Multidimensional Mapping of Spin-Exchange Optical Pumping in Clinical-Scale Batch-Mode 129Xe Hyperpolarizers

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Multidimensional Mapping of Spin-Exchange Optical Pumping in Clinical-Scale Batch-Mode $^{129}$Xe Hyperpolarizers

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Supporting Information

ABSTRACT: We present a systematic, multiparameter study of Rb/$^{129}$Xe spin-exchange optical pumping (SEOP) in the regimes of high xenon pressure and photon flux using a 3D-printed, clinical-scale stopped-flow hyperpolarizer. In situ NMR detection was used to study the dynamics of $^{129}$Xe polarization as a function of SEOP-cell operating temperature, photon flux, and xenon partial pressure to maximize $^{129}$Xe polarization ($P_{129}$). $P_{129}$ values of 95 ± 9%, 73 ± 4%, 60 ± 2%, 41 ± 1%, and 31 ± 1% at 275, 515, 1000, 1500, and 2000 Torr Xe partial pressure were achieved. These $P_{129}$ polarization values were separately validated by ejecting the hyperpolarized $^{129}$Xe gas and performing low-field MRI at 47.5 mT. It is shown that $P_{129}$ in this high-pressure regime can be increased beyond already record levels with higher photon flux and better SEOP thermal management, as well as optimization of the polarization dynamics, pointing the way to further improvements in hyperpolarized $^{129}$Xe production efficiency.

INTRODUCTION

The nuclear spins of xenon and other noble gases can be hyperpolarized (HP) to order unity by the process of spin-exchange optical pumping (SEOP).1,2 In this two-step process, the electron spins of an alkali metal vapor such as rubidium are first polarized by the absorption of angular momentum from rubidium by the absorption of angular momentum from circularly polarized light. Spin-exchange collisions between the alkali metal atoms and $^{129}$Xe then transfer the angular momentum to the $^{129}$Xe nuclear spins through Fermi hyperfine interactions, resulting in a high non-Boltzmann distribution of $^{129}$Xe spin states that increases the detection sensitivity of NMR/MRI.3–6 The two most common approaches to hyperpolarize $^{129}$Xe via SEOP are termed continuous flow7–14 and stopped flow15–25 (sometimes also referred to as “batch mode”) with respect to the delivery of Xe gas to and from the polarization cell. N2 gas is typically added to the gas mixture to quench alkali metal fluorescence.7,26,27 The batch-mode/stopped-flow systems are attractive not only because of their relative simplicity but also because they can operate in a xenon-rich regime that obviates the need to separate the polarized Xe from the N2 (or He) via cryocollection, eliminating a potential source of polarization loss26 as well as facilitating applications using quadrupolar noble gas isotopes.5 This production method has also been scaled up for automated production of clinically required quantities.24,28,30

Regardless of the polarization method, HP noble gases have seen wide application varying from fundamental physics experiments31–34 to NMR/MRI applications including molecular biosensors,35–37 probing structural aspects of cage molecules and proteins,18,38–42 and studies of porous materials (to name only a few).15,43–45 However, it has been biomedical applications that have largely driven the development of hyperpolarized MR techniques over the past decade; indeed, for gas imaging in particular, HP $^{129}$Xe can be used to assess lung function and report on functional and microstructural abnormalities.6,46–48 A useful figure of merit for $^{129}$Xe hyperpolarizers is the total $^{129}$Xe magnetization, $M_{129}$, delivered in a clinically useful gas volume, typically ~0.5–1 L at 760 Torr. $M_{129}$ is determined by the product of nuclear spin polarization $P_{129}$ and $^{129}$Xe concentration [Xe], i.e., $M_{129} \propto P_{129}[Xe]$. It is therefore important to maximize $M_{129}$ through both $P_{129}$ and [Xe], which is challenging because $P_{129}$ generally decreases as [Xe] within the SEOP-cell increases16 (mostly because of...
increased alkali metal spin-destruction rates from non-spin-conserving collisions with Xe. But fundamentally laser photons are the source of 129Xe hyperpolarization; thus, the decreasing cost of laser diodes narrowly tuned to the alkali metal rubidium D1 wavelength (794.8 nm) has made economically feasible the higher photon fluxes required to improve \( M_{129Xe} \) when Xe partial pressures are high.

