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### Authors

Campos, Obed

Alaminos-Quesada, Javier

Sincomb, Stephanie

et al.

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# Phantom-Based Evaluation of Time-SLIP MRI for Measuring Spinal-Canal Lagrangian Drift

Obed Campos<sup>1</sup>, Javier Alaminos-Quesada<sup>2</sup>, Stephanie Sincomb<sup>1</sup>, Vadim Malis<sup>3</sup>, Mitsue Miyazaki<sup>3</sup>, Marta Vidorreta<sup>4</sup>, Wilfried Coenen<sup>5,\*</sup>, Cándido Gutiérrez-Montes<sup>6,8</sup>, Martínez-Bazán<sup>7,8</sup>, Geno Pawlak<sup>1</sup>, and Antonio L. Sánchez<sup>1</sup>

<sup>1</sup>University of California - San Diego, Department of Mechanical and Aerospace Engineering, La Jolla, USA

<sup>2</sup>Universidad de Castilla-La Mancha, Departamento de Mecánica Aplicada e Ingeniería de Proyectos, Ciudad Real, Spain

<sup>3</sup>University of California - San Diego, Department of Radiology, San Diego, USA

<sup>4</sup>Siemens Healthineers, Madrid, Spain

<sup>5</sup>Universidad Carlos III de Madrid, Departamento de Ingeniería Térmica y de Fluidos, Leganés, Spain

<sup>6</sup>Universidad de Jaén, Departamento de Ingeniería Mecánica y Minera, Spain

<sup>7</sup>Universidad de Granada, Area de Mecánica de Fluidos, Departamento de Mecánica de Estructuras e Ingeniería Hidráulica

<sup>8</sup>Instituto Interuniversitario de Investigación del Sistema Tierra en Andalucía (IISTA)

\*wcoenen@ing.uc3m.es

## ABSTRACT

The pulsatile motion of cerebrospinal fluid (CSF) in the spinal canal includes a mean Lagrangian drift, representing the cumulative net displacement experienced by the fluid over each oscillatory cycle. Quantifying this motion *in vivo* is challenging because the associated velocities ( $\sim \text{cm min}^{-1}$ ) are much smaller than those of the dominant oscillatory flow ( $\sim \text{cm s}^{-1}$ ), limiting the applicability of conventional phase-contrast (PC) MRI. Here we assess the suitability of Time-Spatial Labeling Inversion Pulse MRI (Time-SLIP) for characterizing this motion using *in vitro* experiments in a spinal-canal phantom. The phantom consists of a flexible tube with a rigid insert forming an eccentric annular canal representative of the spinal subarachnoid space, driven by a 1 Hz sinusoidal flow mimicking cardiac-induced CSF pulsations. Oscillatory velocities were measured with PC-MRI, while net fluid displacement over successive cycles was quantified using Time-SLIP and compared with numerical simulations. The measurements reveal spatially varying Lagrangian drift directed caudally in narrow regions and cranially in wider regions of the annulus, with magnitude scaling with the square of the local stroke volume. These results demonstrate that Time-SLIP can quantify mean Lagrangian motion associated with pulsatile CSF flow.

## Introduction

The cerebrospinal fluid (CSF) that fills the cerebral ventricles and the subarachnoid space (SAS) surrounding the brain and spinal cord undergoes cyclic motion synchronized with the cardiac and respiratory cycles. In the spinal canal, this oscillatory flow reaches peak velocities on the order of a few centimeters per second<sup>1,2</sup>. Although the flow is largely oscillatory, fluid parcels do not return exactly to their original positions at the end of each cycle. This results in a slow net displacement—referred to as Lagrangian drift—superimposed on the fast, periodic motion<sup>3–5</sup>.

While the stroke length of the oscillatory motion in the spinal canal is typically on the order of one centimeter<sup>1,2</sup>, the net particle displacement per cycle is much smaller—only a fraction of a millimeter—corresponding to mean Lagrangian velocities of a few centimeters per minute<sup>5,6</sup>. Being a closed domain, the mean Lagrangian flow inside the spinal canal must have zero net volumetric flux, implying the coexistence of simultaneous caudal and cephalic flow components across any transverse section. This bidirectional behavior, first observed by Di Chiro using radioactive tracers<sup>7</sup>, is believed to play an important role in the transport of nutrients and metabolic waste, as well as in the dispersion of drugs administered intrathecally in the lumbar region<sup>4,6</sup>.

There is considerable interest in noninvasively characterizing oscillatory CSF motion, given its relevance to several central nervous system disorders, including normal pressure hydrocephalus and syringomyelia. A widely used imaging modality is phase-contrast magnetic resonance imaging (PC-MRI), which encodes fluid velocity into the phase of the MR signal, enabling time-resolved measurements of the Eulerian velocity field<sup>8</sup>. PC-MRI has been successfully applied to capture CSF motion driven by cardiac<sup>9</sup> and respiratory<sup>10</sup> cycles in the spinal SAS, as well as in the cerebral ventricles and their connecting

foramina<sup>11,12</sup>.

While PC-MRI provides valuable information about oscillatory flow, it is generally not well suited for quantifying mean Lagrangian motion for two main reasons. In principle, time-resolved PC-MRI measurements of the periodic velocity field can be averaged over a cycle to determine the time-averaged Eulerian velocity. However, when the oscillatory velocity is much larger than its time-averaged component, as is the case for CSF motion in the spinal canal, the technique has been shown to lack the sensitivity required for accurate quantification<sup>13</sup>. Moreover, even when PC-MRI provides sufficient accuracy, the resulting time-averaged Eulerian velocity generally differs from the mean Lagrangian velocity governing fluid-particle displacement because the latter typically includes a significant Stokes-drift contribution that cannot be recovered from the time-averaged Eulerian velocity alone<sup>4,14</sup>.

Previous efforts to capture the slow Lagrangian motion accurately have relied on invasive tracer-based techniques capable of tracking the actual movement of fluid elements, as in the pioneering work of Di Chiro<sup>7</sup> and others (see, e.g.<sup>15</sup>). The starting point of the current analysis is the realization that non-invasive imaging methods based on magnetic resonance spin labeling may be well suited for tracking the Lagrangian motion of the fluid. In particular, we will be using Time-Spatial Labeling Inversion Pulse (Time-SLIP) MRI, a non-contrast technique developed to view and assess fluid displacement<sup>16</sup>. The technique works by first applying a nonselective inversion pulse to invert the entire magnetization, followed by a selective pulse that restores magnetization within a designated region, effectively creating a “tagged” volume of fluid. This tagged region can be tracked, enabling visualization of the underlying Lagrangian motion over subsequent oscillatory cycles. The duration of the time window during which the tagged fluid can be visualized, usually a few seconds, is governed by the relaxation time of the fluid<sup>17</sup>.

The development of Time-SLIP MRI as a tool to quantify CSF flow is due to Yamada et al.<sup>18</sup>, who built on earlier arterial spin-labeling techniques proposed for studying blood flow and perfusion<sup>19–25</sup>. Time-SLIP has since been employed to characterize, for example, the effects of respiration on intracranial CSF motion<sup>26</sup>, pathologic CSF flow in the spinal cord<sup>27,28</sup>, cervical flow in patients with Chiari Type I malformation<sup>29</sup>, and CSF dynamics in the mid-cervical and craniocervical junction regions of adolescents with idiopathic scoliosis<sup>30</sup>. Reviews summarizing the respective strengths of PC and Time-SLIP MRI for diagnosing and managing CSF flow disorders are available in the literature<sup>13,31</sup>. Phantom studies have also been employed to test the predictive capabilities of Time-SLIP in connection with the characterization of different flows. For instance, water phantoms have been employed in Time-SLIP studies of general slow and complex fluid flows<sup>32</sup>, CSF flow around Lilliequist membranes and arachnoid-cyst walls<sup>33</sup>, pulsatile flow in pipes of variable section<sup>34</sup>, salivary flow in the parotid duct<sup>35</sup>, and slow pancreatic juice flow<sup>36</sup>.

