

Using Adaptive Imaging Parameters to Improve PEGylated Ultrasmall Iron Oxide Nanoparticles-Enhanced Magnetic Resonance Angiography

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The PEGylated ultrasmall iron oxide nanoparticles (PUSIONPs) exhibit longer blood residence time and better biodegradability than conventional gadolinium-based contrast agents (GBCAs), enabling prolonged acquisitions in contrast-enhanced magnetic resonance angiography (CE-MRA) applications. The image quality of CE-MRA is dependent on the contrast agent concentration and the parameters of the pulse sequences. Here, a closed-form mathematical model is demonstrated and validated to automatically optimize the concentration, echo time (TE), repetition time (TR) and flip angle (FA). The pharmacokinetic studies are performed to estimate the dynamic intravascular concentrations within 12 h postinjection, and the adaptive concentration-dependent sequence parameters are determined to achieve optimal signal enhancement during a prolonged measurement window. The presented model is tested on phantom and in vivo rat images acquired from a 3T scanner. Imaging results demonstrate excellent agreement between experimental measurements and theoretical predictions, and the adaptive sequence parameters obtain better signal enhancement than the fixed ones. The low-dose PUSIONPs ($0.03 \text{ mmol kg}^{-1}$ and $0.05 \text{ mmol kg}^{-1}$) give a comparable signal intensity to the high-dose one ($0.10 \text{ mmol kg}^{-1}$) within 2 h postinjection. The presented mathematical model provides guidance for the optimization of the concentration and sequence parameters in PUSIONPs-enhanced MRA, and has great potential for further clinical translation.

1. Introduction

Contrast-enhanced magnetic resonance angiography (CE-MRA) has achieved promising success in the early prevention and effective treatment of vascular-related diseases. Long-term CE-MRA is apparently advantageous for the diagnosis and prognosis of various vascular diseases, such as stroke, myocardial infarction, and aortic dissection, by offering real-time and dynamic vascular information.^[1] Gadolinium-based contrast agents (GBCAs) are the most commonly used compounds in T_1 -weighted CE-MRA.^[2] However, recent studies warned that such GBCAs may cause nephrogenic system fibrosis and brain lesions in patients with kidney or liver conditions.^[3] In addition, the pharmacokinetic properties show that the concentration after the intravascular injection will drop rapidly due to the fast renal excretion, which may potentially require multiple contrast agent administrations and thus increase the risk of toxicity.^[4] Recently, ultrasmall superparamagnetic iron oxide nanoparticles (USIONPs, e.g., Fe_3O_4 nanoparticles) have shown great

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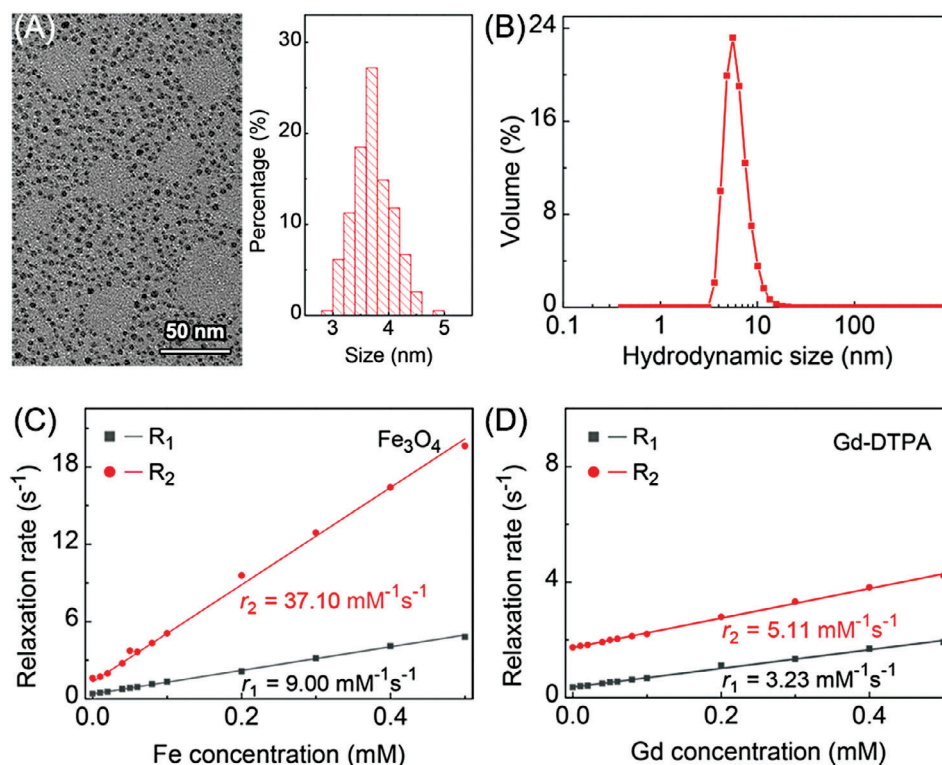


Figure 1. A) The transmission electron microscope (TEM) and particle size statistics of hydrophilic Fe₃O₄ nanoparticles; B) The hydrodynamic size of Fe₃O₄ nanoparticles; relaxivity values (r_1 and r_2) of C) Fe₃O₄ nanoparticles and D) Gd-DTPA.

potential as a safe alternative to GBAs because of their intrinsic nontoxic and biodegradable properties. USIONPs can be naturally metabolized into the hemoglobin and effectively cleared from patients' bodies. More importantly, compared to GBAs, USIONPs have longer blood residence time, thus enabling multiple imaging for monitoring the vascular conditions such as the location of embolization, the dynamic changes of vascular stenosis, and the postrecanalization treatment outcomes for the vascular embolism.^[5]

The image quality of CE-MRA largely relies on the contrast agent concentration and the parameters of the pulse sequences, such as the echo time (TE), repetition time (TR) and flip angle (FA).^[6] Since the concentration and the sequence parameters affect the T_1 -weighted signal nonlinearly, making the full optimization of all factors quite complex. Previous studies used empirical observations to only optimize the contrast agent concentration at fixed pulse sequence parameters.^[7] Whereas it was only specific to the GBAs used in the studies and may not produce the global optima for other sequence parameter combinations. To overcome these drawbacks, Reeder et al. developed mathematical models to automatically optimize the contrast agent concentration and parameters for the spoiled gradient echo sequence.^[8] Imaging results have shown that these mathematical models can successfully predict the optimal concentration and sequence parameters for various contrast agent types, e.g., gadobenate, gadoteridol, and ferumoxytol. However, the proposed mathematical models were only evaluated on phantoms or contrast agent-filled catheters and may cause suboptimal results in more physiological environments, particularly for CE-MRA.^[9] Besides, although

the long blood half-lives of USIONPs make it feasible to perform the multiple imaging in a prolonged measurement window, the intravascular concentration will change dynamically after the injection, which may require adaptive concentration-dependent sequence parameters to achieve the optimal signal enhancement during the multiple imaging process. To the best of our knowledge, this effect has not been investigated in the present mathematical optimization studies.