In the present work, a 200 W laser diode array (LDA) was used in a 3D-printed, automated 129Xe polarizer to study SEOP dynamics as a function of xenon density, laser power, and SEOP-cell temperature. More specifically, the SEOP polarization conditions at several partial pressures of natural abundance Xe (26.44% 129Xe isotope enrichment) were studied: (i) 275 Torr Xe and 1725 Torr N2, (ii) 515 Torr Xe and 1485 Torr N2, (iii) 1000 Torr Xe and 1000 Torr N2, (iv) 1500 Torr Xe and 500 Torr N2, and (v) 2000 Torr Xe and 200 Torr N2, where the gases were loaded with an accuracy of ±25 Torr. The reader is also directed to Supporting Information for detailed descriptions of the experimental setup, which represents the second-generation device of our HXTC consortium (Figure 1). For each SEOP cell loading, data were obtained for a range of incident laser power levels (approximately 100, 125, 140, or 170 W) and variable SEOP-cell surface temperatures ranging from 42 to 92 °C. For each condition, measurement of 129Xe polarization dynamics allowed the rate constant for \( P_{129Xe} \) accumulation \( (\gamma_{SEOP}) \) and the maximum attainable steady-state \( P_{129Xe} \) value \( [P_{129Xe}(t \rightarrow \infty)] \) to be determined from exponential fits. The temperature of the SEOP cell was monitored by a thermistor mounted directly to its surface; temperature control allows the Rb concentration in the gas phase to be varied.

## METHODS

Spin-Exchange Optical Pumping (SEOP) Polarizer. The SEOP 3D-printed portable polarizer (Figure 1) consists of a 200 W frequency narrowed volume holographic grating (VHG) laser diode array (LDA), a custom 3D-printed thermoelctric cooling (TEC) optical pumping (OP) oven, a 0.5 L SEOP cell, an electromagnet providing 47 kHz 129Xe and 1H Larmor frequencies, in situ NMR polarimetry endowed by a Magritek Kea2 system, and a Magritek 88 mm bore magnet for ex situ NMR polarimetry and MRI (Magritek, Wellington, New Zealand). The components of the polarizer have been discussed in detail previously and thus are only discussed briefly here.

In situ Low-Field NMR and IR Spectroscopy. In situ NMR polarimetry for these experiments was performed via single-shot 129Xe NMR at 47 kHz (Figure 2a) calibrated against 1H NMR at the same frequency from a sample of thermally polarized water doped with 10 mM CuSO4 inside a 0.5 L SEOP-cell phantom (200 000 scans, Figure 2b). The polarizer allows the Rb electron spin polarization, \( P_{Rb} \), to be estimated by comparing the integrated intensities of transmitted laser spectra measured with and without the applied magnetic field (e.g., Figure 2c). For each set of conditions, \( P_{129Xe} \) was sampled every 5–20 min throughout SEOP; the process is repeated by either destroying the 129Xe polarization with a series of “crusher” pulses or allowing it to decay with the laser off. The time-course examples in Figure 2d,e show the excellent reproducibility of \( P_{129Xe}, P_{Rb} \), and \( \gamma_{SEOP} \) in these experiments (and those values were not sensitive to the application of the rf pulses). Once steady-state 129Xe polarization was achieved, growth curves can be extracted (e.g., Figure 2f) and fit to an exponential: \( P_{129Xe}(t) = P_{max}[1 - \exp(-\gamma_{SEOP}t)] \). In the absence of SEOP, in-cell room-temperature (rt) measurement of the spin–lattice relaxation time constant \( (T_1) \) can be obtained after steady-state \( P_{129Xe} \) has been achieved by quickly bringing the cell to room temperature to minimize the Rb gas-phase concentration, turning off the laser, and performing in situ NMR polarimetry while the polarization decays; for example, the data in Figure 2g were fit to an exponential decay curve: \( P_{129Xe}(t) = P_{max}[1 - \exp(-\gamma_{SEOP}t)] \), where \( \Gamma_{129Xe} = (1/T_1) \) is the 129Xe spin-destruction rate, here exhibiting an ultralong in-cell 129Xe relaxation time \( T_1 \) of 150.5 ± 2.5 min (or 2.5 h). Particularly when optimizing SEOP under the regimes of high Xe and laser power, it is also important to be observant for the onset of positive feedback effects that give rise to dramatic increases in [Rb] and laser absorption over time (and ultimately poorer \( P_{129Xe} \)). Examples showing the manifestation of such “Rb-runaway” are provided in Figure 2h, which shows behavior where relatively small increases in cell surface temperature result not only in reduced peak \( P_{129Xe} \) but also in reduced \( P_{129Xe} \) over time. Such effects are discussed in greater detail in Results and Discussion.

