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Accessibility
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 ($P_{\text{Xe}}$). $P_{\text{Xe}}$ 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 $P_{\text{Xe}}$ 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 $P_{\text{Xe}}$ 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 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 flow,15−25 (sometimes also referred to as “batch mode”) with respect to the delivery of Xe gas to and from the polarization cell. $N_2$ 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 $N_2$ (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,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 technologies 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, $M_{\text{Xe}}$, delivered in a clinically useful gas volume, typically $\sim$0.5−1 L at 760 Torr. $M_{\text{Xe}}$ is determined by the product of nuclear spin polarization $P_{\text{Xe}}$ and $^{129}$Xe concentration [Xe], i.e., $M_{\text{Xe}} \propto P_{\text{Xe}}[\text{Xe}]$. It is therefore important to maximize $M_{\text{Xe}}$ through both $P_{\text{Xe}}$ and [Xe], which is challenging because $P_{\text{Xe}}$ 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 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_{Xe} 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_{Xe} accumulation (Γ_{SEOP}) and the maximum attainable steady-state P_{Xe} value [P_{Xe}(t → ∞) or 129Xe P_{max}] 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 thermoelectric 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 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_{Xe} accumulation (Γ_{SEOP}) and the maximum attainable steady-state P_{Xe} value [P_{Xe}(t → ∞) or 129Xe P_{max}] 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.

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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 3H 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 (200000 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 at the frequency of the reference sample of thermally polarized sodium 1-13C-acetate dissolved in D₂O (Figure 4a). The 129Xe T₁ relaxation time inside the polypropylene phantom sphere was ~9.2 min (Figure 4c), which is sufficient for short-term storage of 129Xe. Moreover, this 129Xe T₁ 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 T₁ decay and excitation rf pulses. A y-slice

Figure 1. (a) Spin exchange optical pumping (SEOP) 3D-printed polarizer used to perform all in situ experiments. (b) Side view of laser aligned to the SEOP oven, SEOP cell, and near-IR spectrometer. (c) Top view, with the oven lid removed to show SEOP cell.
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–l); 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]$_i$. This dependence of $\gamma_{\text{SEOP}}$ on [Rb]$_i$ 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

projection of fast gradient echo (GRE) imaging with millimeter-scale spatial resolution without slice selection shows the excellent $^{129}$Xe signal intensity (Figure 5a). All 20 images (Figure 5b–e, selected images shown) were acquired identically with TE = 4.0 ms, TR = 80 ms (limited by the spectrometer electronics response time), 50% k-space sampling, 64 × 64 imaging matrix with 72 × 72 mm$^2$ field of view (FOV), and a spectral width of 20 kHz. Given the relatively long $T_1$ in the phantom (Figure 4c), the decay of the hyperpolarized signal was primarily due to rf-pulse-induced polarization loss in Figure 5f. The calibrated rf pulse width for the flip angle (2.7° ± 0.1°) was used for calculation of % $P_{\text{Xe}}$ for the HP $^{129}$Xe post-transfer in Figure 4 (see Supporting Information for details).

...
reflects the spin-exchange rate, since generally \( k_{\text{SE}[\text{Rb}]} > \Gamma_{\text{Xe}} \) or
\( k_{\text{SE}[\text{Rb}]} > \Gamma_{\text{Xe}} \) under our conditions. (At the highest
temperatures studied, \( k_{\text{SE}[\text{Rb}]} > \Gamma_{\text{Xe}} \) 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.56)

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

\[
P_{\text{max}} = \frac{k_{\text{SE}[\text{Rb}]} + \Gamma_{\text{Xe}}(P_{\text{Rb}})}{k_{\text{SE}[\text{Rb}]} + \Gamma_{\text{Xe}}(P_{\text{Rb}})}
\]
(2)

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

\[
P_{\text{Rb}}(r) = \frac{\gamma_{\text{OP}}(r)}{\gamma_{\text{OP}}(r) + \Gamma_{\text{Rb}}}
\]
(3)