In this work, we developed and investigated a mathematical model to automatically optimize the imaging parameters for PEGylated ultrasmall iron oxide nanoparticles (PUSIONPs)-enhanced MRA using the 3D fast low-angle shoot (3D FLASH) sequence and the fast spin echo (FSE) sequence. The pharmacokinetic studies were conducted to estimate the intravascular concentration within 12 h after the injection. The estimated dynamic concentration was incorporated into the presented mathematical model to determine the adaptive sequence parameters and to obtain the optimal signal enhancement in a prolonged acquisition window. The imaging performance and blood residence time were compared between the GBAs and PUSIONPs. The phantom and in vivo rat CE-MRA experiments were performed on a 3T animal scanner to validate the mathematical model.

2. Results

2.1. Relaxivities of the Fe₃O₄ Nanoparticles and Gd-DTPA

The core size and hydrodynamic size of the Fe₃O₄ nanoparticles were 3.72 ± 0.35 nm and 7 nm, respectively (Figure 1A,B). The

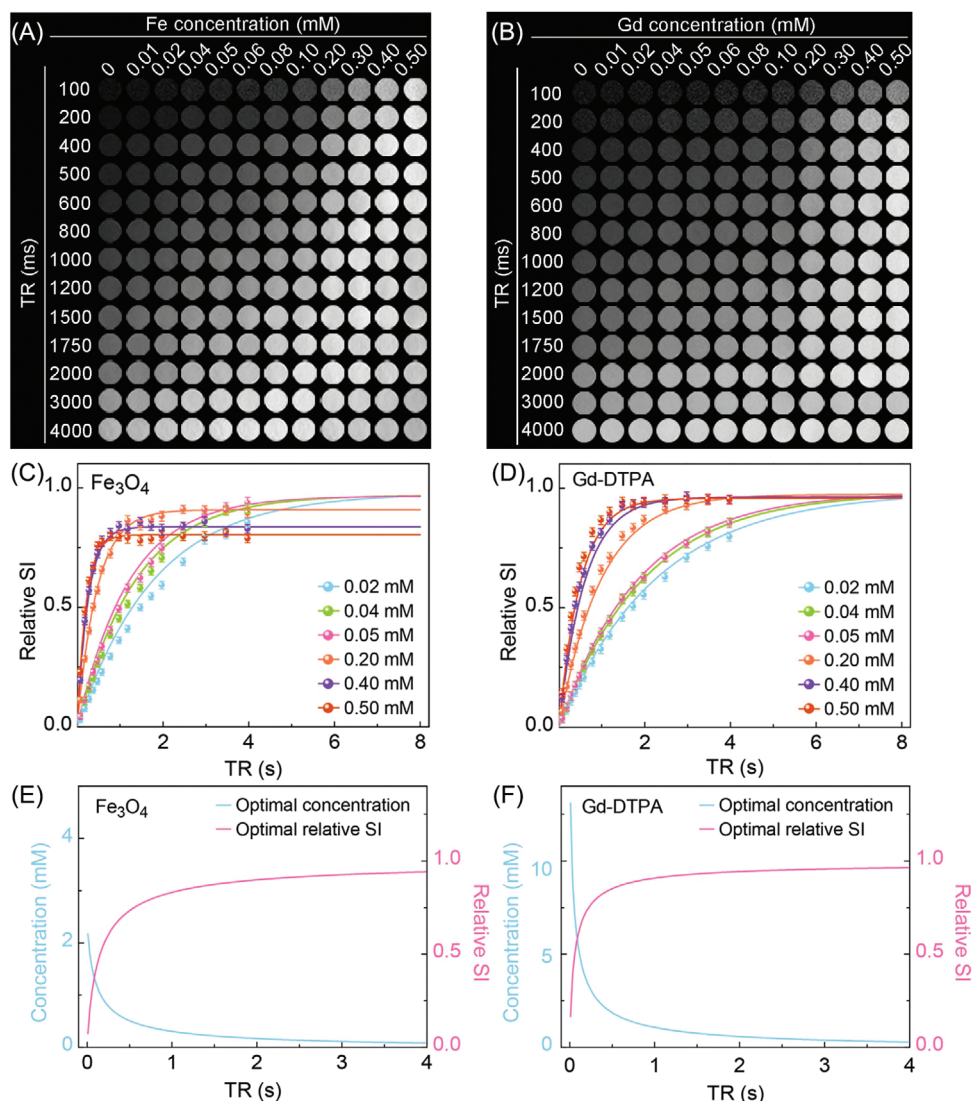


Figure 2. Phantom images acquired with the FSE sequence using A) Fe_3O_4 nanoparticles and B) Gd-DTPA. Various concentrations ($0\text{--}0.50 \times 10^{-3}$ M) and TR values (100–8000 ms) were tested. The fitting of theoretically calculated (lines) and experimental (solid points) relative SI for (C) Fe_3O_4 nanoparticles ($R^2 = 0.99$) and D) Gd-DTPA ($R^2 = 0.96$) at TE value of 11 ms. The optimal relative SI and concentration of E) Fe_3O_4 nanoparticles and F) Gd-DTPA with respect to TR were calculated by the proposed mathematical model.

r_1 and r_2 values of the Fe_3O_4 nanoparticles were 9.00 and $37.10 \text{ mM}^{-1} \text{ s}^{-1}$, respectively, remarkably higher than the relaxivity values of the commercial Gd-DTPA ($r_1 = 3.23 \text{ mM}^{-1} \text{ s}^{-1}$ and $r_2 = 5.11 \text{ mM}^{-1} \text{ s}^{-1}$), as shown in Figure 1C,D. The root mean square error of the linear fitting was 0.05 (r_1 for Fe_3O_4 nanoparticles), 0.04 (r_1 for Gd-DTPA), 0.29 (r_2 for Fe_3O_4 nanoparticles), and 0.03 (r_2 for Gd-DTPA), respectively.

2.2. Phantom Results

Phantom images of the Fe_3O_4 nanoparticles and Gd-DTPA acquired with the FSE sequence using various concentrations ($0\text{--}0.50 \times 10^{-3} \text{ M}$) and TR values (100–8000 ms) were shown in Figure 2A,B. When the applied TR was short, the signal intensity (SI) increased with the contrast agent concentration. For the case

with long TR, the SI remained relatively stable with increasing concentrations. Relative SI was normalized with the S_0 value. The theoretically calculated and experimental relative SI as a function of TR values (Figure 2C,D) were plotted using a range of concentrations ($0.02 \times 10^{-3} \text{ M}$, $0.04 \times 10^{-3} \text{ M}$, $0.05 \times 10^{-3} \text{ M}$, $0.20 \times 10^{-3} \text{ M}$, $0.40 \times 10^{-3} \text{ M}$ and $0.50 \times 10^{-3} \text{ M}$) at a minimal achievable TE value of 11 ms. A good consistency between experimental and theoretical data was shown for the Fe_3O_4 nanoparticles and Gd-DTPA with R^2 values of 0.99 and 0.96 , respectively. Figure 2E,F plot the calculated optimal concentration and relative SI with respect to TR values. The optimal concentration decreases with increasing TR values, while the relative SI peaked and then plateaued as TR increased.