Ex situ Low-Field NMR Spectroscopy and MRI Imaging. Ex situ \( P_{129Xe} \) at 47.5 mT was calculated by comparing the HP 129Xe signal with the 13C signal at 508 kHz 13C Larmor frequency from a reference sample of thermally polarized sodium 1-13C-acetate dissolved in D2O (Figure 4a). The 129Xe relaxation time inside the polypropylene phantom sphere was ~9.2 min (Figure 4c), which is sufficient for short-term storage of HP 129Xe. Moreover, this 129Xe \( T_1 \) value was used in parallel experiments to precisely calibrate the rf excitation pulse for the 47.5 mT rf probe shown in Figure 5f; the image signal decay is due to both \( T_1 \) decay and excitation rf pulses. A y-slice...
**RESULTS AND DISCUSSION**

The dependence of $^{129}$Xe polarization and its dynamics as functions of temperature, photon flux, and xenon partial pressure was systematically studied under stopped-flow operation in the regimes of high xenon density and photon flux. Results for five Xe:N$_2$ SEOP-cell compositions at four different LDA incident powers (approximately 100, 125, 140, and 170 W) with SEOP-cell surface temperatures ranging from 42 to 92 °C are displayed in Figure 3: Figure 3a provides example plots of % $P_{\text{max}}$ and $\gamma_{\text{SEOP}}$ as functions of SEOP-cell surface temperature for a cell containing 1000 Torr of Xe and 1000 Torr of N$_2$ and illuminated by 100 W of laser power from the LDA. Such data were used to create contour plots ("maps") of $^{129}$Xe % $P_{\text{max}}$ and $\gamma_{\text{SEOP}}$ for each Xe density as functions of laser power and SEOP-cell surface temperature (Figures 3c–i); the highest values achieved for % $P_{\text{max}}$ for each Xe:N$_2$ mix studied are summarized in Figure 3b and Table 1 (corresponding numerical values for all data points in Figure 3 are tabulated in the Supporting Information, Table S1).

The data in Figure 3 exhibit several trends. First, increasing cell surface temperature gives rise to an exponential increase in $\gamma_{\text{SEOP}}$ (e.g., Figure 3a), consistent with the expected exponential increase in the Rb gas-phase concentration [Rb]. This dependence of $\gamma_{\text{SEOP}}$ on [Rb] arises from the relation

$$\gamma_{\text{SEOP}} = \gamma_{\text{SE}} + \Gamma_{\text{Xe}} = k_{\text{SE}}[\text{Rb}] + \Gamma_{\text{Xe}}$$

where $\gamma_{\text{SE}}$ and $k_{\text{SE}}$ are the Rb/$^{129}$Xe spin-exchange rate and cross-section, respectively. Thus, the behavior of $\gamma_{\text{SEOP}}$ mostly

