Numerical approximation to the general kinetic model for ASL quantification

Nam G. Lee1 | Ahsan Javed2 | Terrence R. Jao1 | Krishna S. Nayak2

1Department of Biomedical Engineering, University of Southern California, Los Angeles, California, USA
2Ming Hsieh Department of Electrical and Computer Engineering, University of Southern California, Los Angeles, California, USA

Purpose: To develop a numerical approximation to the general kinetic model for arterial spin labeling (ASL) quantification that will enable greater flexibility in ASL acquisition methods.

Theory: The Bloch-McConnell equations are extended to include the effects of single-compartment inflow and outflow on both the transverse and longitudinal magnetization. These can be solved using an extension of Jaynes’ matrix formalism with piecewise constant approximation of incoming labeled arterial flow and a clearance operator for outgoing venous flow.

Methods: The proposed numerical approximation is compared with the general kinetic model using simulations of pulsed labeling and pseudo-continuous labeling and a broad range of transit time and bolus duration for tissue blood flow of 0.6 mL/g/min. Accuracy of the approximation is studied as a function of the timestep using Monte-Carlo simulations. Three additional scenarios are demonstrated: (1) steady-pulsed ASL, (2) MR fingerprinting ASL, and (3) balanced SSFP and spoiled gradient-echo sequences.

Results: The proposed approximation was found to be arbitrarily accurate for pulsed labeling and pseudo-continuous labeling. The pulsed labeling/pseudo-continuous labeling approximation error compared with the general kinetic model was less than 0.002% (<0.002%) and less than 0.05% (<0.05%) for timesteps of 3 ms and 35 ms, respectively. The proposed approximation matched well with customized signal expressions of steady-pulsed ASL and MR fingerprinting ASL. The simulations of simultaneous modeling of flow, $T_2$, and magnetization transfer showed an increase in steady-state balanced SSFP and spoiled gradient signals.

Conclusion: We demonstrate a numerical approximation of the “Bloch–McConnell flow” equations that enables arbitrarily accurate modeling of pulsed ASL and pseudo-continuous labeling signals comparable to the general kinetic model. This enables increased flexibility in the experiment design for quantitative ASL.

A preliminary version of this work was presented at ISMRM 2019 (Abstract #2191).
1 | INTRODUCTION

Tissue perfusion is an important indicator of organ health that can be measured by MRI with or without contrast agents. Arterial spin labeling (ASL) is the most widely used noncontrast approach, and has been applied extensively to brain, kidney, and more recently heart. Arterial spin labeling involves labeling upstream blood using RF pulses, and then imaging tissue as it is perfused, within the relatively short window of $T_1$ relaxation.

The ASL quantification was first demonstrated using Detre’s “apparent $T_1$” approach, which combines the longitudinal component of the Bloch equations with single-compartment kinetics and derives an analytical expression for the longitudinal magnetization in the presence of flow. Buxton’s general kinetic model (GKM) reformulates Detre’s apparent $T_1$ approach as a convolution problem without requiring the Bloch equations, under a general setting in which the transit delay and bolus duration are taken into account. The GKM is used widely because it is simple, analytical, and provides excellent intuition into signal formation. However, it is nontrivial for GKM to model the effects of flow with magnetization transfer (MT), $T_2$ effects, off-resonance, and irregular timing of labeling.

Many previous approaches in ASL have generalized the Bloch equations to include transit delay and bolus duration, MT effects, water exchange, and dispersion. However, all approaches tried to generalize only the longitudinal component of the Bloch equations; therefore, simultaneous modeling of flow with $T_2$ effects and off-resonance has not been demonstrated.

Unlike the approaches in ASL, the full Bloch equations (containing both transverse and longitudinal magnetization) have been extended with additional terms to model the physical phenomenon of interest. Examples include the Bloch–Torrey equations for diffusion and velocity, and the Bloch-McConnell equations for MT and CEST. These modified Bloch equations are efficiently solved with a variant of propagator approaches (ie. matrix formalism). Inspired by its great flexibility to model various effects, this work seeks to develop a framework based on matrix formalism that can simultaneously model the effects of flow with the aforementioned effects. We extend the Bloch equations with MT effects (a binary spin-bath model) by adding single-compartment inflow and outflow terms. We denote these as “Bloch–McConnell flow” (BMF) equations.

To solve the BMF equations, we derive an extension of Jaynes’ matrix formalism with two approximations. This approach retains the advantages of Jaynes’ matrix formalism, such as the ability to include off-resonance, the slice excitation profile, and $B_1$ transmit ($B_1^T$) inhomogeneity. This numerical approach is particularly attractive for ASL scenarios that have been cumbersome for existing GKM-based approaches, such as irregular timing of labeling, transient-state signal evolutions such as balanced SSFP (bSSFP) steady-pulsed ASL (spASL) and MR fingerprinting ASL (MRF-ASL).