Phantom images of the Fe_3O_4 nanoparticles and Gd-DTPA acquired with the 3D FLASH sequence among various FA values ($10\text{--}60^\circ$) and concentrations ($0\text{--}3 \times 10^{-3} \text{ M}$) were shown in

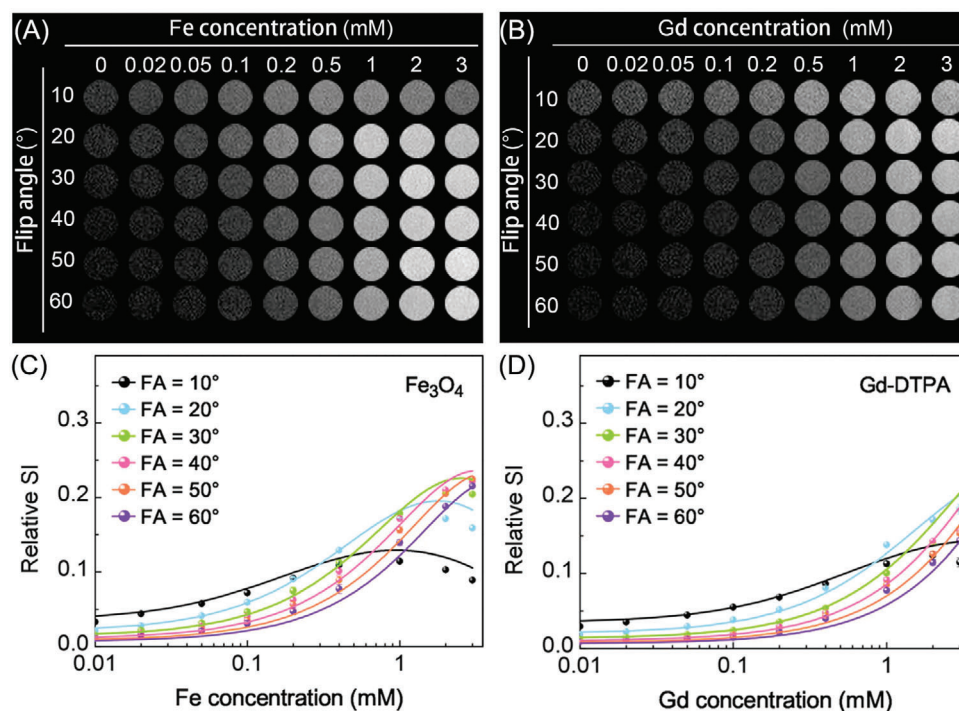


Figure 3. Phantom images acquired from the 3D FLASH sequence using A) Fe_3O_4 nanoparticles and B) Gd-DTPA with TR = 10 ms, various concentrations ($0\text{--}3 \times 10^{-3}$ M) and FA values ($10\text{--}60^\circ$). The fitting of theoretically calculated (solid lines) and experimental (points) relative SI against concentrations with various FA values ($10\text{--}60^\circ$) for C) Fe_3O_4 nanoparticles ($R^2 = 0.97$) and D) Gd-DTPA ($R^2 = 0.96$).

Figure 3A,B. The fitting of theoretically calculated and experimental relative SI against various concentrations for a range of FA values ($10\text{--}60^\circ$) and TR value = 10 ms was plotted in Figure 3C,D. A good agreement between the theoretically calculated and experimental relative SI was demonstrated in these graphs with $R^2 = 0.97$ (Fe_3O_4 nanoparticles) and $R^2 = 0.96$ (Gd-DTPA). It was also noticeable that the relative SI increased with increasing concentration of Gd-DTPA; whereas in the case of Fe_3O_4 nanoparticles, the relative SI peaked and then dropped gradually as the concentration increased, indicating that the inherent relaxation properties of distinct contrast agents may lead to the different optimal concentration, under the same combinations of TR, TE and FA values.

2.3. In Vivo Rat Results

The CE-MRA images of rats with Gd and iron doses of $0.10 \text{ mmol kg}^{-1}$ were compared in Figure 4A,B. The blood vessels became vague after 1 min in Gd-DTPA-enhanced MRA images (Figure 4A); however, these vessels were still clearly visible in Fe_3O_4 nanoparticles-enhanced images (Figure 4B) within 10 h. The jugular vein SI of CE-MRA images over time was plotted in Figure 4E,F. The SI for the Gd-DTPA dropped rapidly after the injection. However, the SI for the Fe_3O_4 nanoparticles kept stable within 10 h, suggesting that the Fe_3O_4 nanoparticles enabled longer blood residence time than the Gd-DTPA. Figure 4C,D shows additional CE-MRA images with iron doses of 0.05 and $0.03 \text{ mmol kg}^{-1}$; the corresponding SI curves are shown in Figure 4G,H. The SI remains at the same level as

the conventional first-pass MRA signal within approximately 2 h and then starts to decline gradually afterwards. The intravascular concentrations of the Gd-DTPA and Fe_3O_4 nanoparticles within 12 h were estimated by a standard two-compartment pharmacokinetic model (see Equation S7 and Table S1, Supporting Information) and were plotted in Figure S1 (Supporting Information). The intravascular concentration dropped rapidly after injecting $0.10 \text{ mmol kg}^{-1}$ Gd-DTPA, while the concentration remained at a high level within 4 h for the same amount of injection of Fe_3O_4 nanoparticles.

Figure 5 shows the Ernst angle, SI at Ernst angle and SI efficiency over time given the combination of the estimated dynamic concentrations, the TE and TR values. As Figure 5A–C indicates, the Ernst angle decreases with the circulation time. For the iron dose of $0.10 \text{ mmol kg}^{-1}$, the SI at Ernst angle peaks at 100 min after the injection and then decreases gradually (Figure 5D). However, for low iron doses (0.05 and $0.03 \text{ mmol kg}^{-1}$), the SI at Ernst angle decreased as the circulation time increased (Figure 5E,F). Figure 5G further reveals that the lowest TR value (10 ms) gives the best SI efficiency within 200 min after the injection of $0.10 \text{ mmol kg}^{-1}$ Fe_3O_4 nanoparticles. The SI efficiency for different TR values stay almost the same after the injection of low-dose Fe_3O_4 nanoparticles, as shown in Figure 5H,I.