Like these previous studies, this paper employs a flow phantom to investigate the capabilities of Time-SLIP MRI in quantifying the mean Lagrangian displacement of CSF driven by cardiac motion in the spinal canal. It is hypothesized that the available measurement window—a few seconds following pulse labeling—is sufficient to capture the Lagrangian displacement of CSF fluid over several cardiac cycles. To test this hypothesis, we designed and built a simplified model of the spinal canal consisting of an eccentric, compliant annular space sealed at one end. The phantom is tested in a 3 T Siemens MRI scanner, using phase-contrast (PC) MRI to characterize the oscillatory flow and Time-Spatial Labeling Inversion Pulse (Time-SLIP) MRI to capture the associated cyclic Lagrangian drift. The measurements are compared with MRI-informed numerical simulations based on the Navier–Stokes equations. Semi-automatic image processing is employed to quantify the cyclic Lagrangian displacements. Analysis of the signal-to-noise ratio provides insight into the limitations of the technique with respect to spatial resolution, as well as its dependence on stroke volume and number of cycles. The results, which highlight both the potential and the limitations of Time-SLIP for characterizing Lagrangian drift, lay the groundwork for future *in vivo* investigations.

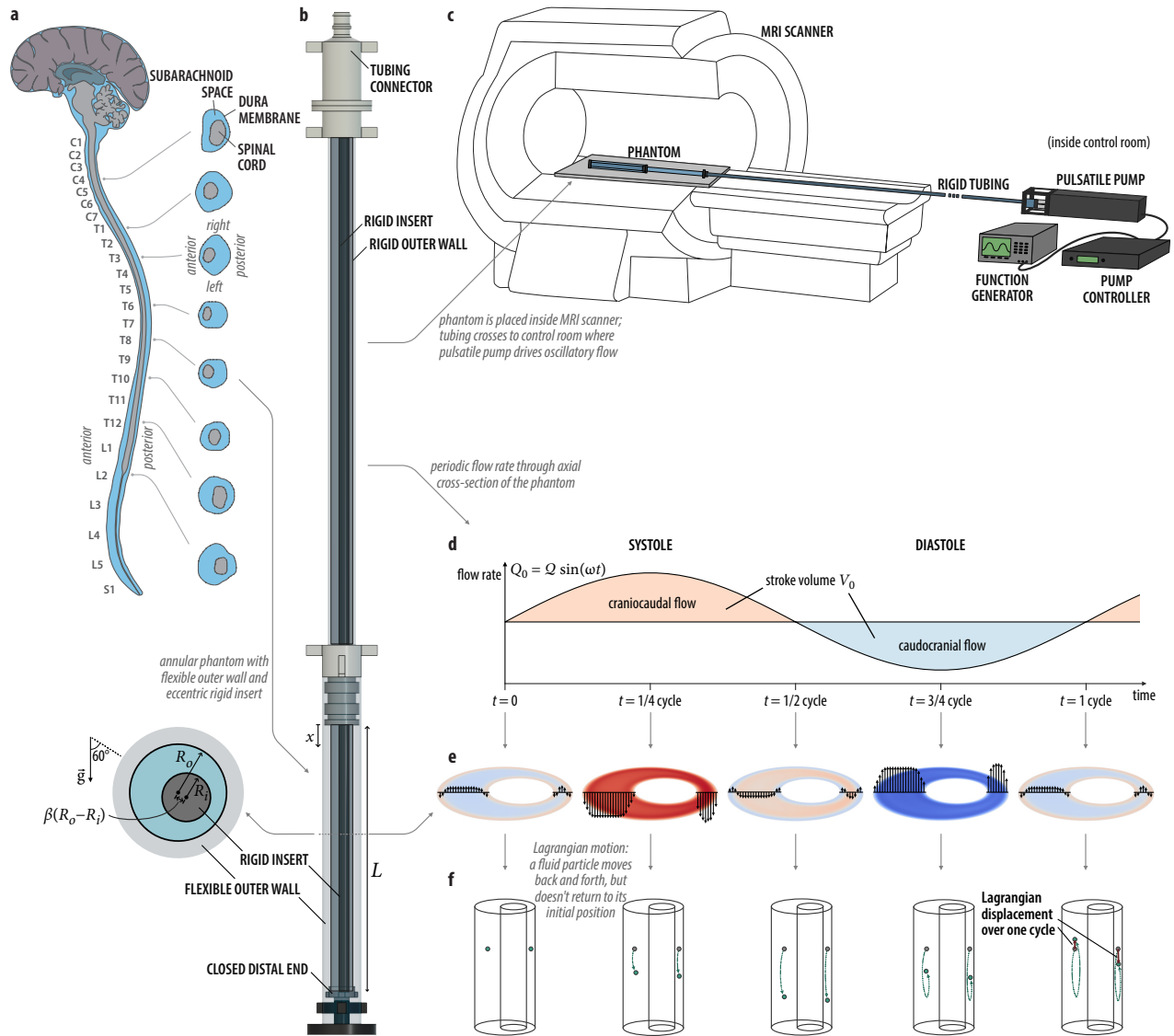
## Methods

### Spinal canal phantom: design and experimental setup

The spinal SAS is a compliant annular channel of length  $L \sim 40\text{--}60$  cm and characteristic width  $h \sim 4$  mm, bounded internally by the pia mater surrounding the spinal cord and externally by the deformable dura membrane. As shown in Fig. 1a, the canal is eccentric: the spinal cord lies closer to the posterior side of the dura in the cervical and lumbar regions, and closer to the anterior side in the thoracic region. This eccentricity has been shown to play an important role in the resulting CSF motion<sup>5</sup>.

The CSF filling the canal undergoes pulsatile motion driven by periodic pressure variations induced by the cardiac and respiratory cycles. These fluctuations are accommodated by venous blood displacement and compression of the fatty tissue in the epidural space surrounding the dural sac. The dominant oscillatory flow, characterized by stroke lengths  $L_s \sim 1$  cm and a nearly zero net flow rate, is spatially non-uniform, promoting nonlinear interactions that give rise to a persistent bidirectional secondary flow that recirculates fluid along the canal.

The phantom, shown in Fig. 1b, is designed to maximize simplicity while retaining the key features of the spinal SAS, namely an eccentric annular geometry with a closed end and a deformable outer boundary. The spinal cord is represented by a rigid rod insert of radius  $R_i = 5$  mm, while the dura membrane is modeled by a coaxial flexible tube (silicone, Ecoflex OO-30)



**Figure 1.** (a) Schematic diagram of the human subarachnoid space, showing the eccentric location of the spinal cord within the spinal canal. (b) Spinal canal phantom, with indication of its rigid and flexible parts, and the eccentric placement of the insert that mimics the spinal cord. (c) The phantom is placed inside the MRI scanner and is connected via rigid tubing to a pulsatile pump inside the control room. (d) The pulsatile pump drives a periodic flow rate through the phantom. (e) Snapshots of the (Eulerian) velocity distribution at different phases of the oscillation cycle. (f) Schematic illustrating how, in every cycle, fluid moves back and forth, but does not return to its initial position, resulting in a net Lagrangian displacement.

of radius  $R_o = 11$  mm and length  $L = 28$  cm. To facilitate flow measurements, the flexible tube is connected upstream to a rigid transparent tube with the same inner radius  $R_o = 11$  mm, providing a non-deformable annular section. As indicated in the inset near the bottom of Fig. 1b, the eccentricity is imposed by offsetting the longitudinal axes of the tube and rod by a distance  $\beta(R_o - R_i)$ , which is kept constant along both the flexible and rigid sections of the phantom. The entire setup is placed inside a custom container that allows the flexible section to rest on a platform, mimicking a subject lying supine in an MRI scanner, as shown in Fig. 1c.

