Kinetic Modeling Framework for Hyperpolarized ^{129}Xe Chemical Exchange Saturation Transfer (HyperCEST) MRI

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ABSTRACT

Purpose: Hyperpolarized chemical exchange saturation transfer (HyperCEST) MRI using ^{129}Xe gas enables detection of signal loss from perfluorooctyl bromide nanodroplets (PFOB NDs). We developed a kinetic model for ^{129}Xe HyperCEST that enables quantitative analysis of these signals, including estimation of nanodroplet volume fraction (v_B).

Methods: In vitro HyperCEST MR spectroscopy was performed by acquiring alternating saturation measurements (CEST OFF/ON) to produce exchange-mediated signal depletion in samples of PFOB NDs (Pool B) suspended in cell media (Pool A). A two-pool kinetic model was developed to generate and fit synthetic HyperCEST signal trains. Nanodroplet geometry was incorporated using per-dataset surface-area-to-volume (S_{np}/V_{np}) ratios to compute droplet size and total surface area. Independently measured v_B values at multiple nanodroplet concentrations were used as ground-truth references for model validation. Model parameters were estimated using a nested optimization strategy: an outer nonlinear least-squares fitter solved for global permeability (P) and pool A and B relaxation rates ($R_{1,A}$, $R_{2,A}$, $R_{1,B}$, $R_{2,B}$), while inner fits estimated dataset-specific v_B by minimizing error between measured and model-generated HyperCEST signals.

Results: The global optimization converged to a set of five kinetic parameters describing exchange permeability and relaxation in pools A and B. Using these calibrated parameters, dataset-specific inner fits recovered vB values that closely matched independently measured vB. Linear regression of fitted versus measured vB demonstrated agreement (R^2=0.999), indicating accurate recovery of nanodroplet volume fraction from HyperCEST measurements.

Conclusion: We developed a kinetic modeling framework that enables accurate quantitative estimation of v_B from HyperCEST measurements. This global fitting strategy calibrates a physically constrained HyperCEST kinetic model across heterogeneous datasets by separating shared exchange and relaxation parameters from dataset-specific v_B. The agreement between fitted and independently measured v_B values supports the use of this modeling framework for in vivo applications, where direct measurement of v_B is not feasible.

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INTRODUCTION

As HyperCEST applications shift toward tracking cell-associated carriers, there is a need for quantitative models that estimate delivered agent concentration in vivo[1]. Here, we present a modeling framework that estimates perfluorocarbon nanodroplet (PFOB ND) volume fraction (v_B) from HyperCEST MRI using a two-pool exchange kinetic model incorporating saturation, relaxation, and exchange effects.

METHODS

A two-pool kinetic model was created to simulate HyperCEST signal evolution (**Figure 1**).

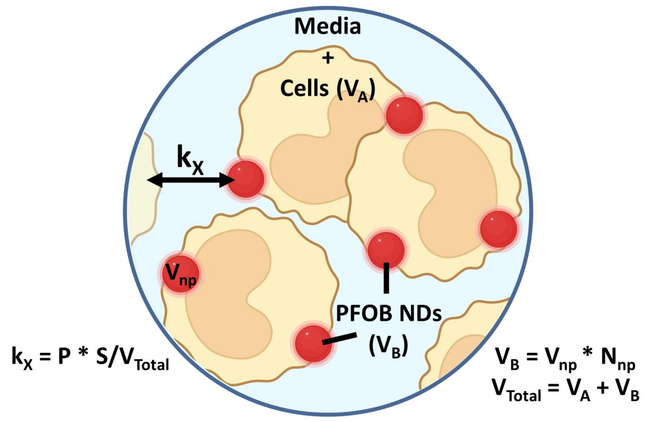

Figure 1. Two-pool kinetic model showing ^{129}Xe exchange (k_X) between dissolved-phase ^{129}Xe in media/cells (Pool A) and PFOB NDs (Pool B).

^{129}Xe exchange (k_X, 1/s) between dissolved-phase ^{129}Xe in media/cells (Pool A) and PFOB NDs (Pool B) was modeled using a permeability-based exchange rate constant:

$$k_X = P\left(\frac{S_{np}}{V_{np}}\right)v_B$$

where P (cm/s) is ^{129}Xe permeability and S_{np}/V_{np} (cm^2/cm^3) is the nanodroplet surface-area-to-volume ratio. The resulting exchange of spins between Pool A and Pool B was described by:

$$\frac{dM_A(t)}{dt} = -k_X\left(\frac{M_A(t)}{\lambda_A v_A} - \frac{M_B(t)}{\lambda_B v_B}\right)$$

$$\frac{dM_B(t)}{dt} = -k_X\left(\frac{M_B(t)}{\lambda_B v_B} - \frac{M_A(t)}{\lambda_A v_A}\right)$$

where M_A and M_B (mol/s) are ^{129}Xe spin pools and λ_A and λ_B are Ostwald solubility coefficients in Pools A and B, respectively. The exchange terms were incorporated into a two-pool Bloch-McConnell framework[2] to simulate HyperCEST signal evolution during RF saturation. Representative equations for Pool A were:

$$\frac{dM_{Ax}(t)}{dt} = -R_{2A}M_{Ax}(t) + \Delta\omega_A M_{Ay}(t) - \left(\frac{P\left(\frac{S_{np}}{V_{np}}\right)v_B}{v_A\lambda_A}\right)M_{Ax}(t) + \left(\frac{P\left(\frac{S_{np}}{V_{np}}\right)}{\lambda_B}\right)M_{Bx}(t)$$

$$\frac{dM_{Ay}(t)}{dt} = -R_{2A}M_{Ay}(t) - \Delta\omega_A M_{Ax}(t) + \omega_1 M_{Az}(t) - \left(\frac{P\left(\frac{S_{np}}{V_{np}}\right)v_B}{v_A\lambda_A}\right)M_{Ay}(t) + \left(\frac{P\left(\frac{S_{np}}{V_{np}}\right)}{\lambda_B}\right)M_{By}(t)$$

$$\frac{dM_{Az}(t)}{dt} = -R_{1A}(M_{Az}(t) - M_{A,th}) - \omega_1 M_{Ay}(t) - \left(\frac{P\left(\frac{S_{np}}{V_{np}}\right)v_B}{v_A\lambda_A}\right)M_{Az}(t) + \left(\frac{P\left(\frac{S_{np}}{V_{np}}\right)}{\lambda_B}\right)M_{Bz}(t)$$

Equivalent equations were defined for Pool B, and HyperCEST signal evolution was solved numerically using matrix exponential methods.

Global P (**Figure 2**) and relaxation parameters ($R_{1,A}$, $R_{2,A}$, $R_{1,B}$, $R_{2,B}$) were fit across all datasets, while dataset-specific v_B were independently estimated.

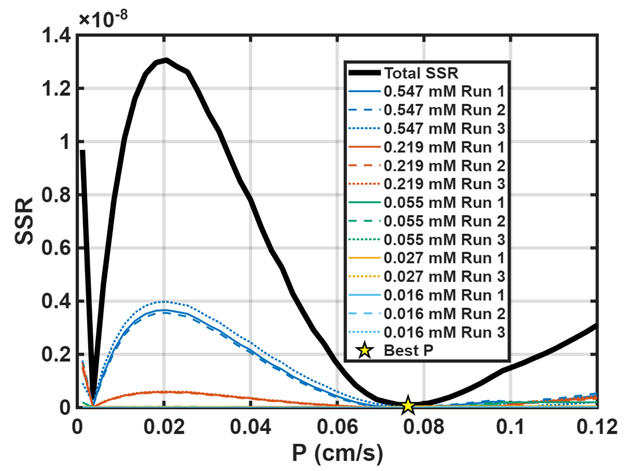

Figure 2. Global permeability (P) optimization showing the minimum SSR (gold star) identifying the optimal global permeability parameter.

RESULTS

Representative HyperCEST signal trains were well described by the model using a single globally optimized parameter set (**Figure 3**).

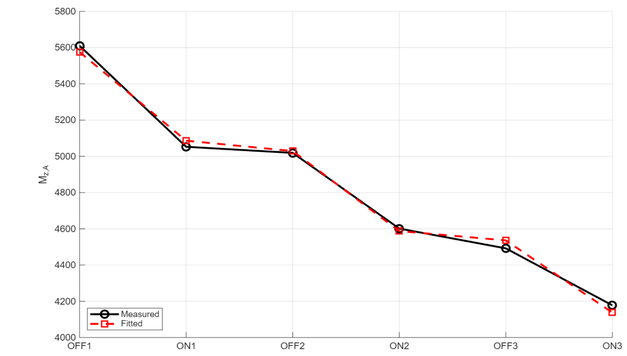

Figure 3. Modeling of HyperCEST signal evolution using globally calibrated parms.

Fitted v_B demonstrated strong agreement with independently measured ground-truth values across multiple concentrations (**Figure 4**).

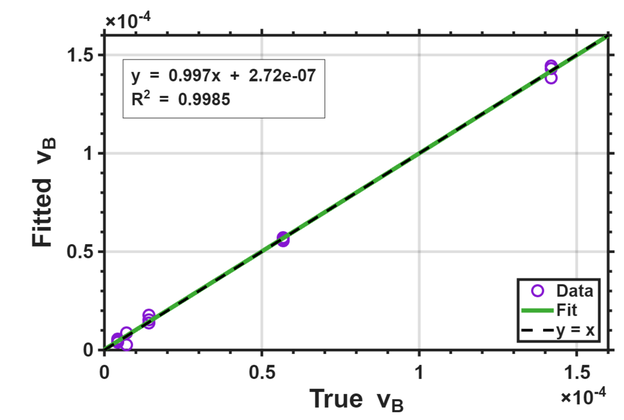

Figure 4. Accurate recovery of PFOB ND v_B across concentrations.

CONCLUSIONS

We developed a kinetic modeling framework for HyperCEST MRI that enables quantitative estimation of v_B from measured HyperCEST signal evolution. The strong agreement between fitted and independently measured v_B values supports future in vivo applications, where direct measurement of delivered PFOB ND concentration is not feasible.

REFERENCES

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