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**Figure 2.** (a) Example of an in situ low-field $^{129}$Xe NMR spectrum from a SEOP-cell during SEOP (single scan, $B_0 = 4.00$ mT). (b) Corresponding $^1$H NMR spectrum from a thermally polarized water reference sample using 200 000 scans, $B_0 = 1.10$ mT. (c) Examples of field-cycled near-IR spectra of laser light transmitted through the SEOP-cell used to estimate $P_{\text{SE}}$: room temperature before SEOP (dark gray), during SEOP with $B_0$ electromagnet on (blue), and during SEOP with $B_0$ electromagnet turned off (red). (d, e) Examples of data sets for studying time-resolved SEOP build-up and decay kinetics using a cell containing 1000 Torr (each) of Xe and N$_2$ gas (143 W laser power, 65 °C). (d) Plot showing reproducibility of $P_{\text{Xe}}$ accumulation following the application of $>500$ rf "crusher" pulses that nearly zero-out the $^{129}$Xe polarization (time periods marked by vertical green bars); $P_{\text{Xe}}$ (red circles) was sampled via field-cycled near-IR spectroscopy (c) before and after application of the crusher pulses. (e) Similar to (d), with $^{129}$Xe NMR signals acquired with different interpulse durations and with polarization decay observed after turning the laser off (times demarked with vertical arrows); here $^{129}$Xe decay was observed with the SEOP cell temperature maintained at 65 °C. Pulse delay (PD) refers to timing between NMR acquisitions during build-up. (f) Exponential buildup of $^{129}$Xe polarization during the SEOP process for a cell filled with 2000 Torr of Xe and 200 Torr of N$_2$. (g) $T_1$ decay of HP $^{129}$Xe at r.t. obtained with the laser turned off. (h) Time-course examples showing the temperature-dependent effects of nonequilibrium "Rb runaway" in a 1500 Torr Xe SEOP cell using only 100 W laser power: a normal build-up curve at 72 °C (black squares), a mildly distorted build-up curve at 82 °C (red circles), and a significantly distorted build-up curve at 92 °C (orange triangles). All spectra were recorded with a surface coil using small radiofrequency (rf) excitation pulses with little to no measurable effect on $^{129}$Xe magnetization. Except for the fitting curves in (f) and (g), connecting lines are meant only to guide the eye.
reflects the spin-exchange rate, since generally \( k_{\text{SE}[\text{Rb}]} > \Gamma_{\text{Xe}} \) or \( k_{\text{SE}[\text{Rb}]} \gg \Gamma_{\text{Xe}} \) under our conditions. (At the highest temperatures studied, \( k_{\text{SE}[\text{Rb}]} \gg \Gamma_{\text{Xe}} \) at the lowest temperatures \( k_{\text{SE}[\text{Rb}]} \) can approach or become less than \( \Gamma_{\text{Xe}} \), but \( \Gamma_{\text{Xe}} \) is expected to have a more mild dependence on surface temperature that trends in the opposite direction.)

However, \( P_{\text{max}} \) exhibits significantly different behavior, for example, peaking at \( \sim 72 \) °C for the data in Figure 3a. \( P_{\text{max}} \) is given by

\[
P_{\text{max}} = \frac{k_{\text{SE}[\text{Rb}]}(r)}{k_{\text{SE}[\text{Rb}]}(r) + \Gamma_{\text{Xe}}(P_{\text{rb}})}
\]

where \( P_{\text{rb}}(r) \) is the spatial average of the local Rb electron spin polarization, \( P_{\text{rb}}(r) \), which itself is determined by

\[
P_{\text{rb}}(r) = \frac{\gamma_{\text{OP}}(r)}{\gamma_{\text{OP}}(r) + \Gamma_{\text{rb}}(r)}
\]

where \( \gamma_{\text{OP}}(r) \) is the local Rb optical pumping rate (the integrated product of the laser flux at position \( r \) and the Rb absorption cross section) and \( \Gamma_{\text{rb}} \) is the Rb electronic spin destruction rate (which is essentially proportional to \( [\text{Xe}] \) under our conditions). Intuitively from eq 2, \( \frac{\text{Xe}}{\text{Rb}} P_{\text{max}} \rightarrow (P_{\text{rb}}) \) when \( k_{\text{SE}[\text{Rb}]}(r) \gg \Gamma_{\text{Xe}}(r) \) which occurs at higher temperatures. However, having higher Rb densities generally translates into greater optical density, which in turn gives rise to reduced transmittance of the laser light and hence poorer illumination throughout the cell, lower \( \gamma_{\text{OP}} \), and ultimately reduced \( P_{\text{rb}}(r) \), thereby decreasing \( P_{\text{max}} \). Thus, \( P_{\text{max}} \) initially grows with increasing temperature as more Rb is vaporized (e.g., Figure 3a), but once \([\text{Rb}]\) becomes too high, overall \( P_{\text{max}} \) decreases in accordance with eq 3, resulting in lower \( ^{129}\text{Xe} \% P_{\text{max}} \) at some of the highest temperatures studied.