We first present the proposed BMF equations, and then the extended matrix formalism with numerical approximation. We demonstrate that accuracy depends on the timestep used for updating magnetization states. The numeric approximation is validated against GKM for the case of single-compartment kinetics with pulsed labeling and pseudo-continuous labeling. Monte-Carlo simulations are then used to investigate the effect of the timestep on the accuracy of a numeric approximation compared with GKM. The flexibility of this approach is demonstrated using two nonstandard ASL pulse sequences. For each sequence our approach was validated against the existing quantification models.

2 | THEORY

2.1 | Bloch flow equations

For simplicity, we assume single-compartment kinetics, instantaneous mixing between arterial blood water and tissue, and only the longitudinal magnetization of inflowing arterial blood is modified. For tissue magnetization $M(t) = [M_x(t), M_y(t), M_z(t)]^T$ under perfusion, the proposed Bloch flow equations (in the rotating frame) model the effects of incoming arterial flow (constant unlabeled and time-varying labeled longitudinal magnetization) and outgoing venous flow on the transverse and longitudinal magnetization as follows:

$$\frac{dM(t)}{dt} = M(t) \times \gamma B(t) - \frac{M(t) + M(0)}{T_1} + \frac{(M_0 - M(t)) k}{T_1}$$

$$+ \left( \frac{k}{\lambda} M_0 + s(t) \right) \bar{k} - \frac{k}{\lambda} \left[ M_x(t) \bar{i} + M_y(t) \bar{j} + M_z(t) \bar{k} \right],$$

(1)

where $M_0$ is the equilibrium magnetization per gram of tissue; $F$ is the perfusion in milliliters of blood per gram of tissue per minute; $\lambda$ is the tissue-blood partition coefficient in milliliters of blood per gram of tissue; and $s(t)$ refers to the ASL bolus signal. Note that the model implicitly assumes $M_0^{blood} = M_0^{tissue} / \lambda$.

Equation 1 can be expressed in matrix-vector notation as follows:
The Bloch Flow equations possess three additional features compared with the original Bloch equations: (1) The clearance of transverse and longitudinal magnetization by venous flow is present in the main diagonal and forms apparent $T_2$ and $T_1$ relaxation times for transverse and longitudinal magnetization, respectively; (2) unlabeled arterial blood is constantly added to the longitudinal magnetization, creating a blood flow–dependent equilibrium magnetization; and (3) time-varying labeled arterial blood decreases the longitudinal magnetization and creates a time-dependent equilibrium magnetization (note that $s(t)$ has the negative sign).

The theory is applicable for different labeling patterns and methods. We assume a perfectly rectangular bolus of arterial blood for pulsed ASL (PASL). The ASL bolus signal is defined differently for PASL and continuous ASL (CASL)/pseudo-continuous ASL (PCASL):

\[
PASL: \quad s(t) = \sum_{i=1}^{M} \frac{F_0}{\lambda} M_0 a_0 e^{-t-\tau_{i}}/T_{1b} - u(t-T_{D,i}) - u(t-T_{D,i} - T_{W,i})\]  

\[\text{(3a)}\]

\[
CASL/(PCASL): \quad s(t) = -\frac{F_0}{\lambda} M_0 a_0 e^{-t/T_{1b}} \times (u(t-T_{D,i}) - u(t-T_{D,i} - T_{W,i}))\]  

\[\text{(3b)}\]

where $M$ is the number of labeling pulses; $\tau_{i}$ is the application of the $i$th labeling; $a_0$ is the labeling efficiency (1 for saturation, 2 for inversion, 0 for control); $T_{1b}$ is the longitudinal relaxation time of arterial blood; $u(t)$ is the Heaviside step function; $T_{D,i}$ is the arterial transit time in seconds; and $T_{W,i}$ is the bolus duration in seconds. In general, the ASL bolus signal $s(t)$ can be obtained from either an analytical expression or a numerical computation (eg. dispersion\textsuperscript{19,21}) as long as it can be evaluated at a particular time $t$.

