# Determination of Optimal Model Sampling Parameters for Hyperpolarized Contrast Agents

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**Introduction:** There have been several studies probing *in vitro* [1, 2] and *in vivo* [3-5] cellular metabolism using dynamic hyperpolarized $^{13}C$ and kinetic model fitting. Hyperpolarized $^{13}C$ modeling of metabolic parameters is difficult because of non-equilibrium $T_1$ decay which results in short imaging times. However, the non-equilibrium state also allows for the flip angle to be varied dynamically, which allows SNR to be an extra degree of freedom in the acquisition which would otherwise not be available. Model fitting, from imaging or spectroscopy, is desirable because it provides quantitative biokinetic parameters, which can be measures of cellular metabolism and transport. The traditional approach has been to sample the compound kinetics with a constant flip angle and a constant temporal spacing between sample points [1-5]. However, as with $T_1$ and $T_2$ quantification [6], magnetization transfer [7], and arterial spin labeling [8], assuming a linear sampling pattern produces sub-optimal fits and therefore increases the noise in the fitted parameters. This work demonstrates a method similar to Cercignani et al. to determine an optimal sampling scheme utilizing the concept of minimizing the Cramer-Rao Lower Bounds (CRLB)[9], which represents the lower bound of the variance of a parameter estimate. Therefore, by minimizing the CRLB with respect to the sampling times, flip angles, and assumed tissue parameters, the minimum fitted parameter variance is also lowered, which is analogous to increasing the SNR of the fitted parameters.

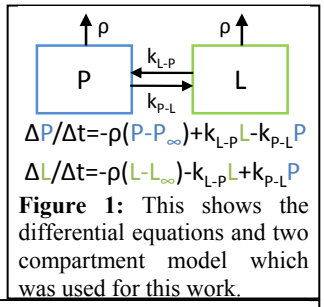


**Figure 1:** This shows the differential equations and two compartment model which was used for this work.

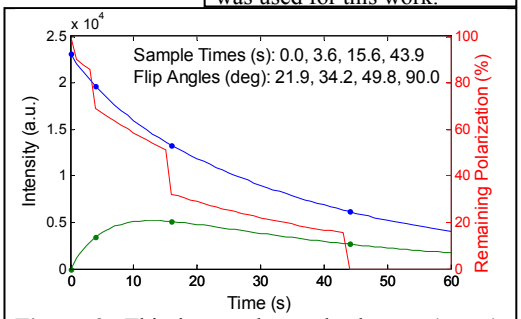


**Figure 2:** This image shows the lactate (green), pyruvate/3 (blue), and remaining polarization (red) curves for $k_{P-L}$=0.018, $k_{L-P}$=0.125, $P_\infty$=1.733, $\rho_P=\rho_L$=0.027. The points represent the optimal sampling locations for the given parameters.

**Theory and Methods:** Let f be the solution to the two-site exchange model [3] shown in **Figure 1**, which are the curves seen in **Figure 2** for a specific parameter set. The solution of the differential equation, f, is then used to calculate the Jacobian, J (**Eq. 1**), with respect to the fixed range of the tissue parameters (rate constants) $p_{tp}$, and the sampling parameters to be optimized: the sample times ($t_i$) and flip angles, which modulate the noise ($\sigma_i^2$). An approximation of the Fisher Information Matrix (FIM), also known in this context as the Hessian, H (**Eq. 2**) can then be calculated. The sampling parameters are then optimized for a single set of tissue parameters using the patternsearch routine in MATLAB (MathWorks, Natick, MA, USA) by minimizing $\Sigma_j[H^{-1}]_{jj}/p_j$ where $[H^{-1}]_{jj}$ is substituted for the unknown $\sigma_j^2$. The optimal sampling parameters (sp) can be calculated over a range of tissue parameters (tp) by maximizing the CRLB over the tissue parameters, and minimizing the CRLB over the sampling parameters at the tissue parameters which have the maximum CRLB (**Eq. 3**). This process is analogous to the G-optimality criterion [7] which is in essence the minimization of the maximum error. A digital phantom was created in order to validate the optimal sampling against a default sampling scheme similar to that used in most studies. The phantom (**Fig. 3**) has two regions, an outer region with model tissue parameter values similar to normal liver tissue as determined by liver spectroscopy, and an inner region with up-regulated lactate exchange. Zero mean Gaussian noise was added to the intensity images with a standard deviation of 700, and the images were then fit to the assumed model using the fmincon routine in MATLAB. The sum of squared differences (ssqd) for each parameter was calculated and normalized to the known parameter value, which provides a metric of sampling robustness. A default sampling scheme which uses a constant 10° flip angle and constant temporal spacing was compared to the optimal sampling scheme which uses flip angles and sample timings determined by the optimality criterion.

