Quantification of perfusion and xenon-transport across the blood-brain barrier in humans with hyperpolarized ^{129}Xe brain MR at 1.5T

Madhwesha Rao[1], Neil Stewart[1], Graham Norquay[1], and Jim Wild[1]
[1]*University of Sheffield, Sheffield, South Yorkshire, United Kingdom*

Target Audience: Brain physiology and function; hyperpolarized noble gas MRI community.

Purpose: When inhaled into the lungs, xenon dissolves in blood, and is carried to the brain via the systemic circulation, where it, crosses the blood-brain barrier (BBB)[1] and dissolves into brain tissues[2-4]. ^{129}Xe exhibits chemically distinct resonances in cerebral blood, grey-matter and white-matter enabling delineation of ^{129}Xe dissolved in each of these compartments as shown in Figure 1. The motivation of this study was to investigate the role of hyperpolarized (HP) ^{129}Xe as a physiological probe of the efficiency of transport across the BBB.

Brain Model Theory: Upon delivery to the brain, the fraction of xenon that crosses the BBB[1] is given by the partition coefficient $\lambda_{g(w)/b}$[5]. This process occurs over a time period of many seconds, such that it can be dynamically studied by HP ^{129}Xe NMR with an appropriate sampling interval. The time course of the HP ^{129}Xe signal dissolved in cerebral blood can be used as an input function, U(t), for the delivery of xenon to the brain. Therefore, we can ignore any factors affecting the ^{129}Xe signal dynamics prior to it reaching the brain tissues. The signal uptake with time of HP ^{129}Xe dissolved in brain tissue (g(t) grey-matter or w(t) white-matter) depends on the input function, U(t), T_1 relaxation of ^{129}Xe in brain tissue and the residual polarization ($r_{g(w)}(t)$) associated with flip angles of less than 90°. The g(t) or w(t) signal is also scaled by constants determined by cerebral blood flow, $CBF_{g(w)}$, mass of the tissue, $M_{g(w)}$ and the partition co-efficient $\lambda_{g(w)/b}$. The residual polarization $r_{g(w)}(t)$ is dependent upon the mean transit time of ^{129}Xe in the brain tissue $MTT_{g(w)}$, the spatial flip angle profile of the coil, $\alpha(x)$ and the corresponding regional tissue density $\rho_{g(w)}(x)$. Thus, we arrive at the model for the time course of signals of ^{129}Xe from grey and white matter (output function g(t), w(t)) as shown in Figure 2.

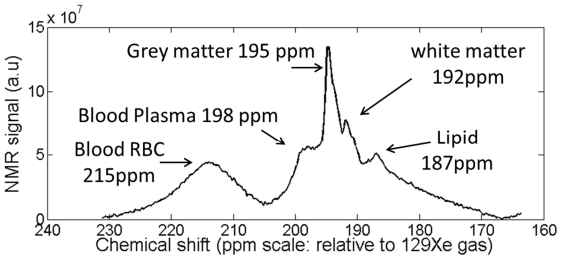
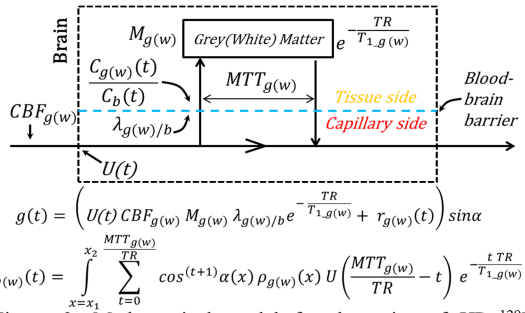


Figure 1: Spectroscopy of HP ^{129}Xe dissolved in human brain at 1.5T



$$g(t) = \left(U(t)\, CBF_{g(w)}\, M_{g(w)}\, \lambda_{g(w)/b}\, e^{-\frac{TR}{T_{1\_g(w)}}} + r_{g(w)}(t) \right) \sin\alpha$$

$$r_{g(w)}(t) = \int_{x=x_1}^{x_2} \sum_{t=0}^{\frac{MTT_{g(w)}}{TR}} \cos^{(t+1)}\alpha(x)\, \rho_{g(w)}(x)\, U\left(\frac{MTT_{g(w)}}{TR} - t\right) e^{-\frac{t\,TR}{T_{1\_g(w)}}}\, dx$$

Figure 2: Mathematical model for dynamics of HP ^{129}Xe dissolved in human-brain.

Methods: In-vivo MR spectroscopy of HP ^{129}Xe dissolved in the human brain was performed on a GE 1.5 T Signa HDx scanner. An 8-leg birdcage coil, tuned to the ^{129}Xe Larmor frequency (17.7 MHz at 1.5 T), was constructed in-house. ^{129}Xe nuclei were hyperpolarized by *SEOP* to 40~50% polarization[6]. HP ^{129}Xe gas was inhaled by the subject in doses of between 400 mL and ~1 L. Data were acquired with a pulse-acquire sequence: the inter-pulse delay time was varied between 0.5~4 s; the excitation flip angle was varied from 20°~90°; the bandwidth was set to 0.6/ 1.2 kHz and the center frequency was set to 197 ppm downfield from the ^{129}Xe gas peak. The subjects tolerated the (10 – 30 second) breath-hold well and vital signs were monitored throughout the scan.