The highest \( P_{\text{max}} \) values in the contour plots of Figure 3c–l were always achieved at the maximum LDA power of 170 W. However, as the Xe density increased, the optimal temperature decreased from 92 to 62 °C, in qualitative agreement with our previous results obtained at a much smaller scale. This inverse relationship between Xe density and optimal cell surface temperature, an effect amplified by the use of frequency-narrowed lasers, may be explained in part by the fact that as \( [\text{Xe}] \) rises, Xe-induced Rb spin-destruction becomes increasingly dominant; thus, lowering the cell temperature helps maintain a sufficient “photon-to-Rb” ratio to ensure high global \( P_{\text{rb}}(r) \) and hence higher \% \( P_{\text{max}} \) (provided that the cell \( ^{129}\text{Xe} T_1 \) is sufficiently long). The effect may also be exacerbated by greater in-cell temperature gradients caused by (i) greater absorption of laser energy and (ii) the several-fold lower thermal conductivity of Xe compared to that of \( \text{N}_2 \). Indeed, the effects of differential heating are also manifested in the \( \gamma_{\text{SE}}(r) \) is not a constant of exterior cell temperature but shows some variation. For example, the value at 100 W, 82 °C for the 2000 Torr Xe gas composition is nearly twice that for the 275 Torr Xe gas composition; overall, apparent \( \gamma_{\text{SE}} \) values tend to increase with increasing laser power and \( [\text{Xe}] \), consistent with higher-than-expected Rb vapor densities (and higher internal temperatures) under these conditions.
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Table 1. Summary of Maximum $^{129}$Xe % $P_{\text{max}}$ $M'_{\text{Xe}}$ ($M'_{\text{Xe}} = (\% P)(\text{C}_{129\text{Xe}}))$, and Other $^{129}$Xe Hyperpolarizer Metrics Achieved for Five Gas Mixtures$^a$

<table>
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<tr>
<th>Xe/N$_2$ partial pressure (Torr)</th>
<th>$C_{129\text{Xe}}$ (mM)</th>
<th>% $P_{\text{max}}$ (max) (%)</th>
<th>% $P_{\text{max(app)}}$ (%)</th>
<th>$M'_{\text{Xe}}$(max) (mM)</th>
<th>production cycle time (min)</th>
<th>apparent production rate (L/h)</th>
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<tr>
<td>275/1725</td>
<td>3.9</td>
<td>95 ± 9</td>
<td>13 ± 1</td>
<td>3.7 ± 0.3</td>
<td>51</td>
<td>0.94</td>
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<tr>
<td>515/1485</td>
<td>7.4</td>
<td>73 ± 4</td>
<td>19 ± 1</td>
<td>5.4 ± 0.3</td>
<td>53</td>
<td>0.91</td>
</tr>
<tr>
<td>1000/1000</td>
<td>14.3</td>
<td>60 ± 2</td>
<td>30 ± 1</td>
<td>8.5 ± 0.3</td>
<td>98</td>
<td>0.49</td>
</tr>
<tr>
<td>1500/500</td>
<td>21.4</td>
<td>41 ± 1</td>
<td>31 ± 1</td>
<td>8.8 ± 0.2</td>
<td>84</td>
<td>0.57</td>
</tr>
<tr>
<td>2000/200</td>
<td>28.6</td>
<td>31 ± 1</td>
<td>28 ± 1</td>
<td>9.0 ± 0.2</td>
<td>98</td>
<td>0.49</td>
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$^a$Apparent or usable $^{129}$Xe hyperpolarization % $P_{\text{max(app)}}$ is computed according to ref 23 to reflect that $^{129}$Xe is diluted by N$_2$ gas as follows: % $P_{\text{max(app)}} = (\% P_{\text{max}})/(P_{\text{Xe}}/P_{\text{tot}})$ where $P_{\text{Xe}}$ is partial pressure of Xe and $P_{\text{tot}}$ is total mixture pressure. The production cycle time (for producing of ~0.8 L of HP $^{129}$Xe/N$_2$ gas mix) is calculated as the sum of $2/\gamma_{\text{SEOP}}$ (i.e., when the bulk (87% of $P_{\text{max}}$) of $^{129}$Xe hyperpolarization is established, in addition to a reasonable (25 min long) interval necessary to unload/reload the OP cell (with cool-down/reheating procedure described in ref 24) with xenon mix; $\gamma_{\text{SEOP}}$ Value corresponding to a maximum value of % $P_{\text{max}}$ was used for every gas composition. The production rate is calculated by dividing ~0.8 L gas volume expanded in the Tedlar bag during each production cycle by the production cycle time.