$$J_k = \frac{\partial f(p)}{\partial p_k} \quad (1)$$

$$H_{jk} = \sum_{i=1}^{N} \frac{1}{\sigma_i^2}\left[J_j(t_i)^T J_k(t_i)\right] \quad (2)$$

$$V_r = \min_{sp}\left\{\max_{tp}\left\{\sum_{j=1}^{Q}\frac{[H^{-1}]_{jj}}{p_{jr}^2}\right\}\right\} \quad (3)$$

**Results:** The digital phantom results (**Fig. 3**) show that the sum of squared difference is decreased by factors between 2 and 7 for all parameters when using an optimal sampling scheme compared to a default sampling scheme. Note that when using a variable flip angle [10] with a linear temporal spacing, the parametric SNR is improved; however it only improves by about a factor of 2, which is worse than the optimal sampling technique for all parameters.

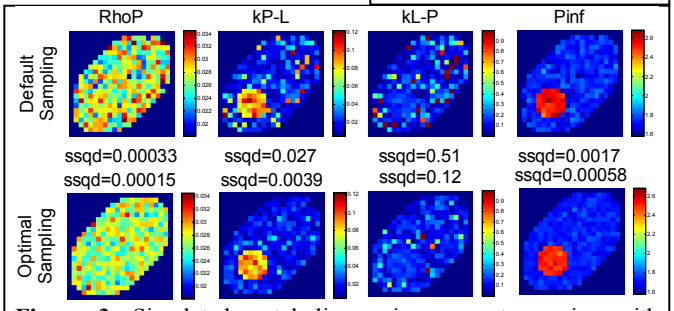


**Figure 3:** Simulated metabolism using an outer region with $\rho_P$=0.027, $k_{P-L}$=0.018, $k_{L-P}$=0.125, $P_\infty$=1.733, and an inner region with $\rho_P$=0.027, $k_{P-L}$=0.088, $k_{L-P}$=0.17, $P_\infty$=2.5. The default sampling is 30 samples between t=0 and 29 s and a flip angle of 10°. The optimal sampling over the range given above suggests samples at 0, 2.9, 13.1, 41.9 s and flip angles of 23.2, 36.6, 47.3, and 90°. Note the decreased error in the sum of squared differences, especially for the noisier k parameters.

**Discussion and Conclusion:** Our preliminary results indicate that the proposed method for sampling parameter determination is a promising technique for improving tissue parameter accuracy for dynamic hyperpolarized $^{13}C$ metabolic studies. The optimal sampling times and flip angles may be performed once, and the results of which can then be used in subsequent studies, provided the expected tissue parameters have not dramatically changed. This approach shows that by intelligently using the available magnetization by using optimal sampling times and flip angles, better parametric SNR is achieved than an approach where the signal is sampled without a priori consideration. Note that while a single RF pulse is assumed per sample, for example spectroscopy or EPSI, multiple RF pulses for imaging could be used without loss of generalization, provided they use the same amount of polarization as the single pulse.

**References:** 1. Harris, T., et al., PNAS, 2009. 2. Keshari, K.R., et al., MRM. 3. Day, S.E., et al., Nat Med, 2007. 4. Zierhut, M.L., et al., *JMR*, 2010. 5. Kettunen, M.I., et al.,*MRM*, 2010. 6. Deoni, S.C.L., et al., MRM, 2004. 7. Cercignani, M. and D.C. Alexander, *MRM*, 2006. 8. Xie, J., et al., *MRM*, 2008. 9. Kay, S.M., Prentice Hall, 1993. 10. Zhao, L., et al., J Magn Reson B, 1996.