### 2.2 Bloch–McConnell Flow equations

The Bloch flow equations can be further extended to include MT effects. The binary spin-bath MT model\textsuperscript{30,31} divides tissue magnetization between a liquid pool $(f)$ of free water and a semisolid pool $(s)$ of protons bound to macromolecules, and neglects net exchange of transverse magnetization due to a very short transverse relaxation time of the semisolid pool ($T_2^s \approx 10$ ms).\textsuperscript{38} Following previous approaches,\textsuperscript{11,13,39} we assume that blood water spins exchange only with the liquid pool of tissue magnetization. For free water and semisolid pool protons $M(t) = [M'_f(t), M'_l(t), M''_l(t), M''_s(t)]^T$ under perfusion, the BMF equations are then written as

\[
\frac{dM(t)}{dt} = (\Omega(t) + \Lambda + \Gamma + \Xi) M(t) + D(t), \quad \text{(4)}
\]

where

\[
\Omega(t) = \begin{bmatrix}
0 & \gamma G(t) \cdot r + 2\pi \Delta f & -\gamma B_{1,y}(t) & 0 \\
(\gamma G(t) \cdot r + 2\pi \Delta f) & 0 & \gamma B_{1,x}(t) & 0 \\
0 & -\gamma B_{1,x}(t) & 0 & 0 \\
0 & 0 & 0 & -W(\Delta(t), t)
\end{bmatrix},
\]

\[
\Lambda = \begin{bmatrix}
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & -k^f & k^s & 0 \\
0 & 0 & k^s & -k^f
\end{bmatrix},
\]

\[
\Gamma = \begin{bmatrix}
-\frac{F_0}{\lambda} & 0 & 0 & 0 \\
0 & -\frac{F_0}{\lambda} & 0 & 0 \\
0 & 0 & -\frac{F_0}{\lambda} & 0 \\
0 & 0 & 0 & -\frac{F_0}{\lambda}
\end{bmatrix},
\]

\[
\Xi = \begin{bmatrix}
0 & 0 & 0 & 0 \\
0 & -\frac{1}{T_2^f} & 0 & 0 \\
0 & 0 & -\frac{1}{T_1^f} & 0 \\
0 & 0 & 0 & -\frac{1}{T_1^f}
\end{bmatrix},
\]

and

\[
D(t) = \begin{bmatrix}
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
\left(\frac{1}{T_1^s} + \frac{F_0}{\lambda}\right) M'_s + s(t) & 0 & 0 & 0 \\
\frac{1}{T_1^s} M'_s & 0 & 0 & 0
\end{bmatrix}.
\]
where matrix $\Omega(t)$ describes evolution due to gradients, off-resonance (no separate free precession operator), and RF pulses; $A$ describes evolution due to exchange; $G$ describes evolution due to the clearance of transverse and longitudinal magnetization by venous flow; $Z$ describes evolution due to relaxation; $D(t)$ is the time-dependent equilibrium magnetization; $M_0^f$ and $M_0^s$ denote the equilibrium magnetizations for the liquid and semisolid pools, respectively; $k^f$ and $k^s$ refer to forward ($f \rightarrow s$) and reverse ($s \rightarrow f$) exchange rates between two compartments in $\text{sec}^{-1}$; and the fundamental rate constant $k$ relates them by $k = k^f/M_0^s = k^s/M_0^f$. The semisolid pool fraction $f$ is denoted as $f = M_0^s/M_0^f$ and relates forward and reverse exchange rates by $k^s = k^f/f$. The instantaneous saturation rate $W(\Delta(t), t)$ describes the effects of pulsed irradiation (frequency offset $\Delta$) on the longitudinal magnetization of the semisolid protons and is defined as $W(\Delta(t), t) = \pi f^2 ||B_1(t)||^2 G(\Delta(t), T_2'')$ in rad/sec, where $G(\Delta(t), T_2'')$ is the absorption lineshape of the semisolid pool in seconds, and $\Delta(t) \equiv \Delta_{\text{offset}} = (\gamma G(t) \cdot \mathbf{r} + 2\pi \Delta f)$. The adjusted time-dependent frequency offset $\Delta_{\text{offset}}$ accounts for local field shifts by gradient fields and off-resonance on the absorption response.

### 2.3 Extended matrix formalism

The Bloch equations can be solved efficiently using Jaynes' matrix formalism. Here we derive evolution operators for the BMF equations. We assume that the duration of a signal evolution is divided into $N$ timesteps, and each timestep is associated with an RF pulse ($x$ and $y$ components) ($B_i$), gradient ($G_i$), start time ($t_i$), measurement time ($\xi_i$), and duration ($\tau_i$) of the timestep. Assuming a piecewise constant RF pulse and $G(t)$ over each timestep, the magnetization evolves due to gradients and RF pulses as $M(t_i + \tau_i) = R_i M(t_i)$ where $R_i = \exp(\Omega(t_i) \cdot \tau_i)$. This operator $R_i$ consists of a rotation matrix $R_i(\mathbf{u}_i, \theta_i)$ about the axis $\mathbf{u}_i = [u_x, u_y, u_z]^T$ of an angle $\theta_i$ for the free water and a saturation term for the semisolid pool:

$$R_i = \begin{bmatrix} R_i(\mathbf{u}_i, \theta_i) & 0 \\ 0 & \exp(-W(\Delta(t_i), t_i) \cdot \tau_i) \end{bmatrix},$$

where

$$R_i(\mathbf{u}_i, \theta_i) = \begin{bmatrix} \cos \theta_i + u_x^2 (1 - \cos \theta_i) & -u_y u_x (1 - \cos \theta_i) + u_z \sin \theta_i \\ -u_x u_y (1 - \cos \theta_i) + u_z \sin \theta_i & \cos \theta_i + u_y^2 (1 - \cos \theta_i) \\ -u_x u_z (1 - \cos \theta_i) - u_y \sin \theta_i & u_z u_y (1 - \cos \theta_i) - u_x \sin \theta_i \end{bmatrix}.$$

Using a piecewise constant approximation of $s(t)$ over duration $\tau_i$, that is, $D(t) = D(t_i)$ for $t_i \leq t \leq t_i + \tau_i$, and this formula $\int_{t_i}^{t_i + \tau_i} e^{\lambda \mathbf{A} + \mathbf{X} \mathbf{E} \tau_i} \cdot M(t) \cdot e^{\lambda \mathbf{A} + \mathbf{X} \mathbf{E} \tau_i} = e^{\lambda \mathbf{A} + \mathbf{X} \mathbf{E} \tau_i} \cdot \mathbf{M}(t_i)$, we simplify the integral equation and obtain a closed-form expression as follows:

$$M(t_i + \tau_i) = e^{(\mathbf{A} + \mathbf{X} \mathbf{E} \tau_i)} \cdot M(t_i) + \int_{t_i}^{t_i + \tau_i} e^{(\mathbf{A} + \mathbf{X} \mathbf{E} \tau_i)} \cdot D(t) \cdot d\tau.$$

With the second approximation that relaxation and exchange can be decoupled, we get $\exp((\mathbf{A} + \mathbf{X} \mathbf{E} \tau_i)) \equiv \exp(\mathbf{A} \tau_i) \cdot \exp(\mathbf{X} \mathbf{E} \tau_i) = \mathbf{A}(\tau_i) \cdot \mathbf{C}(\tau_i) \cdot \mathbf{E}(\tau_i)$, where exchange $\mathbf{A}(\tau_i)$, clearance $\mathbf{C}(\tau_i)$, and relaxation $\mathbf{E}(\tau_i)$ operators are defined as

$$\mathbf{A}(\tau_i) = \begin{bmatrix} f + 1 & 0 & 0 \\ 0 & f + 1 & 0 \\ 0 & 0 & f + \exp(-f + 1) \cdot k^f \tau_i) \end{bmatrix}, \quad \mathbf{C}(\tau_i) = \begin{bmatrix} e^{-\tau_i F/\lambda} & 0 & 0 \\ 0 & e^{-\tau_i F/\lambda} & 0 \\ 0 & 0 & e^{-\tau_i F/\lambda} \end{bmatrix}, \quad \text{and} \quad \mathbf{E}(\tau_i) = \begin{bmatrix} e^{-\tau_i F/\lambda} & 0 & 0 \\ 0 & e^{-\tau_i F/\lambda} & 0 \\ 0 & 0 & e^{-\tau_i F/\lambda} \end{bmatrix}.$$
Therefore, the temporal evolution in the absence of RF for the BMF equations can be approximated as

\[ M(t_i + \tau) = A(\tau_i) C(\tau_i) E(\tau_i) M(t_i) + (1 - A(\tau_i) C(\tau_i) E(\tau_i)) s(\tau_i) T_{app} \]

where \( T_{app} = 1/T_1 + F/\lambda \) is the apparent \( T_1 \) relaxation time for the (liquid pool) longitudinal magnetization. Note that with the first approximation, the amount of labeled blood over a timestep is estimated by multiplying the ASL bolus signal \( s(t) \) at the start time \( t_i \) of the \( i \)th timestep with duration \( \tau_i \) (see Figure 1). This approximation is valid, provided that the \( T_1 \) decay of labeled blood is slow (or negligible) over the duration of each timestep. For the BMF equations without MT effects (Bloch flow equations), we do not need the second approximation, as \( \Gamma E = \Xi T \). The temporal evolution in the absence of RF for the Bloch flow equations can be obtained by setting \( M'_0 = 0, k' = 0, k'' = 0, A(\tau_i) = I \) in Equation 10. Note also that without considering MT effects, for each timestep the liquid pool protons (tissue water) relax with a new time-dependent pseudo-equilibrium magnetization as follows: \( M'_0 + s(t_i) T_{app} \)