Water was used as the working fluid because its density,  $\rho \simeq 10^3$  kg/m<sup>3</sup>, kinematic viscosity,  $\nu \simeq 0.7 \times 10^{-6}$  m<sup>2</sup>/s, and magnetization properties are similar to those of CSF. To mimic cardiac-driven flow, a programmable piston pump (SuperPump AR, ViVitro Labs, Victoria, Canada), located outside the MRI room, was connected to the rigid section of the phantom through corrugated PVC tubing. Although the waveform of the spinal-canal flow rate is nonsinusoidal<sup>9</sup>, our previous numerical analyses<sup>37</sup> have shown that the magnitude of the Lagrangian displacement depends primarily on the stroke volume, rather than on the specific waveform of the imposed flow rate. Therefore, for simplicity, the experiments employed the sinusoidal flow

rate  $Q_0(t) = \mathcal{Q} \sin(\omega t)$  shown in Fig. 1d, with peak amplitude  $\mathcal{Q}$  and angular frequency  $\omega = 2\pi \text{ s}^{-1}$  (60 beats per minute), corresponding to a cardiac period  $T = 2\pi/\omega = 1 \text{ s}$ . The associated Womersley number,  $\alpha = [\omega(R_o - R_i)^2/\nu]^{1/2} \simeq 18$ , is comparable to, although somewhat larger than, that characterizing flow in the human spinal SAS ( $\alpha \simeq 12$ ). As shown in<sup>3</sup>, such differences in Womersley number do not lead to significant qualitative changes in the resulting mean Lagrangian motion.

The local flow rate  $Q$ , equal to  $Q_0$  in the rigid section of the canal, decreases with distance from the entrance of the flexible tube  $x$  and vanishes at the closed end of the canal ( $x = L$ ). Correspondingly, the stroke volume  $V_s(x) = \frac{1}{2} \int_t^{t+T} |Q| dt$  and the associated stroke length  $L_s(x) = V_s(x)/[\pi(R_o^2 - R_i^2)]$  also decrease from their entrance values  $V_s(0) = V_0 = \frac{1}{2} \int_t^{t+T} |Q_0| dt = 2\mathcal{Q}/\omega$  and  $L_s(0) = L_0 = V_0/[\pi(R_o^2 - R_i^2)]$  to zero at  $x = L$ . Because the tubing connecting the pump to the phantom is not fully rigid, small—yet non-negligible—spatial variations of the flow rate can be expected to occur along the feed line, so that the stroke volume at the phantom entrance,  $V_0 = V_s(0)$ , can differ from the pump output. Consequently, separate provisions were made to measure  $V_0$ , as described below.

### Phase-Contrast MR: acquisition and analysis

MR imaging was performed at the Mind, Brain, and Behavior Research Center of the University of Granada on a 3T Magnetom Prisma Fit scanner (Siemens Healthineers, Forchheim, Germany) using a 32-channel spine coil. A 2D PC-MRI sequence with the section orientation perpendicular to the lengthwise axis of the phantom was applied to acquire the fluid velocity data at different transverse sections  $x = (7, 14, 21) \text{ cm}$  along the flexible part of the phantom, corresponding to dimensionless distances  $x/L = (0.25, 0.5, 0.75)$ . To accurately evaluate the entrance stroke volume  $V_0$ , additional measurements were acquired in the rigid tube at a location 15 cm upstream from the phantom entrance. The PC-MRI parameters included the following: flip angle =  $10^\circ$ , field of view =  $160 \times 160 \text{ mm}^2$ , matrix =  $256 \times 205$ , in-plane resolution =  $0.625 \times 0.78 \text{ mm}^2$  reconstructed to  $0.625 \times 0.625 \text{ mm}^2$ , section thickness =  $10 \text{ mm}$ .

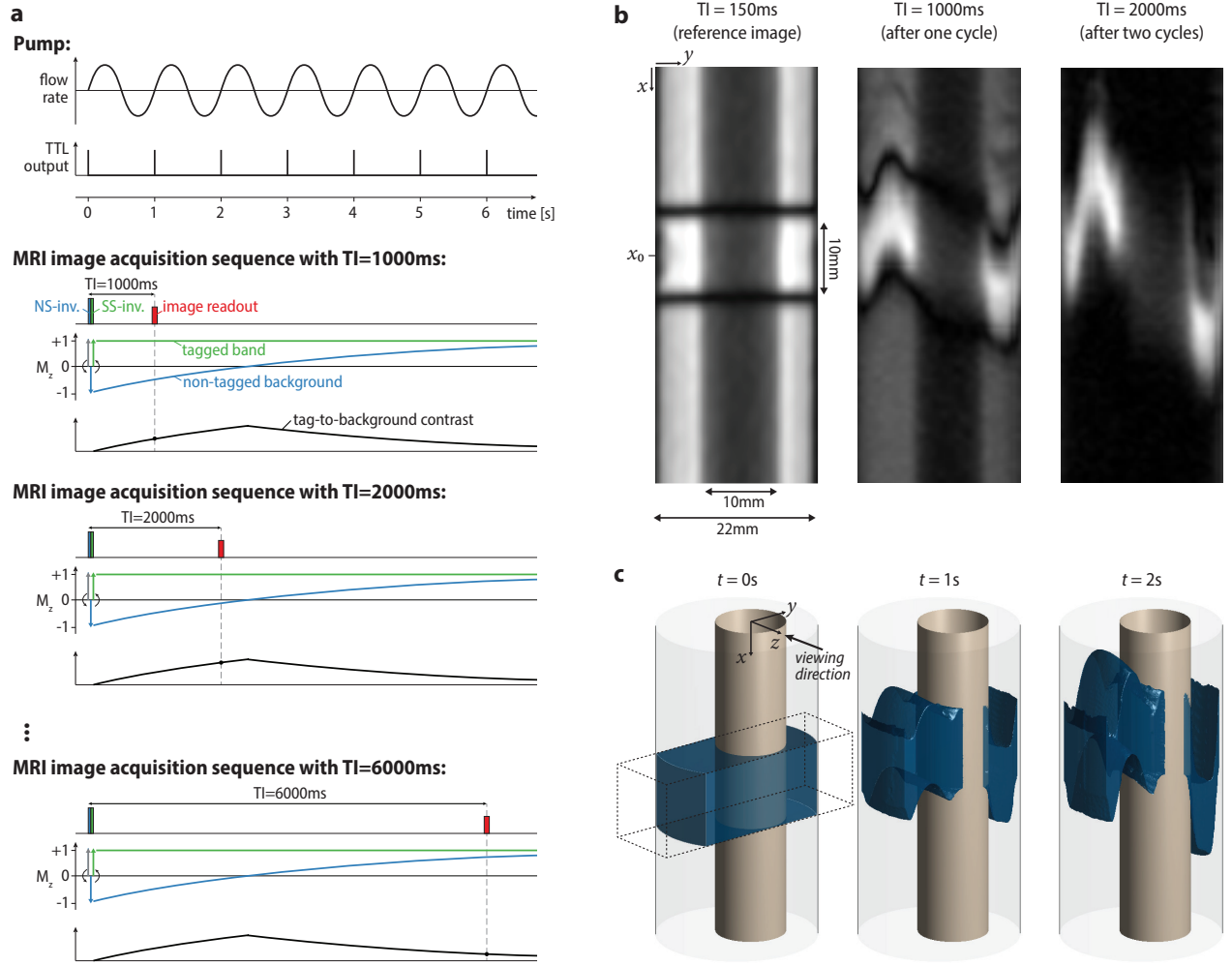
For each value of the pump stroke volume and measurement location, the velocity encoding was adjusted to the anticipated optimum (ranging from 10 cm/s to 35 cm/s), with echo times and repetition times varying correspondingly between 6.38 and 7.2 ms and 21.06 and 94.38 ms, respectively. The piston position of the pulsatile pump was used as an external signal for the retrospective gating of the PC-MRI protocol. Each acquisition yielded 40 phases per cycle. The PC-MRI images were processed using custom MATLAB code to obtain the 2D distribution of longitudinal fluid velocity at each measured cross-section of the phantom for each phase. Owing to the canal eccentricity, the resulting oscillatory velocity field exhibits strong azimuthal non-uniformity, as schematically illustrated in Fig. 1e. The velocity fields were then numerically integrated over the cross-sectional area to obtain the flow rate  $Q(x, t)$  through each section as a function of time  $t$ . Finally, integration of the flow rate over a complete oscillatory cycle yielded the stroke volume variation  $V_s(x) = \frac{1}{2} \int_0^T |Q(x, t)| dt$ .