To investigate the impact of adaptive sequence parameters on signal enhancement of different iron doses, three rats were administered with iron doses of 0.10 , 0.05 , and $0.03 \text{ mmol kg}^{-1}$, respectively, and then scanned with the 3D FLASH sequence using various TR ($10\text{--}40 \text{ ms}$), FA ($10\text{--}60^\circ$), TE (4 ms), and calculated Ernst angle at 1, 15, 30, 60, 120, 240, 36, 480 and 720 min after the injection. As shown in Figure 6, the theoretically calculated rela-

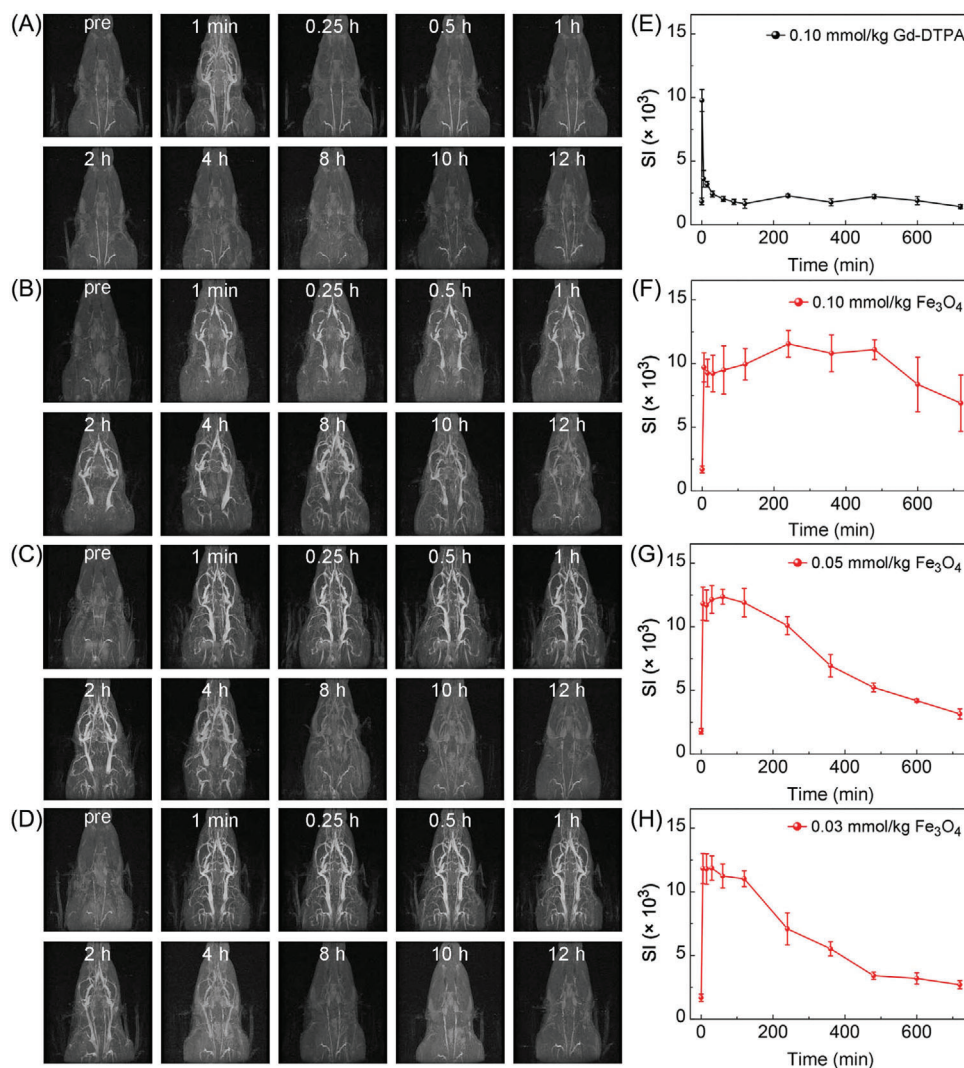


Figure 4. The 3D maximum intensity projection (MIP) reconstructions of rat CE-MRA (TR = 10 ms, TE = 4 ms, FA = 30°) images within 12 h after the injection of A) 0.10 mmol kg⁻¹ Gd-DTPA and B–D) 0.10, 0.05, and 0.03 mmol kg⁻¹ Fe₃O₄ nanoparticles, respectively. The SI values of the jugular vein over time for the injection of E) 0.10 mmol kg⁻¹ Gd-DTPA and F–H) 0.10, 0.05, and 0.03 mmol kg⁻¹ Fe₃O₄ nanoparticles, respectively.

tive SI values are in good consistent with the experimentally measured values, which agrees with the results of Figures 2 and 3. Although the calculated Ernst angle is changed with the circulation time, it generates the highest relative SI values in comparison to other fixed FA values (10°, 30° and 60°), indicating that the adaptive Ernst angle can achieve the optimal signal enhancement.

Figure 7 shows the rat CE-MRA images with full thickness MIP reconstructions acquired with fixed FA values and adaptive Ernst angle values within 6 h after the injection of 0.10 mmol kg⁻¹ Fe₃O₄ nanoparticles at TR = 40 ms. As indicated by red and yellow arrows, the right common carotid artery and left posterior facial vein are almost unseen in the images of the top two rows, while these arteries and veins can be clearly distinguished in the third-row images, which demonstrates that the adaptive Ernst angle can provide better vascular enhancement than the fixed FA values during a prolonged measurement window. Figures S2–S4 (Supporting Information) show the rat CE-MRA images with full thickness MIP reconstructions acquired with fixed FA

values and adaptive Ernst angle values within 6 h after the injection of 0.10 mmol kg⁻¹ Fe₃O₄ nanoparticles at TR = 10 ms, TR = 20 ms and TR = 30 ms, respectively, which are consistent with results in Figure 7. In addition, we also tested the performance of the proposed model on the thin MIP reconstructions, and the Figure S5 (Supporting Information) demonstrated that the adaptive Ernst angle can achieve better image enhancement than the fixed FA, which is consistent with full thickness MIP reconstructions in Figure 7.