Using the extended matrix formalism, the magnetizations in the \( i \)th timestep of Figure 1 can be expressed as follows:

**Initialization:** \( M_b[i] = M_d[i-1] \) \hspace{1cm} (12)

**RF excitation:** \( M_b[i] = R(M_d[i]) \) \hspace{1cm} (13)

The magnetization vector \( M_b[i] \) at \( \xi_i \) for each timestep is

\[ M_c[i] = A(\xi_i) C(\xi_i) E(\xi_i) M_b[i] + (1 - A(\xi_i) C(\xi_i) E(\xi_i)) \left[ 0, 0, \ldots, (M'_0 + s(t_i) T_{app}) \right]^T \]

\[ M_d[i] = A(\tau_i - \xi_i) C(\tau_i - \xi_i) E(\tau_i - \xi_i) M_c[i] + (1 - A(\tau_i - \xi_i) C(\tau_i - \xi_i) E(\tau_i - \xi_i)) \left[ 0, 0, \ldots, (M'_0 + s(t_i) T_{app}) \right]^T \]

**FIGURE 1** Illustration of the Bloch simulation with flow effects. The extended matrix formalism is demonstrated over a few timesteps. The \( T_1 \) decay of labeled arterial blood (green) over each timestep is exaggerated. The symbols \( u, \theta, t, \xi, t_i \) and \( \xi_i \) indicate the rotation axis, rotation angle, start time, measurement time, and duration for the \( i \)th timestep. Using a piecewise constant approximation, the actual amount of labeled blood over the \( i \)th timestep of duration \( \tau_i \) (green) is overestimated by the area of a rectangle (dashed red box). During each timestep, tissue magnetization relaxes with a new pseudo \( M_0 \) term: \( M_0 + s(t_i) T_{app} \). The magnetization of the previous timestep \( M_d[i-1] \) is set to the initial magnetization \( M_b[i] \) for the \( i \)th timestep (black arrow). The \( i \)th RF excitation yields \( M_b[i] \) (blue arrow), and \( M_d[i] \) is obtained after subsequent applications of relaxation, clearance, and exchange operators. This figure indicates the flexibility of the extended matrix formalism, in which each timestep can have varying parameters.
$T_D = 700\,\text{ms}, T_W = 800/1800\,\text{ms},$ and $\alpha$ (labeling efficiency) = 0.98/0.85. When MT effects are not considered, superscripts are omitted. Simulation parameters for a typical gray-matter voxel were $F = 0.6\,\text{mL/g/min}, T_f/T_{1b} = 1200/1650\,\text{ms}, M_0 = 1, \lambda = 0.9,$ and $a_0 = 2\alpha$ (inversion).

For both labeling methods, the labeling pulse was applied at 0 seconds. The duration of signal evolution was 4 seconds. The number of timesteps was calculated as $N = T/T',$ where $T$ is the total duration and $T'$ is the timestep used for numeric approximation. The ASL signals were calculated with two timesteps: $T' = 3\,\text{ms}$ and $T' = 35\,\text{ms}.$ The shorter timestep, 3 ms, was chosen based on its use as the imaging TR in cardiac ASL.42 The longer timestep, 35 ms, was chosen based on its use as the imaging TR in MRF-ASL.37

For the numeric approximation, control and label signals without and with labeling were first calculated at measurement times $\{\xi_i\}_{i=1}^N = \{\tau_i\}_{i=1}^N = \tau$: then, a difference between these signals was set to the PASL/PCASL signal. For GKM, PASL and PCASL signals were calculated by evaluating Equations 3 and 5 of Buxton et al.6 respectively.

3.2 | Numerical accuracy

We investigated the effect of the timestep ($\tau$) on the accuracy of the approximation. We tested 500 timesteps linearly spaced from 0 ms to 50 ms in increments of 0.1 ms. The ASL signals with inversion labeling were generated with GKM (denoted as $\Delta M_{GKM}(t)$) and the numeric approximation (denoted as $\Delta M_{numeric}(t)$) while sweeping parameters for transit delay $T_D$ and bolus duration $T_W.$ The range of each parameter and fixed parameters were adapted from the recent consensus paper1 and listed in Supporting Information Table S1. The accuracy of the numeric approximation was assessed using two metrics: (1) overall normalized RMS error (NRMSE) = $\|\Delta M_{GKM}(t) - \Delta M_{numeric}(t)\|_2 / \|\Delta M_{GKM}(t)\|_2,$ and (2) maximum deviation between GKM and the numeric approximation (max deviation) = $\max |\Delta M_{GKM}(t) - \Delta M_{numeric}(t)|$.