The Eulerian mean velocity field was computed by averaging the phase-resolved PC-MRI velocity fields over one oscillation cycle. To account for the periodic deformation of the flexible outer wall, the inner and outer boundaries of the canal were detected automatically in MATLAB at each of the 40 phases. Each cross-sectional velocity field was then mapped onto a common reference cross-section, chosen as that corresponding to the phase at which the canal width equaled its cycle-averaged value, before averaging over the 40 phases.

### Time-SLIP: acquisition and analysis

As explained in previous analyses<sup>3,4,6</sup>, the spatial non-uniformity of the oscillatory velocity field implies that, at the end of each motion cycle, individual fluid particles do not return to their exact initial locations but instead experience a small net displacement, as schematically illustrated in Fig. 1f. The accumulation of these small displacements over subsequent cycles produces the net bulk motion first observed by Di Chiro<sup>7</sup>.

To measure the net cyclic displacement in our phantom, 2D sagittal Time-SLIP images were acquired using a gated, NATIVE (Non-contrast MRA of ArTerles and VEins) TrueFisp sequence with inversion preparation and balanced steady-state gradient echo readout. The short echo time associated with the acquisition helps to limit signal dephasing and image blurring. The acquisition parameters included an echo time of  $TE = 1.57 \text{ ms}$ , a receiver bandwidth of  $770 \text{ Hz/pixel}$ , and a receiver dwell time of  $2.7 \mu\text{s}$ . The relatively high bandwidth and short dwell time contribute to preserve a sharp appearance of the tagged region<sup>38</sup>. The inversion preparation consisted of a non-selective volumetric inversion and a slice-selective inversion applied to a 10mm-width band (the “tagged” fluid volume) along the phantom’s cross-section, with an in-plane resolution of  $0.379 \times 0.379 \text{ mm}^2$ . The contrast mechanism underlying this sequence is illustrated in Fig. 2a. As a result of the signal preparation at  $t = 0$ , the magnetization within the tagged volume is tipped back to its original value and thereafter remains constant, while the surrounding inverted background recovers exponentially with relaxation time  $T_1$ . Upon image readout after a time  $t = TI$  (known as the “inversion time”), the tagged volume consistently appears bright, whereas the background image intensity depends on the extent to which the magnetization has been able to recover during the time  $TI$ . Because the relaxation time  $T_1$  of water is approximately 3–4s, the resulting contrast between the tagged volume and the background, which occurs when the magnetization of the background crosses zero, is maximum around 2–3s (see Fig. 2a). After 5–6s, the tagged volume



**Figure 2.** (a) Time-SLIP MR sequence synchronized with the pulsatile pump, using TI equal to 1 up to 6 complete oscillation cycles. (b) Time-SLIP yields 2D images that show the net Lagrangian displacement of a band of tagged fluid over one or more oscillation cycles. (c) 3D numerical simulation replicates the Lagrangian motion of the tagged fluid region.

is only weakly distinguishable from the background.

To quantify the net cyclic displacement of the fluid, i.e. the displacement over a number  $n$  of complete oscillation cycles (with period  $T = 1$  s), we employ inversion times equal to  $TI = nT$ . In particular, for each stroke volume and measured location along the phantom, we performed six acquisitions, using  $TI = 1000\text{ms}, 2000\text{ms}, \dots, 6000\text{ms}$ . The position  $x_0$  of the tagged volume at  $t = 0$  was determined from a reference image taken in the absence of fluid motion. Note that the Time-SLIP sequence was synchronized with the programmable pump using its TTL output, such that  $t = 0$  corresponds to zero flow rate in the phantom (top panel of Fig. 2a). Figure 2c shows the initial location of the tagged fluid, and after one and two oscillation periods, reflecting the cumulative net Lagrangian displacement.

The image acquisition plane of the Time-SLIP technique is set along the symmetry plane of the phantom. The technique outputs a two-dimensional image corresponding to an average over the viewing direction perpendicular to this plane, with image brightness being proportional to the volume of tagged fluid across the section (Fig. 2b). As a result, the Time-SLIP images exhibit a distinct band of enhanced signal intensity associated with the tagged fluid displaced during the oscillatory motion. Note that due to the annular shape of the phantom, a weak signal intensity is obtained at the location of the cylindrical insert.

To quantitatively characterize the spatial location of this band, we reduce its two-dimensional extent to a single representative curve  $x_w(y)$ , which describes the longitudinal position of the tagged fluid as a function of the transverse coordinate  $y$ . Each point  $x_w$  is extracted independently from the longitudinal intensity profile  $I(x)$  at a given  $y$  using the following image-processing procedure, implemented in MATLAB. First, the images were cropped to the interior of the phantom (Fig. 3a). For each spanwise

position  $y$ , the corresponding longitudinal intensity profile  $I(x)$  was extracted and normalized (Fig. 3b).

The approximate location of the tagged band—identified as a broad peak in  $I(x)$ —and the background region were first determined using a threshold mask. To estimate the slowly varying background baseline, the contiguous high-intensity region containing the tagged-band peak was excluded, and a cubic smoothing spline was fitted to the remaining background samples using the MATLAB function *csaps* with smoothing parameter  $p = 10^{-5}$ . The spline was used exclusively for baseline estimation and was not applied to smooth the measured intensity profile. The fitted baseline was evaluated over the complete longitudinal profile, with any negative values set to zero, and subsequently subtracted from  $I(x)$ . A second threshold mask was then applied to the background-subtracted profile to refine the identification of the lower and upper bounds  $x_a$  and  $x_b$  of the intensity peak (Fig. 3c,d). Finally, the band location  $x_w$  was computed as an intensity-weighted average,  $x_w = \int_{x_a}^{x_b} I^n(x) x dx / \int_{x_a}^{x_b} I^n(x) dx$ , where the exponent  $n$  controls the relative weighting of the peak intensity within the band. For the results presented here,  $n = 8$  was found to provide good visual agreement between the extracted curve  $x_w(y)$  and the bright band observed in the Time-SLIP images (Fig. 3e). Using the same decomposition of the intensity profile into peak and background regions, we additionally define a spanwise signal-to-noise ratio  $\text{SNR}(y)$  to assess the reliability of the extracted displacement. The signal is quantified as the integrated intensity within the band,  $S(y) = \int_{x_a}^{x_b} I(x) dx$ , while the noise level is estimated from the root-mean-square intensity fluctuations in the background region  $\Omega_b = \{x \notin [x_a, x_b]\}$ ,  $\sigma_b(y) = \left[ \frac{1}{L_b} \int_{\Omega_b} (I(x) - \bar{I}_b)^2 dx \right]^{1/2}$ , where  $\bar{I}_b(y) = \frac{1}{L_b} \int_{\Omega_b} I(x) dx$  is the average background intensity and  $L_b$  denotes the longitudinal extent of the background region. The signal-to-noise ratio is then defined as  $\text{SNR}(y) = S(y)/\sigma_b(y)$ . All integrals are evaluated numerically from the discretely sampled intensity profiles.