3. Discussion

Due to the extracellular nature, the intravascular concentration of conventional GBCAs decreases rapidly after injection, and thus, GBCAs-enhanced MRA typically applies first-pass arterial phase imaging with limited acquisition time. In this work, the pharmacokinetic studies show that the intravascular concentration of PUSIONPs is maintained considerably longer than the com-

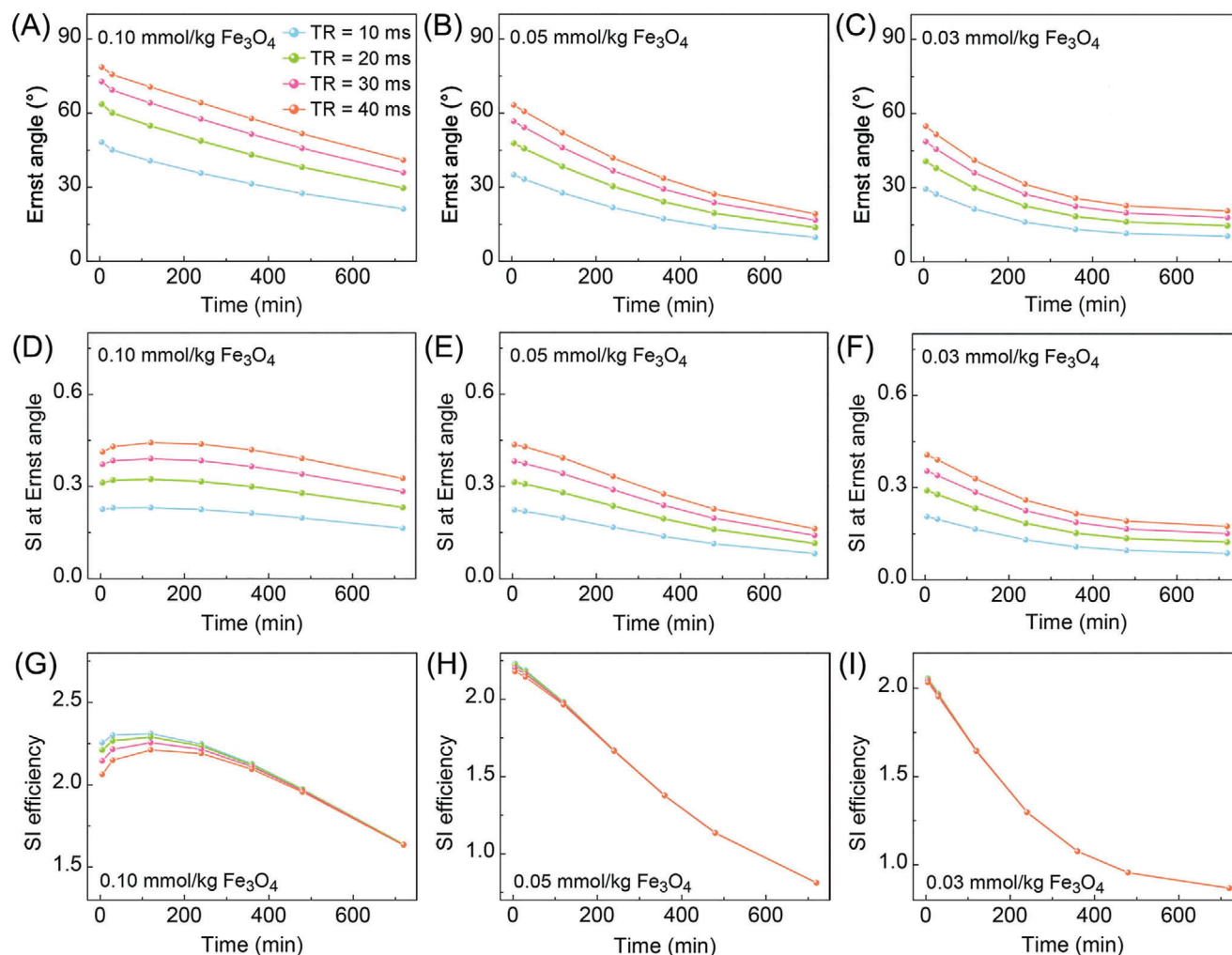


Figure 5. Theoretically calculated A–C) Ernst angle, D–F) SI at Ernst angle, and G–I) SI efficiency against the blood residence time given the combination of the estimated dynamic concentrations, TE = 4 ms and various TR values (10–40 ms). The calculations used the known T_1 (1527 ms) and T_2 (147 ms) blood relaxation times.

monly used GBAs, enabling a sufficient time window for prolonged acquisitions. This advantage would facilitate diagnoses and treatments of arteriovenous malformations, which often require multiple imaging measurements pre- and post-therapy.^[10] Stroke is the leading cause of deaths from cardiovascular diseases worldwide. Computed tomography (CT) has been widely used as the primary imaging in patients to rule out intracranial hemorrhage in the clinical practice. However, CT has a significantly low sensitivity to depict the acute ischemic stroke (AIS) with a sensitivity of only 12% in the first 3 h and 57–71% in the first 24 h after onsite symptoms, making it difficult to diagnose the AIS precisely and timely in such medical emergencies.^[11] On the contrary, magnetic resonance imaging (MRI) has greater sensitivity than CT for the AIS detection, which although is not as widely available as CT and has been utilized as a necessary follow-up imaging for accurately diagnosing AIS and avoiding stroke mimics. There are two routinely used MRA techniques including time-of-flight MRA (TOF-MRA) and CE-MRA. CE-MRA has shown better diagnostic accuracy compared with TOF-MRA, par-

ticularly for identifying occlusion locations and visualizing collateral vascular. Thrombolytic drugs are clinically applied for the AIS treatment and such thrombolytic therapy is sometimes accompanied by intracranial hemorrhages, causing stroke-related disabilities or even case fatality.^[12] Therefore, monitoring the dynamic changes of the vascular conditions especially at the embolization site is of great importance for evaluating the treatment outcomes. However, the current clinical GBAs are incapable of achieving this goal with only one injection, a multiple injection is therefore required instead. It gives rise to a significant unmet clinical demand for evaluating the post-therapy treatment for stroke patients. The current studies reveal that the long-circulating time allows for multiple imaging measurements within 6 h in rats upon single dose of PUSIONPs, which will enable a serial and real-time assessment of the thrombolytic therapy. In such medical emergency scenario, given the toxicity of the GBAs and the complexity of multiple injections required, the single injection of PUSIONPs may become very attractive for evaluating the thrombolytic treatment through MRI.