Next, there is a clear indication that all the studied Xe densities benefited from the increased laser power (see also Figure 5). Consequently, the use of LDA power greater than 170 W should lead to further increases in % $P_{\text{max}}$. Furthermore, if the increased heat load could be mitigated, greater LDA power would allow for operation in the regimes with higher [Rb], thereby increasing $\gamma_{\text{SEOP}}$ and HP $^{129}$Xe production rate.

Data are absent from some regions of the SEOP maps in Figures 3c–l. These regions were avoided because the build-up rate $\gamma_{\text{SEOP}}$ was found to be excessively long, the % $P_{\text{max}}$ values were clearly low, and/or the conditions would render an unfavorable high [Rb], resulting in undesirable effects dubbed “Rb pre-runaway” or “Rb runaway”. The phenomenon of “Rb runaway” takes place when undissipated heat from laser absorption or cell heating rapidly compounds the amount of Rb in the vapor phase over a short time;9,21 the increasing [Rb] results in decreasing $P_{\text{Rb}}$ in more poorly illuminated regions of the cell and hence more laser absorption and heat dissipation from the gas into the inner surface of the cell (and Rb pools) in a self-reinforcing pattern. The effect can be characterized by its severity: In full Rb runaway, one sees a dramatic decrease in the amount of laser light transmitted through the cell over time which may be followed by deteriorating $P_{\text{Xe}}$ and even elevated exterior cell surface temperatures. The behavior is also hysteretic, as simple temperature reduction to normal operating regimes generally fails to regain efficient SEOP. On the other hand, a more mild condition (here termed “Rb pre-runaway”) does not have as pronounced a manifestation in the transmitted laser’s near-IR spectroscopy but is readily observed during measurements of the kinetics of $P_{\text{Xe}}$ build-up. Examples of “Rb pre-runaway” can be seen in Figure 2h (orange trace), where $P_{\text{Rb}}$ grows, passes the maximum, and then dips. The effect is less pronounced in Figure 2h (red trace) and nonobservable in Figure 2h (black trace). While true “Rb runaway” causes % $P_{\text{Xe}}$ to irreversibly deteriorate and requires a restart of the SEOP procedure from initial conditions to lower [Rb], “Rb pre-runaway” is not hysteretic and can be more easily controlled by reducing the cell temperature. However, it results in lower polarization (Figure 2h). In any case, these deleterious effects are more problematic for higher Xe densities because of the greater Rb spin-destruction rates (and hence greater light absorption from more poorly polarized Rb, as well as any possible contributions from reduced thermal conductivity).

Table 1 summarizes the maximum achieved $^{129}$Xe polarization (% $P_{\text{max}}$) for every Xe:N$_2$ mix studied. The results show not only the trend of decreased % $P_{\text{max}}$ with increasing Xe in-cell pressure but also a corresponding decrease in $\gamma_{\text{SEOP}}$ measured at these optimal conditions, a finding that predominantly reflects the lower concentration of Rb vapor that must be attained to achieve maximal $^{129}$Xe polarization at higher Xe densities. Nevertheless, the optimization process allows the total magnetization ($M'_{\text{Xe}}$) to continue to grow despite the decrease in % $P_{\text{max}}$ as the $^{129}$Xe density increases faster than % $P_{\text{max}}$ decreases. While the $^{129}$Xe polarization values (and amounts) are significantly higher here than those in ref 21, the improvement in $M'_{\text{Xe}}$ from 1000 to 2000 Torr of Xe is...
Figure 5. Hyperpolarized $^{129}$Xe gas MRI at 47.5 mT. (a) y-slice/projection across the center of the image shown in (b). (b–e) Selected MRI gradient echo (GRE) images from a series of 20 images. All 20 images were acquired identically with TE = 4.0 ms, TR = 80 ms (limited by the spectrometer electronics response time), 50% k-space sampling, $64 \times 64$ imaging matrix with $72 \times 72$ mm$^2$ field of view (FOV), and a spectral width of 20 kHz. (f) Decay of HP signal primarily due to rf-pulse-induced polarization loss. The temporal decay of the signal measured between individual images within 20-image series was used to calibrate rf pulse width ($2.7 \pm 0.1^\circ$ corresponding to 20 $\mu$s at around 80 mW) using $T_1$ determined by the data shown in Figure 4c, because the signal decay in Figure 5f is due to both $T_1$ decay and excitation rf-pulse-associated magnetization losses.