For quantitative comparison with the numerical predictions, the displacement-extraction procedure described above was also applied to the numerical simulations particle-distribution maps. This yielded transverse displacement profiles  $\delta_{\text{MRI}}(y)$  and  $\delta_{\text{Sim}}(y)$  for each inversion time and axial location. The numerical simulations profiles were interpolated onto the transverse coordinates of the corresponding Time-SLIP profiles, and the root-mean-square difference was calculated as

$$\text{RMSE} = \left[ \frac{1}{N} \sum_{i=1}^N (\delta_{\text{MRI}}(y_i) - \delta_{\text{Sim}}(y_i))^2 \right]^{1/2}, \quad (1)$$

where  $N$  is the number of transverse positions at which both profiles were available. The absolute difference between the maximum displacements,

$$E_{\text{max}} = \left| \max_i |\delta_{\text{MRI}}(y_i)| - \max_i |\delta_{\text{Sim}}(y_i)| \right|, \quad (2)$$

for the narrow and for the wide side was also calculated.

Measurement repeatability and processing robustness were also examined. In particular, Time-SLIP acquisitions were repeated for six cases, yielding consistent displacement profiles. In addition, the threshold values and smoothing-spline parameter employed for the baseline estimation were varied independently by approximately 10% without appreciable changes in the extracted tagged-band locations.

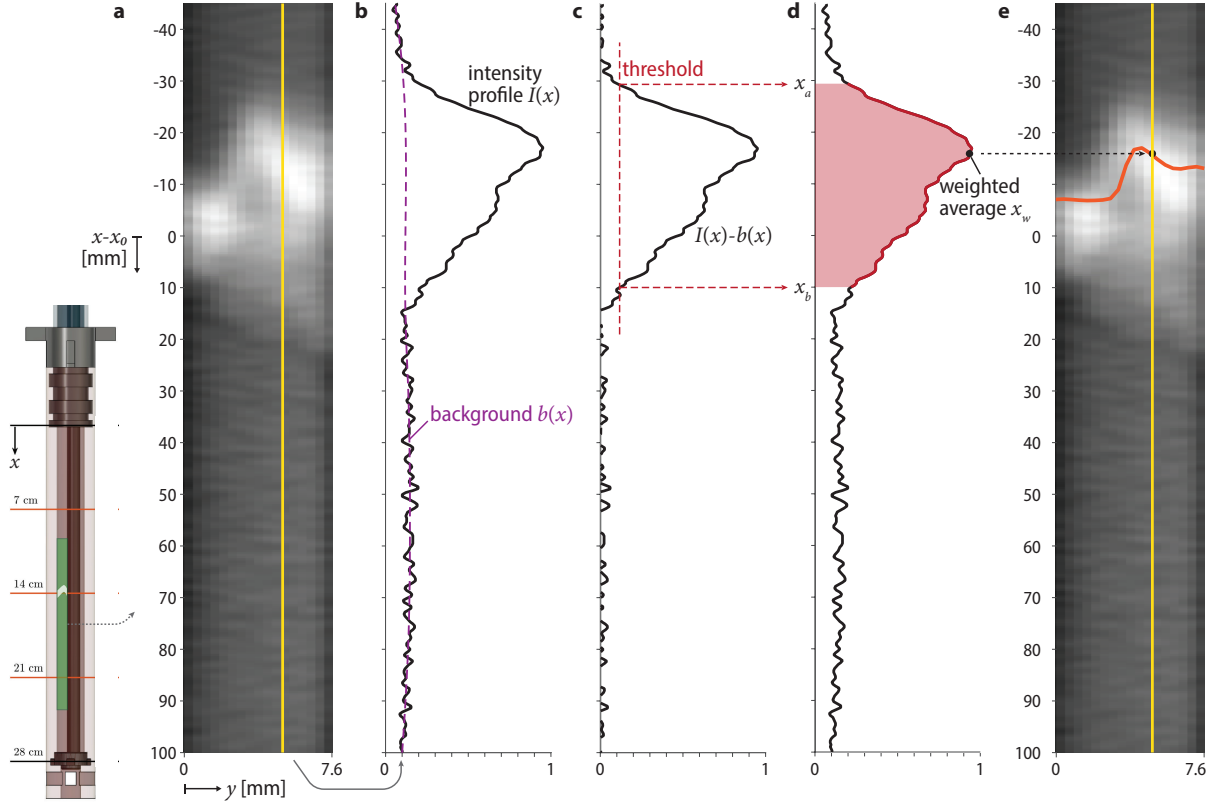
### Numerical Simulation: computations and analysis

Three-dimensional, unsteady, fully resolved numerical simulations of the experimentally observed laminar flow were performed to complement the MRI measurements. The computational domain, representing the annular canal, was generated using ANSYS Fluent Meshing (2023 R1; Ansys Inc., Pennsylvania) and consisted of a structured hexahedral grid comprising approximately  $2 \times 10^6$  cells. The maximum and minimum edge lengths were 0.0500 and 0.0076 cm, respectively, with the spatial resolution increased close to the walls to properly resolve the near-wall flow dynamics. In particular, a grid-sensitivity analysis was carried out to confirm that the selected mesh provides adequate spatial resolution to resolve the finest flow scales present in the simulations and to ensure grid-independent results. The Navier–Stokes equations for an incompressible Newtonian fluid, with density and viscosity equal to those of the water used in the experiments, were solved numerically using the finite-volume solver ANSYS Fluent (2023 R1; Ansys Inc., Pennsylvania). The numerical integration of the equations employed second-order accuracy in both space and time.

A dynamic mesh approach was employed to account for the deformation of the flexible tube<sup>14,39–41</sup>, whose radius  $R$  varies periodically in time from its unperturbed value  $R_o$  as dictated by the integral continuity balance

$$\frac{\partial}{\partial t} (\pi R^2) + \frac{\partial Q}{\partial x} = 0. \quad (3)$$

As discussed later, the PC-MRI measurements reveal a nearly linear axial distribution of the flow rate, consistent with a spatially uniform tube radius that varies in time according to  $\pi(R^2 - R_o^2) = -\int Q_0 dt / L = \mathcal{Q} \cos(\omega t) / (L\omega)$ , as follows from integration



**Figure 3.** Sample image post-processing for the case  $TI = 4000$  ms,  $V_0 = 17.32$  ml, and  $x_0 = 14$  cm. The overview schematic indicates the location and extent of the processed region, in green, within the phantom. **(a)** Time-SLIP MR image showing the band of tagged fluid (left/wide side). **(b)** Longitudinal intensity profile  $I(x)$  extracted at the fixed spanwise position  $y$  indicated by the yellow line in panel (a). **(c)** Background-subtracted intensity profile, used to identify the region of elevated signal intensity corresponding to the tagged band, bounded by  $x_a$  and  $x_b$ . **(d)** Determination of the band location  $x_w$  as an intensity-weighted average over the interval  $[x_a, x_b]$ . **(e)** Band location  $x_w(y)$  shown superimposed on the original image.