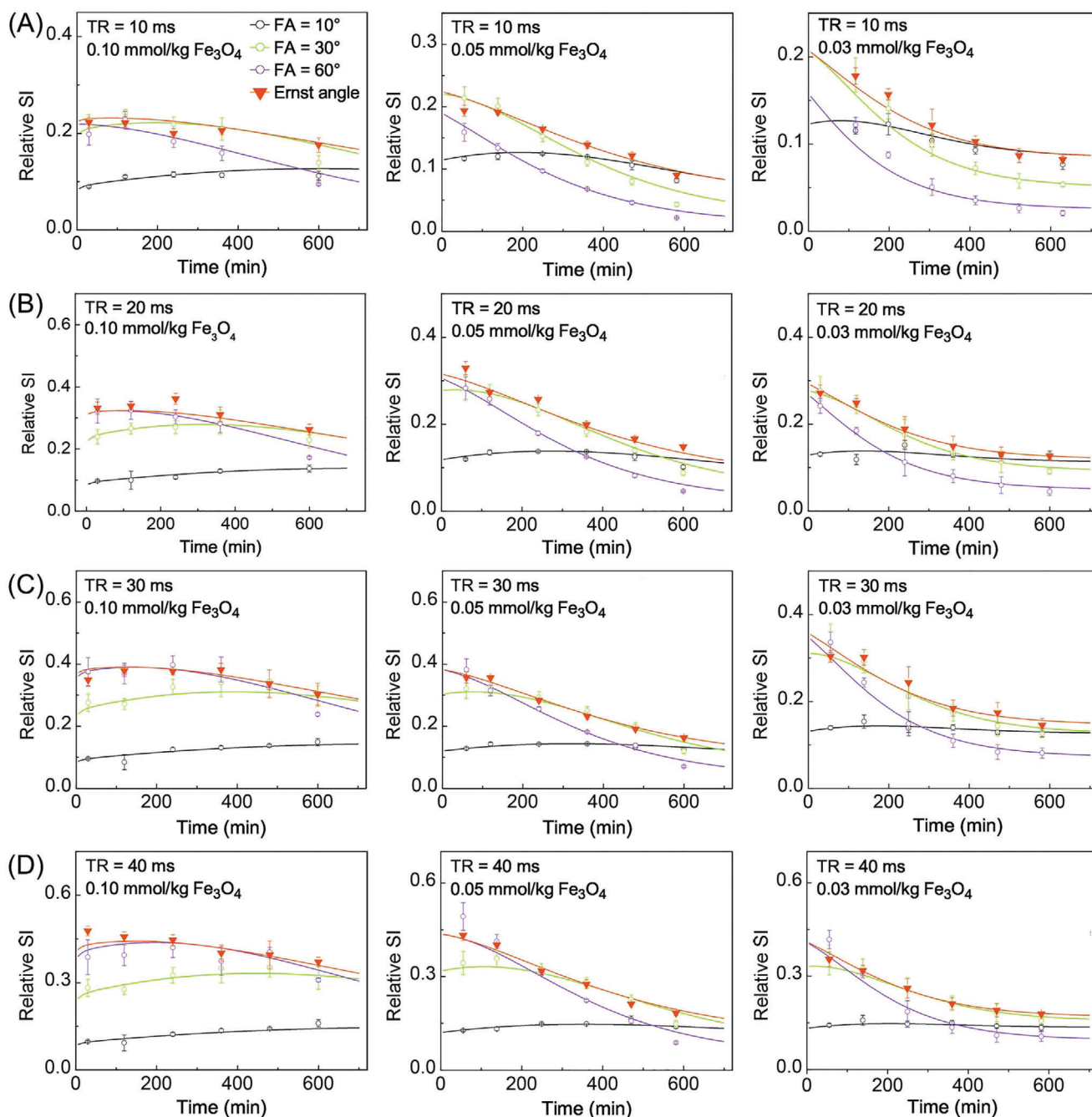


Figure 6. Theoretical (solid lines) and experimental (points) relative SI values of rat CE-MRA images over time after the injection of 0.10, 0.05, and 0.03 mmol kg⁻¹ Fe₃O₄ nanoparticles, with TE = 4 ms, various FA values (10–60°) and Ernst angle at A) TR = 10 ms, B) TR = 20 ms, C) TR = 30 ms, and D) TR = 40 ms.

Since the intravascular concentration of PUSIONPs changes dynamically during the long blood residence time, the adaptive concentration-dependent sequence parameters are essentially required to obtain the optimal signal enhancement. Given the dynamic intravascular concentration, TR and TE values, the adaptive FA (Ernst angle) values were calculated with the presented model, and the imaging results have shown that it generated higher relative SI than the fixed FA values. It thus suggested that

the presented mathematical optimization model could provide adaptive acquisition parameters to attain the best image quality for the CE-MRA during a prolonged acquisition. Although the proposed mathematical optimization model has been only tested on PUSIONPs, it is readily applicable to other contrast agents with known information on relaxivity and concentration.

Various injected concentrations of PUSIONPs were tested for the in vivo rat CE-MRA, and the results showed that the low-dose

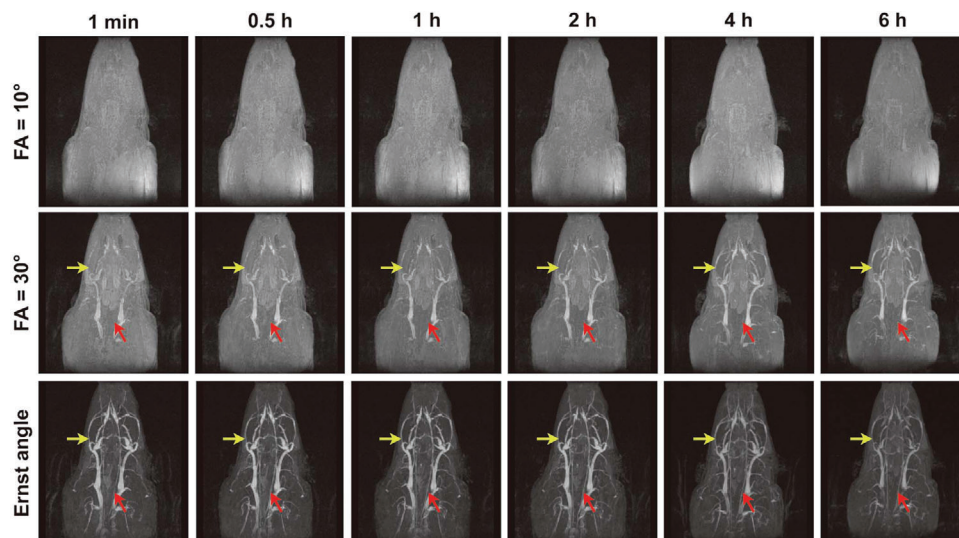


Figure 7. The 3D MIP reconstructions of rat CE-MRA images within 6 h after the injection of $0.10 \text{ mmol kg}^{-1} \text{ Fe}_3\text{O}_4$ nanoparticles acquired with the fixed FA values (10° and 30° , the top two rows) and the adaptive Ernst angle values (the third row), respectively at $\text{TR} = 40 \text{ ms}$ and $\text{TE} = 4 \text{ ms}$. The red and yellow arrows denote the right common carotid artery and left posterior facial vein, respectively.

contrast agents (e.g., 0.03 and $0.05 \text{ mmol kg}^{-1}$) gave comparable SI to the high-dose one ($0.10 \text{ mmol kg}^{-1}$) within 2 h after the intravenous injection, indicating that the high relaxivity and long blood half-lives of PUSIONPs are beneficial for reducing the injected doses for the CE-MRA applications. These experimental validations would also be helpful for guiding the contrast agent dosing protocols. Moreover, the maximal possible SI predicted for a given concentration, TR and TE combination, could be used to quantify the imaging performance of a contrast agent. As shown in the mathematical equations, the SI is increased monotonically with TR. However, when the TR is too long, the T_1 -weighted effect will be weakened due to the longitudinal magnetization recovery. It may explain that the relative SI is almost the same when TR is larger than 4 s in Figure 1C,D. It is notable that increasing TR also increases the acquisition time, making it impractical for some fast CE-MRA applications, e.g., catheter-based interventions and interactive coronary MRA.^[13] Therefore, we define herein the SI efficiency that is monotonically increased with decreasing TR, leading to a trade-off between SI and efficiency. Recently, MR acceleration techniques such as compressed sensing and parallel imaging have shown promise for the dynamic MRA.^[14] We will investigate the application of PUSIONPs-enhanced MRA to MR acceleration problems to further reduce the acquisition time in the future.