more marginal. Higher laser power may provide further improvements in % $P_{\text{max}}$ and $M'_\text{Xe}$ at high [Xe] by allowing operation with higher Rb densities and hence higher $\gamma_{SEOP}$ performance summarized in Table 1 include the apparent % $P_{\text{Xe}}(\text{max})$ due to Xe dilution by N$_2$ gas (% $P_{\text{Xe}}(\text{max,app})$), production cycle time, and apparent production rate of hyperpolarized gas (L/h). % $P_{\text{Xe}}(\text{max,app})$ is a useful metric, because it takes into account HP Xe dilution by N$_2$ gas, which has not been eliminated because the HP Xe cryocollection step was obviated. Production cycle time corresponds to the time necessary to complete the production of $\sim0.8$ L of HP Xe/N$_2$ gas composition and return the hyperpolarizer (i.e., gas reloading, etc.) to the same step in the operational cycle. Computed in this fashion production cycle time was used for estimating the apparent production rate of the hyperpolarizer in liters of hyperpolarized Xe/N$_2$ mixture per hour. The production rate in L/h is truly the characteristic of continuous-flow hyperpolarizers, and the apparent production rate values computed in Table 1 should be used with care for direct comparison with continuous-flow hyperpolarizers, because the batch-mode method used here produces a single batch per each production cycle, and there is no produced HP $^{129}$Xe until the cycle is finished.

To validate the in situ NMR results, the polarized contents of the SEOP-cell filled with 1000 Torr of Xe and 1000 Torr of N$_2$ was transferred into an evacuated ($<10^{-3}$ Torr) 0.05 L hollow polypropylene sphere located in a rf probe of a 47.5 mT imaging system 54,59,60 (see Supporting Information for details). In-cell $P_{\text{Xe}}$ was measured in situ as $54 \pm 5%$ before the transfer, and a $P_{\text{Xe}}$ value of $51 \pm 2%$ was detected in the 47.5 mT preclinical MRI scanner (558.6 kHz $^{129}$Xe Larmor frequency), corresponding to polarization enhancement $\epsilon > 11,000,000$ after the gas transfer (Figure 4b). The HP $^{129}$Xe transfer from the polarizer was performed without a cryocollection process.24,25,30 Figure 5 also demonstrates the feasibility of millimeter-scale MRI of hyperpolarized $^{129}$Xe at very low magnetic fields using frequency optimized rf coils.54

■ CONCLUSIONS

Simultaneous optimization of various SEOP conditions (Xe density, cell surface temperature, and photon flux) combined with previously reported SEOP hardware improvements24,29,30 yielded greatly improved % $P_{\text{Xe}}$. Indeed, very high values of % $P_{\text{Xe}}$ and $M'_\text{Xe}$ were demonstrated here for dense (up to 2000 Torr of Xe in 2200 Torr total) Xe gas mixtures, in part enabled by optimized laser illumination throughout the cell, ultralong in-cell $^{129}$Xe relaxation times, and efficient thermal management that also allows for diligent avoidance of “Rb runaway” regimes. The SEOP condition maps provide guidance for the production of highly polarized $^{129}$Xe gas at different xenon densities for a wide variety of applications ranging from materials science to biomedical imaging. Furthermore, our results indicate that the $P_{\text{Xe}}$ values at higher Xe densities are still laser-power-limited. Thus, while the benefit in total Xe magnetization was less substantial at the highest Xe densities studied, the advantage will likely be improved when more powerful LDA instrumentation is available provided that the greater thermal loads can be mitigated. Finally, the highly reproducible maps of $\gamma_{SEOP}$ build-up rates, combined with automated fine control of cell conditions and real-time spectroscopic feedback, should also allow optimization of multiexponential Xe polarization dynamics, pointing the way to multifold improvements in HP $^{129}$Xe production efficiency.
ASSOCIATED CONTENT

Supporting Information
Detailed information regarding the SEOP setup used, the preparation processes, and experimental parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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