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).29,30 intuitively from eq 2, \( 129\text{Xe} P_{\text{max}} \rightarrow
(P_{\text{Rb}}) \) when \( k_{\text{SE}[\text{Rb}]} > \Gamma_{\text{Xe}} \) 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 \( P_{\text{Rb}} \),
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 \( P_{\text{Rb}} \) decreases
in accordance with eq 3, resulting in lower \( 129\text{Xe} \) \% \( P_{\text{eff}} \) 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.21,51 This
inverse relationship between Xe density and optimal cell surface
temperature, an effect amplified by the use of frequency-
narrowed lasers,28 may be explained in part by the fact that as
\( [\text{Xe}] \) rises, Xe-induced Rb spin-destruction becomes increas-
ingly dominant; thus, lowering the cell temperature helps
maintain a sufficient "photon-to-Rb" ratio to ensure high global
\( P_{\text{Rb}} \) and hence higher \% \( P_{\text{max}} \) (provided that the cell \( 129\text{Xe} \) \% \( P_{\text{max}} \)
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 \( \text{N}_2 \).57,58 Indeed,
the effects of differential heating are also manifested in the \( \gamma_{\text{SEOP}} \)
maps: \( \gamma_{\text{SEOP}} \) (and hence \( \gamma_{\text{SE}} \)) 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 \( \gamma_{\text{SEOP}} \) 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.
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 % $P_{max}$. Furthermore, if the increased heat load could be mitigated, greater LDA power would allow for operation in the regimes with higher $Rb$ in the vapor phase over a short time;9,21 the increasing $[Rb]$, thereby increasing power would allow for operation in the regimes with higher LDA densities benefiting from the increased laser power.

Table 1. Summary of Maximum $^{129}$Xe % $P_{max}$, $M'_{Xe}$ (M'$_{Xe}$ = (% P)($C_{129Xe}$)), and Other $^{129}$Xe Hyperpolarizer Metrics Achieved for Five Gas Mixtures

<table>
<thead>
<tr>
<th>Xe/N$_2$ partial pressure (Tor)</th>
<th>C$_{129Xe}$ (mM)</th>
<th>$P_{Xe}$(max) (%)</th>
<th>$P_{Xe}$(max,app) (%)</th>
<th>$M'_{Xe}$(max) (mM)</th>
<th>production cycle time (min)</th>
<th>apparent production rate (L/h)</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<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>
</tr>
</tbody>
</table>

$^a$Apparent or usable $^{129}$Xe hyperpolarization % $P_{max}$(app) is computed according to ref 23 to reflect that $^{129}$Xe is diluted by N$_2$ gas as follows: % $P_{Xe}$(max,app) = $P_{Xe}$(max)$/(P_{Xe}/P_{tot})$ where $P_{Xe}$ is partial pressure of Xe and $P_{tot}$ 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 2/3$\gamma_{SEOP}$ (i.e., when the bulk (~75% of $P_{max}$) 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; $\gamma_{SEOP}$ Value corresponding to a maximum value of % $P_{max}$ 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.

Figure 4. Ex situ 47.5 mT NMR spectroscopy of HP $^{129}$Xe gas expanded into a phantom. (a) $^{13}$C NMR spectroscopy using thermal $^{13}$C polarization (% $P_{13C} = 4.1 \times 10^{-6}$%) of a 17.5 mL reference sample of 5.2 g of sodium $^{13}$C-acetate dissolved in D$_2$O. 256 averages were acquired at 508 kHz resonance frequency with a 90° square excitation rf pulse. (b) $^{129}$Xe NMR spectroscopy of HP $^{129}$Xe gas ejected from the polarizer, 0.61 mmol of $^{129}$Xe spins (% $P_{129Xe} = 51 \pm 2%$); cell loading was 1000 Torr of Xe and 1000 N$_2$. The spectrum is acquired at 586.6 kHz $^{129}$Xe resonance frequency with a single scan (2.7° excitation rf pulse) and TR = 200 ms. The rf pulse is calibrated by monitoring signal decay in the MRI images (see Figure 5) and accounting for $T_1$ relaxation of the HP $^{129}$Xe in the phantom (c).

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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 $T_{\text{SEOP}}$ rates. Other useful metrics describing the overall hyperpolarizer performance summarized in Table 1 include the apparent % $P_{\text{Xe}}(\text{max})$ due to Xe dilution by N₂ 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 metric²³ because it takes into account HP Xe dilution by N₂ 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 ~0.8 L of HP Xe/N₂ 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/N₂ 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 N₂ 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 system¹⁴,⁵⁹,⁶⁰ (see Supporting Information for details). In-cell $P_{\text{Xe}}$ was measured in situ as 54±5% before the transfer, and a $P_{\text{Xe}}$ value of 51±2% was detected in the 47.5 mT preclinical MRI scanner (558.6 kHz $^{129}$Xe Larmor frequency), corresponding to polarization enhancement $\varepsilon > 11\,000\,000$ 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 $y_{\text{SEOP}}$ build-up rates, combined with automated fine control of cell conditions and real-time spectroscopic feedback, should also allow optimization of mult'exponential Xe polarization dynamics, pointing the way to multifold improvements in HP $^{129}$Xe production efficiency.
ASSOCIATED CONTENT

Supporting Information
Details 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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