Blood flow $F$ was not chosen as a sweeping parameter, because a change in blood flow does not affect the NRMSE but linearly affects the max deviation. Simulations of two perfusion values (0.3 mL/g/min and 0.6 mL/g/min) for gray matter were performed. The effects of a change in spin-lattice

![Figure 2](https://example.com/figure2.png)

**FIGURE 2** Comparison of simulated pulsed arterial spin labeling (PASL) and pseudo-continuous arterial spin labeling (PCASL) signals obtained with Buxton’s general kinetic model (GKM) and the proposed numeric approximation (numeric). Simulation parameters for PASL/PCASL are $F = 0.6\,\text{mL/g/min}, T_f = 700\,\text{ms}, T_W = 800/1800\,\text{ms}, T_f/T_{1b} = 1820/1650\,\text{ms}, M_0 = 1, \lambda = 0.9, \alpha$ (labeling efficiency $(PASL/PCASL) = 0.98/0.85,$ and $a_0 = 2\alpha$ (inversion). The PASL signals are calculated with single RF labeling and a fixed timestep of $\tau = 3$ (A) and $\tau = 35$ ms (B). The PCASL signals are calculated with a fixed timestep of $\tau = 3$ (C) and $\tau = 35$ ms (D). Gray bars indicate application of RF labeling. The signal differences between the GKM and the numeric approximation are shown in the second row (E-H). In case of $\tau$ less than or equal to 35 ms, the maximum signal difference was always less than 0.06% for both labeling methods.
relaxation $T_1$ on the two metrics are negligible; therefore, spin-lattice relaxation $T_1$ was omitted.

### 3.3 Numerical validation against spASL and MRF-ASL

To demonstrate the generality of the framework to various unconventional sequences, we validated the numeric approximation without MT effects against the customized signal expressions of spASL$^{34,35,43}$ and MRF-ASL.$^{36}$ Each sequence’s own customized signal expression is analytically derived with GKM and described in a respective reference in detail.

For spASL, theoretical signal evolutions in Figure 1 of Capron et al$^{34}$ were reproduced using the numeric approximation with $TR = \tau = 10$ ms. A spASL pulse sequence consists of four phases: imaging during label, recovery, imaging during control, and recovery. The duration of an acquisition phase is denoted as “tp” and the recovery delay as “RD.” These four phases are repeated for N lines (number of k-space lines). Four spASL simulations of the mouse heart with different imaging parameters (N lines, tp, and RD) were performed assuming no transit delay and $T_1$ relaxation of arterial magnetization. Other fixed parameters were $T_1 = 1400$ ms, $\theta = 8^\circ$, $F = 6$ mL/g/min, $\lambda = 0.95$, and $a_0 = 2\beta = 1$ (saturation). The numeric approximation incorporates perfect spoiling at the end of TR to simulate FLASH readouts.

For MRF-ASL, a simulation study of Su et al$^{36}$ was reproduced with $\tau = 1$ ms. An MRF-ASL pulse sequence consists of randomly ordered control and label scans, each consisting of a period of pulsed labeling and an acquisition without a post-labeling delay. We used 30 TRs (a total of 30 scans) for a clear illustration of signal evolutions. A labeling duration time series was generated with a half-cycle cosine function gradually decreasing from 450 ms to 72 ms. A pseudo-randomized order of label and control was used. Other fixed parameters were $\theta = 40^\circ$, $F = 0.6$ mL/g/min, $T_D/T_1/T_{1b} = 1000/1200/1650$ ms, $M_0 = 1$, $\lambda = 0.9$, and $a_0 = 2\alpha = 2$ (inversion). A single-compartment model consisting of a tissue compartment without a pass-through artery compartment was used for both GKM and the numeric approximation. The $T_2$ decay of transverse magnetization was not considered when deriving theoretical signal evolutions with GKM. Off-resonance ($\Delta f = 30$ Hz) and $T_2$ effects ($T_2 = 80$ ms) were simulated with the numeric approximation.

**FIGURE 3** Performance of the proposed approximation depends on the timestep used. Here, we plot normalized RMS error (NRMSE), maximum deviation (max deviation), and computation time as a function of timestep (τ, x-axis). Each plot shows the mean (line) ± 1 SD (shaded area). A, The NRMSE for PASL. B, The NRMSE for PCASL. C, The max deviation between GKM and the proposed numeric approximation for PASL. D, The max deviation between GKM and the proposed numeric approximation for PCASL. E, Computation time for PASL. F, Computation time for PCASL. Simulation parameters for both labeling methods are listed in Supporting Information Table S1
3.4 | Modeling flow and MT effects in bSSFP and SPGR