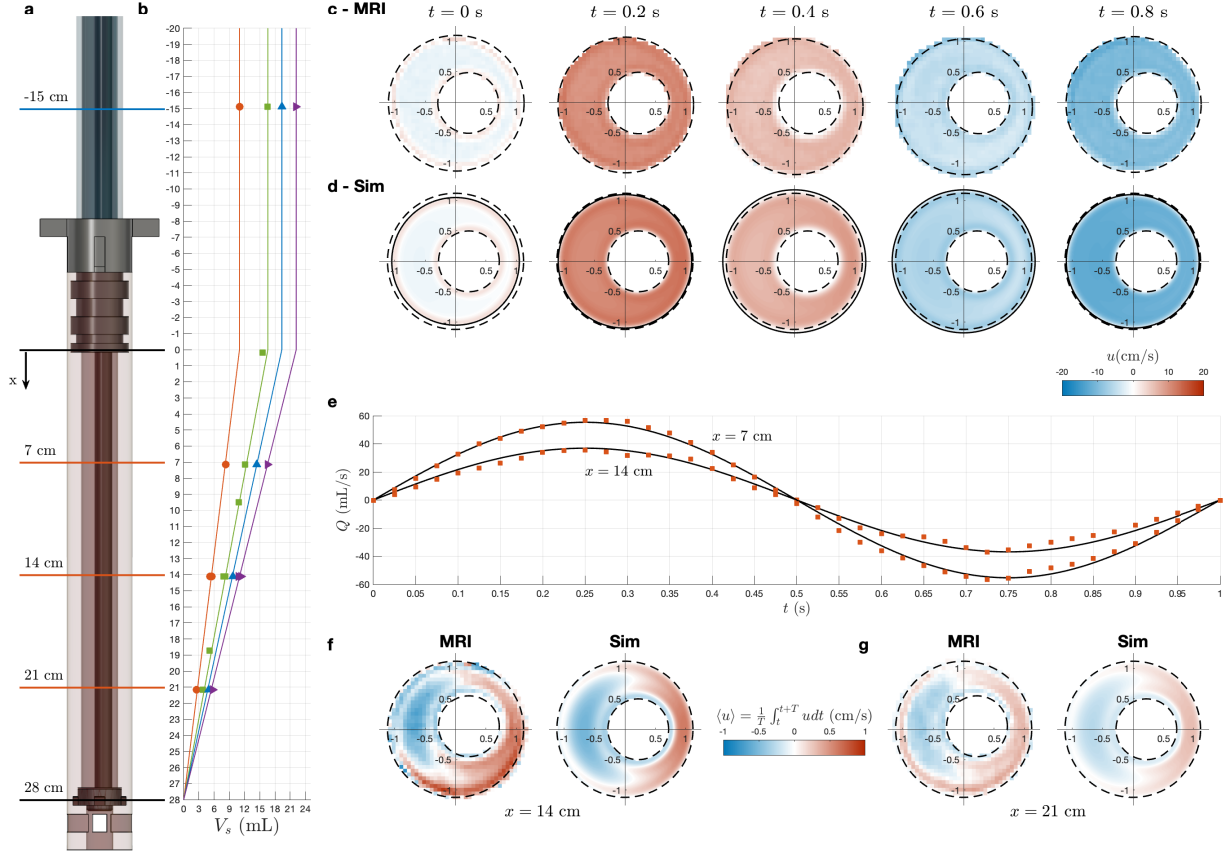
of (3), finally yielding

$$\frac{R}{R_o} = \left[ 1 + \frac{V_0}{2\pi R_o^2 L} \cos(\omega t) \right]^{1/2} \quad (4)$$

for the tube-radius variation from its unperturbed value  $R_o$ . Note that the deformation imposed is relatively small, since  $V_0 \ll 2\pi R_o^2 L \simeq 212.88$  mL in all experiments and corresponding numerical computations. Additional boundary conditions included no-slip conditions at the canal walls, and a zero-gauge static pressure condition at the entrance of the canal. Furthermore, the computational domain incorporated a buffer region of length  $0.2L$ , which was added to account for part of the rigid section of the phantom and avoid boundary-induced effects.

For comparison with the PC-MRI measurements, the phase-resolved numerical velocity fields at the corresponding axial locations were mapped onto the same reference cross-sections used for the experimental data and averaged over one oscillation cycle. The resulting Eulerian mean velocity fields were compared directly with their PC-MRI counterparts.

Tracer particles were used to compute the mean Lagrangian displacement<sup>6,42</sup>. Specifically, a cloud of massless particles, initially occupying the region corresponding to the Time-SLIP measurements (10 mm in thickness and 10 mm in axial extent), was tracked over six oscillatory cycles. The particle cloud position after each cycle provided the instantaneous location and shape of the tagged region, as illustrated in the sample results shown in Fig. 2c. For comparison with the two-dimensional Time-SLIP maps, a transverse average was performed across the thickness of the region, yielding a two-dimensional image, in which the local intensity at a given  $x - y$  location is linearly proportional to the number of particles found in the transverse direction (i.e. the *viewing* direction indicated in the first panel of Fig. 2c), analogous to the tagged fluid in the Time-SLIP MR images.



**Figure 4.** (a) Schematic of the phantom with an indication of the cross sections where PC-MRI was taken. (b) Streamwise distribution of stroke volume corresponding to four different pump outputs. (c) PC-MRI velocity measurements measured at  $x = 14$  cm for  $V_0 = 23.5$  mL and five different instants of time, with the dashed circles representing the surface of the inset and the surface of the unperturbed flexible tube (d) Velocity predictions from numerical simulations (Sim) for the conditions and locations described in (c), with the solid circle representing the instantaneous location of the flexible tube, as determined from (4). (e) Temporal variation of the flow rate at  $x = 7$  cm and  $x = 14$  cm for  $V_0 = 23.5$  mL (symbols) and accompanying theoretical prediction  $Q = (\omega V_0/2)(1 - x/L) \sin(\omega t)$ . (f), (g) Cycle-averaged axial velocity distributions, representing the Eulerian steady-streaming flow, obtained from the PC-MRI measurements and numerical simulations (Sim).

## Results

### Phase Contrast MR measurements

The oscillatory motion was characterized using PC-MRI, with the results summarized in Fig. 4. Measurements were performed at several axial locations, indicated in Fig. 4a, for four different pump stroke volumes. The measured velocity fields were used to evaluate the local stroke volume, with the results shown in Fig. 4b. The stroke volume, which is constant along the rigid tube, is observed to decay linearly with the distance  $x$  from the entrance of the flexible tube. This behavior is consistent with an outer radius undergoing an axially uniform temporal variation, thereby justifying the use of Eq. (4) in the numerical computations.

Representative PC-MRI velocity distributions measured at the midsection of the flexible tube ( $x = 14$  cm) for an entrance stroke volume  $V_0 = 23.5$  mL are shown in Fig. 4c at five equally spaced instants over the oscillatory cycle. For reference, the dashed circles denote the surface of the cylindrical inset of radius  $R_i$  and the surface of the unperturbed flexible tube of radius  $R_o$ . The images reveal a small but non-negligible variation of the cross-sectional area, with the tube adopting a slightly non-circular shape due to the influence of the resting platform. This asymmetry was quantified using the cross-sectional circularity,  $C = 4\pi A/P^2$ , where  $A$  and  $P$  denote the cross-sectional area and perimeter, respectively. For the experiment shown in Fig. 4, the computed circularity was  $C = 0.9945$ , i.e. very close to that of a circle. Similar values were obtained in all the experiments, indicating that platform- and gravity-induced deviations from axisymmetry were small.

The periodic temporal variation of the flow rate  $Q(t)$ , computed by integrating the velocity over the spinal-canal cross sections at  $x = (7, 14)$  cm, is shown in Fig. 4e. Results are reported for the 40 phases sampled over one cycle. The measurements closely follow the sinusoidal variation  $Q = (\omega V_0/2)(1 - x/L) \sin(\omega t)$ , with no measurable phase lag between the two locations, consistent with the prescribed tube-radius variation given in Eq. (4).

