ADC'(t_m) = ADC(1 - \sigma e^{-t_m \cdot AXR})$$