We demonstrated simultaneous modeling of flow, $T_2$, and MT effects in simulations using steady-state imaging sequences: bSSFP$^{29,44}$ and SPGR.$^{45}$ Steady-state bSSFP and SPGR signals were obtained at flip angles from 1° to 80° in increments of 1°. We assumed instantaneous RF rotation; therefore, the mean saturation rate averaged over TR was used.$^{8,40,41}$ Signals for four cases were generated: (1) no MT, no flow; (2) no MT, flow; (3) MT, no flow; and (4) MT, flow. The second approximation was compared with the exact evaluation (ie. matrix exponential). Simulation parameters (white matter at 1.5 T) were obtained from Gloor et al$^{29}$: $M_0^f = 1$, $T_1^f = 585$ ms, $T_2^f = 81$ ms, $f = 0.157$, $k = 4.45$, $T_s^1 = 1000$ ms, $T_s^2 = 12 \mu$s, $G = 14 \mu$s, $F = 4$ mL/g/min, $\lambda = 0.9$, and $\tau = 4 \mu$sec; for bSSFP, pulse duration = 230 $\mu$s, TR = 2.92 ms, and TE = TR/2; and for SPGR, pulse duration = 200 $\mu$s, TR = 5 ms, and TE = TR/2.

4 | RESULTS

Figure 2 compares the PASL and PCASL signals obtained with GKM and the numeric approximation using fixed timesteps of 3 ms and 35 ms. For timesteps of 3 ms and 35 ms, the maximum deviations between GKM and the numeric approximation were 0.002% and 0.05% for PASL (Figure 2E,F), and 0.002% and 0.042% for PCASL (Figure 2G,H), respectively.

Figure 3 shows the NRMSE, maximum deviation, and computation time as a function of the timestep (mean ± 1 SD) for PASL and PCASL with tissue blood flow of 0.6 mL/g/min (see Supporting Information Figure S1 for tissue blood flow of 0.3 mL/g/min). For both labeling methods, the NRMSE increased approximately linearly with respect to timestep (Figure 3A,B). The max deviation also increased linearly with respect to timestep (Figure 3C,D). The mean ($\sigma$) and SD ($\mu$) of the max deviation increased linearly with respect to tissue blood flow, but the coefficient of variation

![Comparison of theoretical signal evolutions for steady-pulsed arterial spin labeling (spASL) obtained with a customized signal expression (cine-ASL) and the proposed numeric approximation (numeric). Figure 1 of Capron et al$^{34}$ is reproduced. The figure shows signal evolutions over six (N lines) repetitions of four phases: imaging during label, recovery, imaging during control, and recovery. Signal evolutions for four different imaging parameters (RD, $t_p$) are shown: short RD = 0.01 seconds, short $t_p = 0.26$ seconds (A); short RD = 0.01 seconds, long $t_p = 3.12$ seconds (B); long RD = 3.50 seconds, short $t_p = 0.26$ seconds (C); and long RD = 0.01 seconds, long $t_p = 3.12$ seconds (D).](image-url)
FIGURE 5  Comparison of MR fingerprinting arterial spin labeling (MRF-ASL) signal evolutions obtained with a customized signal expression based on GKM (GKM) and the proposed numeric approximation (numeric). First row: A labeling time series consists of a pseudo-randomized order of label (red) and control (blue) scans. The horizontal axis represents the duration of a scan (in milliseconds). The duration of excitation and acquisition is neglected. The longitudinal (second row) and transverse (third row) components of MRF-ASL signal evolutions are obtained without magnetization transfer effects for both GKM and the numeric approximation. Green regions indicate “Label.” The numeric approximation calculated without $T_2$ effects and off-resonance shows excellent agreement with GKM (fourth row). The numeric approach can provide more realistic signal evolutions with $T_2$ effects (black) and with $T_2$ effects and off-resonance (orange). For short labeling duration ($\leq 3$ $T_2$), the transverse magnetization is not completely decayed to zero and starts to affect the longitudinal magnetization of an MRF-ASL signal evolution. When a spoiling gradient is used after each acquisition to dephase transverse magnetization, $T_2$ effects would not be a concern, and the numerical simulation results would be consistent with that from GKM.
(CV = σ/μ × 100%) remained the same (Figure 3C and Supporting Information Figure S1C). The linear slope of the NRMSE for PASL was higher than that for PCASL. A larger SD in the NRMSE for PASL was observed compared with PCASL. The linear slope of the maximum deviation for PASL was lower than that for PCASL, while a similar SD was observed for both labeling methods. For 1 ms and 35 ms, the mean computation times were 4.60 ms and 0.14 ms for PASL, and 4.42 ms and 0.14 ms for PCASL, respectively.

Figure 4 compares the theoretical signal evolutions for spASL obtained with a customized signal expression and the numeric approximation. This example demonstrates that the numeric approximation can model the effects of flow under imaging RF pulses. For all cases, the maximum signal difference was less than 0.97%.