The PC-MRI measurements are compared with corresponding numerical results in Fig. 4d, obtained using the prescribed flexible-tube radius variation given by Eq. (4), represented by the solid-line circle. Excellent agreement is observed between the computations and the MR measurements. In both cases, the velocity profile is nearly uniform, as expected for the relatively large Womersley number  $\alpha = 18$  characterizing the flow. Thin, low-velocity Stokes layers are present near both the inner and outer boundaries. The velocity distributions at  $t = 0$  indicate that flow reversal first occurs within the Stokes layers adjacent to the bounding surfaces, a well-known feature of wall-bounded oscillatory flow that is consistently captured by both PC-MRI measurements and numerical simulations.

The cycle-averaged PC-MRI velocity fields at  $x = 14$  cm and  $x = 21$  cm are shown in Figs. 4f and 4g, respectively, together with the corresponding numerical simulations predictions. At both locations, the measurements reveal a bidirectional Eulerian mean flow, directed cranially on the wider side of the annulus and caudally on the narrower side, in qualitative agreement with the numerical results. The magnitude of the mean velocity decreases between  $x = 14$  cm and  $x = 21$  cm, consistent with the downstream reduction in local stroke volume. At  $x = 14$  cm, the measured mean velocities are of order 0.5–1 cm/s, substantially smaller than the peak oscillatory velocities, for which a VENC of 20 cm/s was required.

### Time-SLIP measurements

Sample Time-SLIP images acquired at two axial locations  $x_0 = (14, 21)$  cm using six different inversion times  $TI = 1000$ –6000 ms during oscillatory flow with an entrance stroke volume  $V_0 = 23.5$  mL are shown in grayscale in the left-hand sides of the double panels in Fig. 5. The reference image of the tagged fluid at the initial time, shown in the leftmost panel, was acquired in quiescent fluid using the minimum inversion time available on the scanner ( $TI = 150$  ms). The right-hand side of each panel shows the corresponding numerical results for the same stroke volume, with the integrated concentration of tagged fluid particles at a given location represented in blue scale.

To quantify the agreement shown in Fig. 5, the displacement-extraction procedure described above was applied independently to the Time-SLIP images and the corresponding numerical simulations particle-distribution maps. For inversion times  $TI = (1000, 2000, 3000, 4000, 5000, 6000)$  ms, the resulting RMSE values were (0.53, 0.98, 1.64, 2.13, 2.87, 4.59) mm at  $x_0 = 14$  cm and (0.69, 0.98, 1.53, 2.06, 2.91, 3.92) mm at  $x_0 = 21$  cm. At  $x_0 = 14$  cm, the difference between the maximum displacements was  $E_{\max} = (0.51, 1.27, 2.46, 2.03, 1.68, 0.12)$  mm for the wide side and  $E_{\max} = (1.01, 0.54, 0.44, 1.29, 1.91, 3.02)$  mm for the narrow side, whereas at  $x_0 = 21$  cm, these differences were  $E_{\max} = (0.43, 0.50, 0.87, 1.57, 2.44, 1.26)$  mm and  $E_{\max} = (1.37, 1.34, 1.44, 1.46, 1.46, 1.55)$  mm, respectively. The extracted Time-SLIP profiles consistently reproduce the direction, transverse structure, and progressive accumulation of the Lagrangian displacement predicted by the numerical simulations.

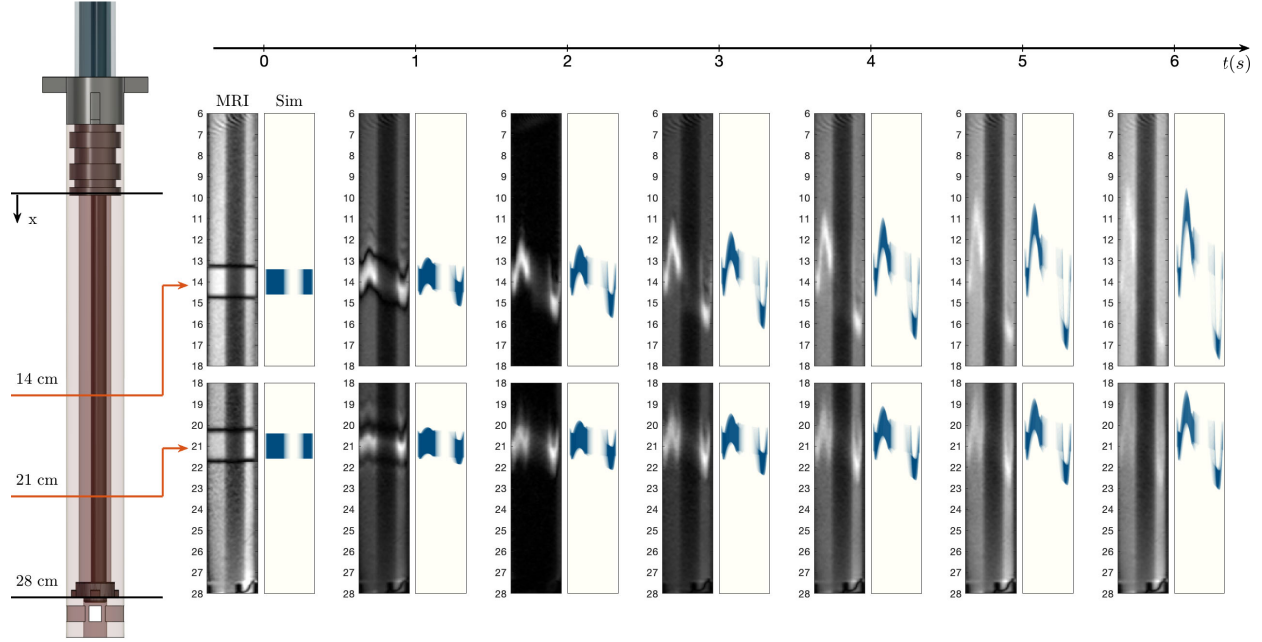
Figure 6 summarises the Time-SLIP measurements of Lagrangian displacement for three different inversion times,  $TI = (1000, 2000, 3000)$  ms – characterizing the motion over three consecutive cardiac cycles – and for entrance stroke volumes in the range  $0 < V_0 < 23.5$  mL. Measurements were obtained across the midsection of the flexible tube ( $x_0 = 14$  cm), where the local stroke volume is half the entrance value,  $V_s = V_0/2$ . For each inversion time and each stroke volume, the panels in Fig. 6a show the spatial variation of the Lagrangian displacement across the canal. As in the results in Fig. 5, the fluid is observed to move *cranially* (i.e. toward the entrance) on the wider side of the eccentric canal and *caudally* (i.e. toward the closed end) on the narrower side.

To further characterize the Lagrangian motion, the figure also shows the dependence of the medial-axis displacement,  $\delta_j$ , on each side of the canal on the local stroke volume,  $V_s$ , where the subscript  $j$  denotes the inversion time (in seconds). Dashed curves corresponding to parabolic fits are included for reference. For completeness, the displacement per cycle,  $\delta_c$ , obtained by dividing  $\delta_j$  by the number of cycles associated with each inversion time  $j$ , is shown in Fig. 6b.