The relaxivity of contrast agents is highly dependent on the physiological environment. Studies have shown that the longitudinal relaxivity of the contrast agent in blood is nonlinear at high concentrations.^[15] Furthermore, the transverse relaxivity would be impacted substantially in the presence of the endogenous erythrocytes, which may result in microscopic magnetic field inhomogeneities.^[16] The mathematical description of the relationship between relaxivity and the environment will be investigated and incorporated into the presented mathematical optimization model in the future to provide more precise predictions.

4. Conclusion

In this work, we proposed a mathematical model that incorporated adaptive concentration-dependent sequence parameters for optimizing PUSIONPs-enhanced MRA. Through both phantom and in vivo rat imaging studies, a good consistency between the experimental measurements and theoretical predictions was obtained. On top of that, with reference to conventional GBAs, a longer acquisition window with a lower dose was enabled for PUSIONPs, which may open up a bright way to precisely diagnose cardiovascular diseases through PUSIONPs-enhanced MRA. Beyond that, the current model may also be applicable for other types of contrast agents in blood pool imaging.

5. Experimental Section

The Mathematical Optimization Model: The SI in the T_1 -weighted FLASH sequence can be formulated as:^[17]

$$\text{SI} = \frac{S_0 \left(1 - e^{-\text{TR}(R_{10}+r_1C)} \right) \sin(\text{FA})}{1 - \cos(\text{FA}) e^{-\text{TR}(R_{10}+r_1C)}} e^{-\text{TE}(R_{20}+r_2C)} \quad (1)$$

where S_0 represents the longitudinal magnetization at equilibrium and FA is the excitation flip angle. R_{10} and R_{20} are the longitudinal and transverse relaxation rates without the presence of contrast agents, and C is the contrast agent concentration. r_1 and r_2 denote the longitudinal and transverse relaxivities of the applied contrast agent, respectively. The aim of the optimization is to determine the values of TE, FA, and TR that maximize the SI.

$$\text{TE}_{\text{optimal}} = \text{TE}_{\text{min}} \quad (2)$$

By taking the derivative of Equation (1) with respect to FA, the optimal FA occurs at the well-known “Ernst angle”.^[18]

$$\text{FA}_{\text{optimal}} = \cos^{-1} \left(e^{-\text{TR}(R_{10}+r_1C)} \right) \quad (3)$$

It is noted that $\cos(\text{FA}_{\text{optimal}}) = e^{-\text{TR}(R_{10}+r_1C)}$ and $\sin(\text{FA}_{\text{optimal}}) = (1 - e^{-2\text{TR}(R_{10}+r_1C)})^{1/2}$. Inserting the optimized TE and FA to Equation (1) can yield the equation below:

$$\text{SI} = S_0 \sqrt{\frac{1 - e^{-\text{TR}(R_{10}+r_1C)}}{1 + e^{-\text{TR}(R_{10}+r_1C)}}} e^{-\text{TE}_{\min}(R_{20}+r_2C)} \quad (4)$$

By taking the derivative of $\ln \text{SI}$ with respect to the concentration C , the C_{optimal} that maximizes the SI can be calculated as:

$$C_{\text{optimal}} = \frac{\ln(D + \sqrt{1 + D^2})}{r_1 \text{TR}} - \frac{R_{10}}{r_1} \quad (5)$$

where $D = (r_1 \text{TR}) / (2r_2 \text{TE}_{\min})$ represents the ratio of longitudinal recovery and transverse decay, and then Equation (1) can be rewritten as:

$$\text{SI} = S_0 \frac{D + \sqrt{1 + D^2} - 1}{D + \sqrt{1 + D^2} + 1} \quad (6)$$

Equation (6) can be used to determine the impact of TR on the maximal SI. Mathematically, as $\partial \text{SI} / \partial D > 0$ and increasing TR will increase the SI. However, increasing TR will also increase the scan time. For some MRA applications such as real-time catheter-directed MRA and fast interactive coronary MRA, one needs to acquire successive images in a relatively short time.^[19] In such cases, we define the SI efficiency $\text{SI}_{\text{efficiency}}$ as the signal-to-noise ratio (SNR) per square root scan time, which can be given by:

$$\text{SI}_{\text{efficiency}} \propto \frac{(1 - e^{-\text{TR}(R_{10}+r_1C)}) \sin(\text{FA})}{(1 - \cos(\text{FA}) e^{-\text{TR}(R_{10}+r_1C)}) \sqrt{\text{TR}}} e^{-\text{TE}(R_{20}+r_2C)} \quad (7)$$

With the optimized values of TE and FA, Equation (7) can be rewritten as:

$$\text{SI}_{\text{efficiency}} \propto \sqrt{\tan h \frac{(R_{10} + r_1 C) \text{TR}}{2}} \frac{e^{-\text{TE}_{\min}(R_{20}+r_2C)}}{\sqrt{\text{TR}}} \quad (8)$$

The derivative of Equation (8) with respect to TR is strictly negative with the condition $R_1 \text{TR} < \sinh(R_1 \text{TR})$. Studies have shown that the condition is always true for all feasible values of R_1 and TR, which suggests that Equation (8) is monotonically increasing with decreasing TR. Therefore, the optimized TR with the best SI efficiency can be governed by:

$$\text{TR}_{\text{optimal}} = \text{TR}_{\min} \quad (9)$$

It is noted that when $\text{FA} = 90^\circ$, Equation (1) describes the SI in the FSE sequence and the mathematical optimization model is detailed in Equations S1–S6 in the Supporting Information.