Figure 5 compares the MRF-ASL signal evolutions obtained with GKM and the numeric approximation. The numeric approximation shows excellent agreement with GKM with a maximum signal difference of 0.002%. The numeric approximation deviates from GKM when $T_2$ effects and off-resonance are modeled. When a spoiling gradient is used after each acquisition to dephase transverse magnetization, $T_2$ effects would not be a concern, and the numerical simulation results would be consistent with that from GKM.

Supporting Information Figure S2 shows steady-state bSSFP and SPGR signals for white matter at 1.5 T calculated for four combinations of MT and flow effects. The constant unlabeled inflow causes an increase in both steady-state bSSFP and SPGR signals. Signals obtained with the second approximation show excellent agreement with those obtained with exact evaluation. This justifies the use of the second approximation to replace computationally expensive evaluation of the matrix exponential.

5 | DISCUSSION

We have demonstrated a numerical approximation to the general kinetic model for ASL quantification. We have also characterized the tradeoff between accuracy and computation time, through the selection of the timing interval. This numeric approximation is first validated against GKM for PASL and PCASL, and further validated against customized signal expressions of nonstandard ASL pulse sequences, spASL and MRF-ASL. The numerical approach provides an excellent approximation to GKM as long as the timestep is sufficiently small (Figures 2 and 3). The important feature of the numerical approach is the piecewise constant approximation of blood inflow between excitation “i” and “i + 1.” As the distance between consecutive excitations becomes longer, the error in the estimation of the amount of labeled blood increases.

One advantage of the proposed approach is that both transient-state and steady-state signal evolutions can be generated in the presence of flow, $T_2$ effects, off-resonance, MT effects, and irregular timing of RF labeling. This key feature (1) makes it applicable to highly challenging ASL scenarios, including cardiac ASL, which suffers from irregular timing due to electrocardiographic gating and heart variability, and (2) enables more flexible and irregular quantitative ASL experiments such as recent attempts at MRF-ASL. Another advantage of the proposed approach is that dispersion effects can be easily incorporated, because $s(t)$ can be numerical functions.

There are several possible extensions to this work. Although we demonstrate simultaneous modeling of MT effects and ASL perfusion in simulation studies, experimental verification still remain. For nonbalanced gradient-echo sequences, signal evolutions can be efficiently predicted using the extended phase graph framework instead of time-intensive isochromat-based Bloch simulations. Incorporating the proposed modeling approach to the extended phase graph framework could provide time-efficient computation of ASL signal evolutions for a broad range of pulse sequences. Recent progress in MRF-ASL might also benefit from this work, particularly (and interestingly) those using deep learning approaches. The proposed numerical approximation with matrix formalism can potentially be combined with deep learning to further improve quantification of flow.

6 | CONCLUSIONS

We demonstrate and validate an extension to the Bloch equations, termed Bloch–McConnell flow equations, which can simultaneously model the effects of flow with various other effects. We also demonstrate and validate an extension to Jaynes’ matrix formalism to provide a numeric approximation to these BMF equations. In simulation, the proposed approach provides an arbitrarily accurate approximation to the GKM. A single timestep tuning parameter allows one to tradeoff accuracy for computational speed. The proposed approach will enable quantification of transient-state ASL and ASL with irregular timing of RF labeling and/or severe off-resonance, which are challenging for current techniques.

DATA AVAILABILITY STATEMENT

The code and data that support the findings of this study are openly available in GitHub at https://www.github.com/usc-mrel/Bloch_Flow_MT.
REFERENCES


SUPPORTING INFORMATION
Additional Supporting Information may be found online in the Supporting Information section.

FIGURE S1 Performance of the proposed approximation for tissue blood flow of 0.3 mL/g/min. (a) NRMSE for PASL. (b) NRMSE for PCASL. (c) Max deviation between GKM and the proposed numeric approximation for PASL. (d) Max deviation between GKM and the proposed numeric approximation for PCASL. (e) Computation time for PASL. (f) Computation time for PCASL

FIGURE S2 Simulations of steady-state (left) bSSFP and (right) SPGR signals for white matter at 1.5T obtained (blue) without MT and flow effects, (red) without MT and with flow effects, (orange) with MT and without flow effects, and (purple) with both MT and flow effects. Lines and dots indicate steady-state signals calculated without (Exact) and with (Approx.) the second approximation, respectively

TABLE S1 Simulation parameters for Figure 3

How to cite this article: Lee NG, Javed A, Jao TR, Nayak KS. Numerical approximation to the general kinetic model for ASL quantification. Magn Reson Med. 2020;84:2846–2857. https://doi.org/10.1002/mrm.28304