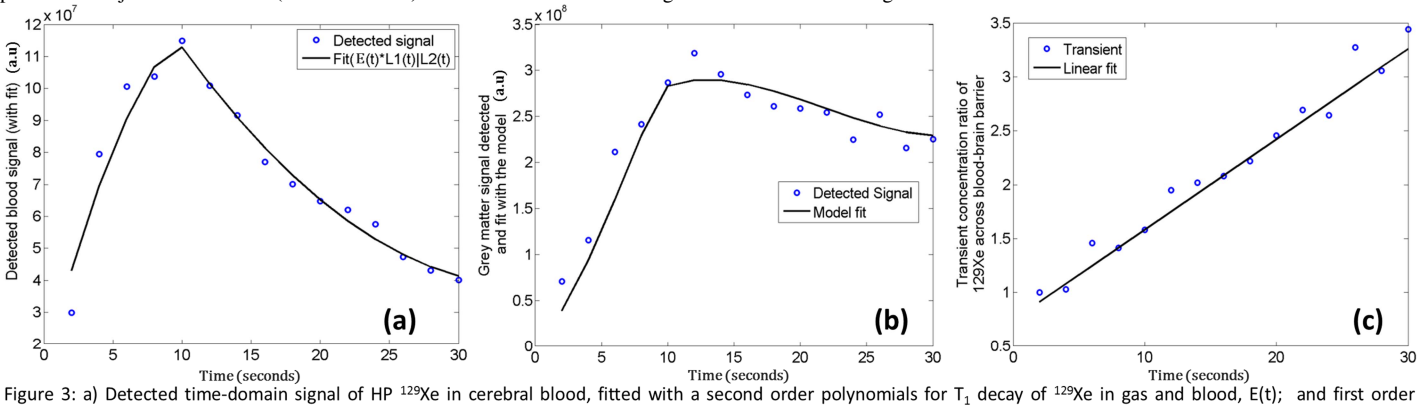


Figure 3: a) Detected time-domain signal of HP ^{129}Xe in cerebral blood, fitted with a second order polynomials for T_1 decay of ^{129}Xe in gas and blood, E(t); and first order polynomials for inhalation (L_1) and changes in the gas reservoir of the lungs (L_2). This function is the input function for xenon uptake and delivery to the brain. b) Detected time-domain signal of HP ^{129}Xe in grey-matter, fitted with the output function of the brain model. c) Transient ratio of concentration of ^{129}Xe in grey-matter to blood. The slope of the phenomenological linear fit is proposed as a physiological marker of blood-brain barrier permeability and integrity.

Results and Discussion: The blood-brain barrier separates HP ^{129}Xe in blood (capillary) and brain tissue as shown in Figure 2. To arrive at the permeability of the barrier, the time course signal of HP ^{129}Xe detected in both blood and brain tissue should be accounted for. This is achieved by normalizing the detected ^{129}Xe signal dissolved in brain tissue (grey/white matter, Figure 3(b)) by the input function U(t) (Figure 3(a)) and brain-model output function for grey(white) matter (g(t) or w(t)) for constant ratio of concentration of ^{129}Xe in tissue to blood. Thus we arrive at a transient response of the concentration ratio as shown in Figure 3(c). This "transient concentration ratio" of HP ^{129}Xe between brain tissue and blood, we believe, describes the intrinsic permeability of the blood-brain barrier to xenon. We propose, therefore, that the slope of the linear-fit (Figure 3(c)) is a physiological indicator of blood-brain barrier integrity and permeability. Although, it should be noted that the detected blood signal represents a global measurement over the whole head, therefore comprising a mixture of arterial and venous blood signals. The separation of these two components is essential for accurate characterization of the blood-brain barrier permeability. As this is preliminary work, the sensitivity and tolerance of the ^{129}Xe brain model to variations in each parameter is currently under study, and the results must be further substantiated with additional subjects.

Conclusions: A novel model for non-invasive quantification of the blood-brain barrier from HP ^{129}Xe MR is demonstrated.

References: **1**. Rengachary, S.S. et al, Principles of Neurosurgery. Elsevier Mosby, 2005. **2.** W. Kilian, et al, MRM, 51 (2004), 843-47. **3.** K. Nakamura, et al, MRM, 53 (2005), 528-34. **4.** J. P. Mugler Iii, et al, MRM, 37 (1997), 809-15. **5.** John S. Meyer, MD. et al. Stroke. 1981 Jul-Aug;12(4):426-36. **6.** G. Norquay, et al., Journal of Applied Physics, 113 (2013).