Materials and Characterization: The hydrophilic Fe_3O_4 nanoparticles from Suzhou XinYing Bio-Medical Technology Co., Ltd. and the Gd-DTPA from Bayer HealthCare were used as PUSIONPs and GBCAs, respectively in this work. The PUSIONPs used in this study were synthesized through the thermal decomposition of iron organic precursor and produced through an advanced flow synthesis method developed in the previous work.^[20] High-temperature thermal decomposition synthesis ensured uniform particle size distribution, particularly for particles smaller than 5 nm, which is very important for achieving excellent relaxation properties. The diphosphonate methoxy polyethylene glycol (DP-PEG) was used to modify the surface for better colloidal stability, biocompatibility, and prolonged blood residence time. All these facts make the current PUSIONPs significantly different from the conventional superparamagnetic iron oxide nanoparticles (SPIOs) and ultrasmall superparamagnetic iron oxide

nanoparticles (USPIOs). The size of the Fe_3O_4 nanoparticles was characterized by a transmission electron microscope (TEM, FEI Tecnai G2 F20, FEI Inc., Washington, DC, USA) with an acceleration voltage of 200 kV. The hydrodynamic diameter of the nanoparticles was measured by using a Malvern Zetasizer (Nano ZS 90, Malvern Ltd., Malvern, UK) equipped with a solid-state He-Ne laser ($\lambda = 633 \text{ nm}$).

Relativity Measurements: The relativity measurements were performed on a 3T animal MRI system (MR Solutions Ltd., Guildford, Surrey, UK) with 65 mm diameter quadrature bird cage coil and the gradient strength of 585 mT m^{-1} . The inversion recovery fast low-angle shoot (IR FLASH) sequence was used to measure the longitudinal relaxation time, and the sequence parameters were set as: TR = 12 ms, TE = 6 ms, FA = 8° , image size = 256×128 , field of view (FOV) = $30 \text{ mm} \times 30 \text{ mm}$, inversion time range = 74–6170 ms and slice thickness = 2 mm. The multiecho multislice (MEMS) images were acquired to measure the transverse relaxation time with the sequence parameters of TR = 1400 ms, TE range = 15–450 ms, FA = 90° , image size = 256×192 , FOV = $30 \text{ mm} \times 30 \text{ mm}$ and slice thickness = 2 mm. The T_1 and T_2 mapping were obtained from the scanner to calculate R_1 and R_2 values, which were then used to determine the relativity values (r_1 and r_2) by performing linear regression of R_1 and R_2 values against contrast agent concentration.

Phantom Experiments: To validate the mathematical optimization model, phantoms with serially diluted PUSIONPs and GBCAs were constructed with the following concentrations: $0.01 \times 10^{-3} \text{ M}$, $0.02 \times 10^{-3} \text{ M}$, $0.04 \times 10^{-3} \text{ M}$, $0.05 \times 10^{-3} \text{ M}$, $0.06 \times 10^{-3} \text{ M}$, $0.08 \times 10^{-3} \text{ M}$, $0.10 \times 10^{-3} \text{ M}$, $0.20 \times 10^{-3} \text{ M}$, $0.30 \times 10^{-3} \text{ M}$, $0.40 \times 10^{-3} \text{ M}$, $0.50 \times 10^{-3} \text{ M}$, $1 \times 10^{-3} \text{ M}$, $2 \times 10^{-3} \text{ M}$ and $3 \times 10^{-3} \text{ M}$. The phantoms with pure water were also constructed for comparison. The FSE and 3D FLASH sequences were used to scan the phantoms. A TR range of 100–8000 ms was tested for the FSE sequence with the following parameters: TE = 11 ms, FA = 90° , image size = 256×252 , FOV = $30 \text{ mm} \times 30 \text{ mm}$ and slice thickness = 2 mm. A FA range of 10 – 60° was used for the 3D FLASH sequence with the parameters of TR = 10 ms, TE = 4 ms, image size = 192×154 , FOV = $30 \text{ mm} \times 30 \text{ mm}$ and slice thickness = 1 mm. The region of interest (ROI) of each phantom was selected to measure the SI, and the data analysis was performed in MATLAB (R2018b, MathWorks, Natick, MA, USA).

In Vivo Experiments: Female rats (Sprague Dawley, 9–10 weeks old, weight 250–300 g) were used for the pharmacokinetic ($N = 3$ biologically independent animals) and MRA study. All the rats were anesthetized with 3% isoflurane through a nose cone during the MRI scan. All the animal studies were performed according to the guidelines approved by the Ethics and Animal Care Committee of Soochow University.

The iron doses of 0.10, 0.05, and 0.03 mmol kg^{-1} were injected through the tail vein. A Gd dose of 0.10 mmol kg^{-1} was also injected for comparison. Blood samples of each rat were collected at 1, 15, 30, 60, 120, 240, 360, 480, and 720 min after the intravascular injection. To eliminate the interference of endogenous iron in the blood, the plasma containing Fe_3O_4 nanoparticles was obtained through ultracentrifugation. Then, the Fe or Gd content of each plasma/blood sample was quantified using inductively coupled-plasma atomic emission spectroscopy (ICP-AES) (Agilent 7900, Agilent Technologies, Santa Clara, California, USA). Based on the blood sample measurement, a standard two-compartment pharmacokinetic model was used to estimate the dynamic intravascular concentrations at any time point after the intravascular injection.^[21] CE-MRA images with a Gd dose of 0.10 mmol kg^{-1} and iron doses of 0.10, 0.05, and 0.03 mmol kg^{-1} were acquired using the 3D FLASH sequence (TR = 10 ms, TE = 4 ms, FA = 30° , image size = 192×154 , FOV = $70 \text{ mm} \times 70 \text{ mm}$, and slice thickness = 1 mm) at 1, 15, 30, 60, 120, 240, 360, 480 and 720 min after the injection. The SI of Gd- and iron-enhanced MRA images at each time point were compared. To investigate the effect of dynamic intravascular concentrations after the PUSIONPs injection, the Ernst angle at each time point was calculated. CE-MRA images with iron doses of 0.10, 0.05, and 0.03 mmol kg^{-1} were acquired with the calculated Ernst angle. In addition, CE-MRA images were also acquired with a range of FA values (10 – 60°) and TR values (10–40 ms) for comparison. All CE-MRA images were reconstructed by the MIP method.

Statistical Analysis: Data were presented as the mean $\pm$ standard derivation (SD) ($n = 3$) and were carried out using Excel Software.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

C.L. and S.S.S. contributed equally to this work. Conceptualization: C.L., S.S.S. and J.F.Z.; Investigation: L.C., M.J.A. and D.D.K. Methodology: C.L., K.L., H.Z.W. and N.W.; Writing-original draft: C.L., S.S.S. and C.Y.L.; Writing-review and editing: M.Y.G., Y.G., and F.L.; Supervision: M.Y.G., S.S.S., and J.F.Z.; Funding acquisition: M.Y.G., S.S.S., J.F.Z., and L.C. All authors contributed to the general discussion. The final version of the manuscript was approved by all authors.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords

adaptive sequence parameters, CE-MRA, dynamic concentration, mathematical optimization model, PEGylated ultrasmall iron oxide nanoparticles

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