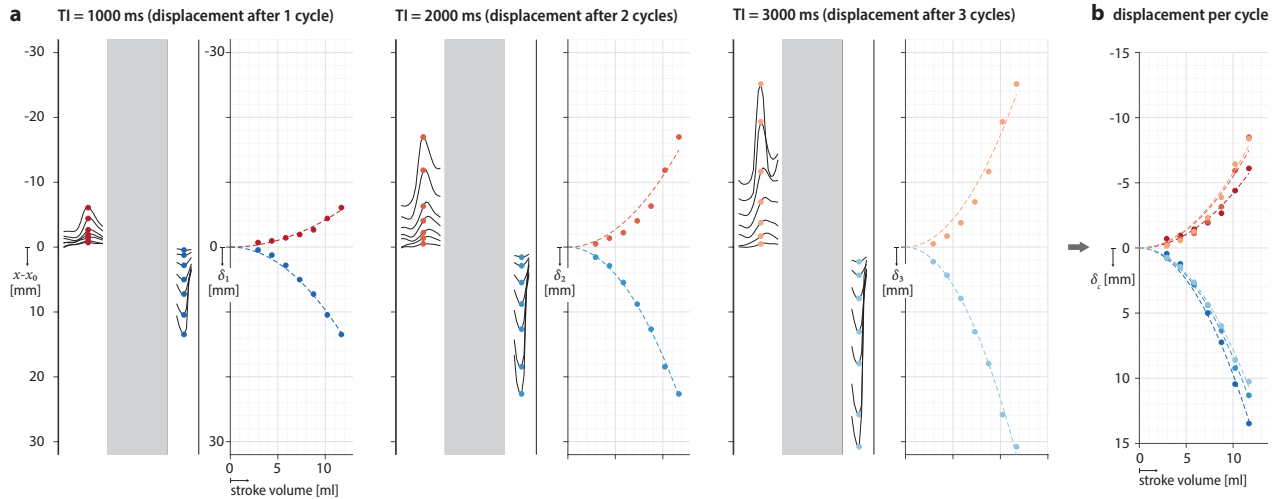
The SNR of the Time-SLIP measurements was evaluated to examine the variation in image quality with inversion time and with stroke volume. Results for the section at  $x_0 = 14$  cm are presented in Fig. 7 for the seven stroke volumes shown in Fig. 6. The central panels show the spatial distribution of SNR across the spinal canal for six different inversion times, corresponding to displacements accumulated over six consecutive cardiac cycles. To examine the effects of the walls, the transverse distribution of the SNR averaged over inversion times and stroke volumes is shown in the upper panels. Similarly, the influence of inversion time is quantified in side bar graphs showing SNR values averaged spatially across the canal and over all stroke volumes.

### Discussion

A central advantage of Time-SLIP is that it directly tracks tagged fluid and therefore captures the net Lagrangian displacement, including the contributions from both Eulerian steady streaming and Stokes drift. By contrast, cycle-averaging the PC-MRI velocity field yields only the Eulerian steady-streaming component. Nevertheless, the cycle-averaged PC-MRI results in Figs. 4f

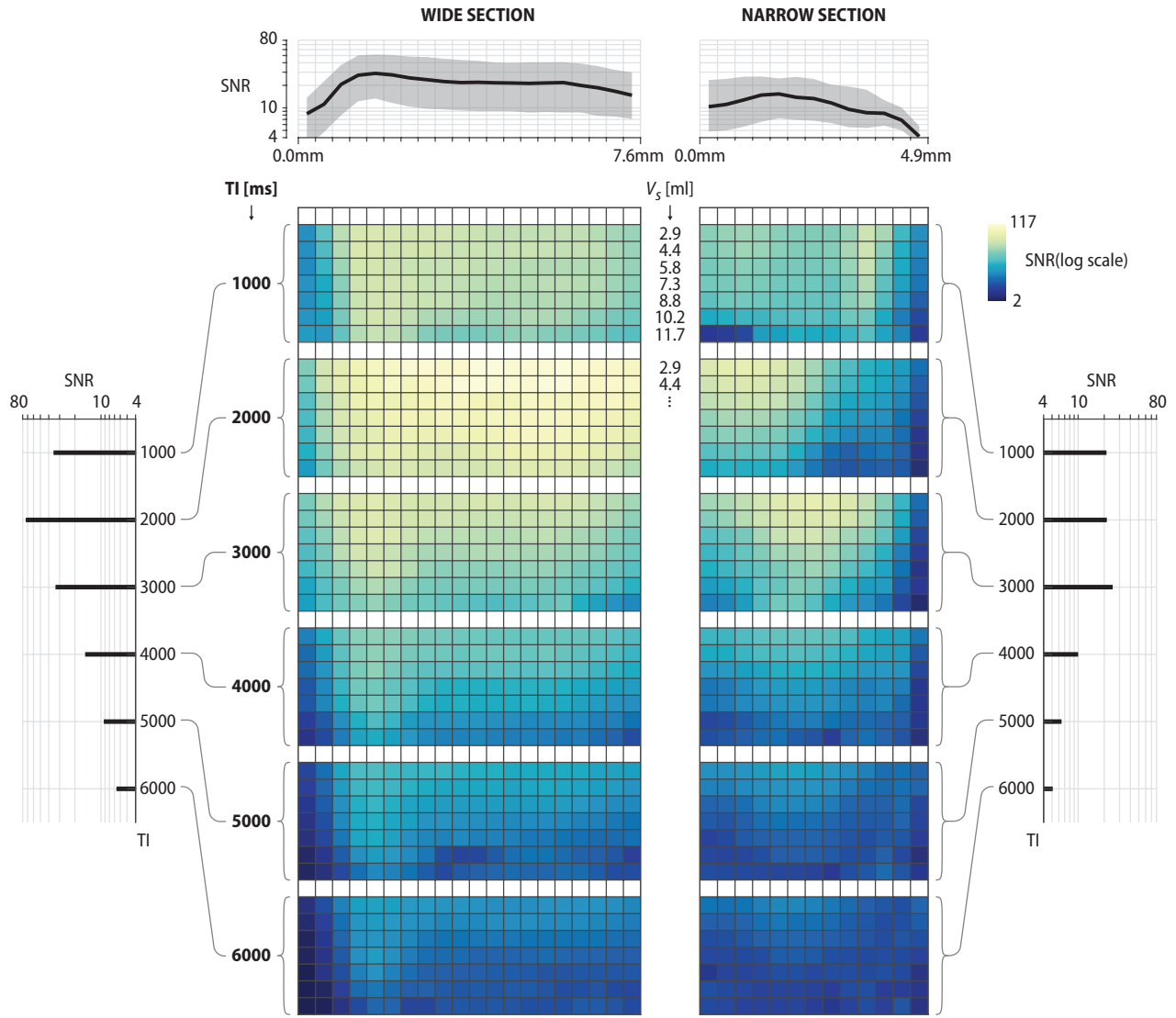


**Figure 5.** The seven double panels show Time-SLIP images acquired at different inversion times at  $x_0 = (14, 21)$  cm for an entrance stroke volume  $V_0 = 23.5$  mL (left, black-and-white), together with the corresponding numerical predictions of the tagged-particle distribution at the end of six successive cardiac cycles (right, color).



**Figure 6.** Systematic evaluation of mean Lagrangian displacement from a series of Time-SLIP measurements at  $x_0 = 14$  cm for  $TI = (1000, 2000, 3000)$  ms and  $V_s = (2.9, 4.4, 5.8, 7.3, 8.8, 10.2, 11.7)$  mL. **(a)** Transverse profiles along with the corresponding variation with  $V_s$  of the displacement at the median axis on both sides of the canal after one ( $\delta_1$ ), two ( $\delta_2$ ), and three ( $\delta_3$ ) cycles. **(b)** Corresponding cyclic displacement evaluated according to  $\delta_c = (\delta_1, \delta_2/2, \delta_3/3)$ .

and 4g demonstrate that, under the flow conditions considered here, PC-MRI can resolve the bidirectional Eulerian mean flow and thereby provide complementary validation of the Time-SLIP measurements. In the simple canonical geometry considered here, the close similarity between the Eulerian and Lagrangian flow patterns indicates that steady streaming provides the dominant contribution, although this may not hold in more complex geometries such as the human spinal canal. Moreover, the comparatively high VENC required to capture the peak oscillatory velocities without aliasing limits sensitivity to the Eulerian mean velocities, which are an order of magnitude smaller. This limitation becomes increasingly important as the stroke volume



**Figure 7.** The color plots show the local signal-to-noise ratio (SNR) systematically evaluated from a series of Time-SLIP measurements at  $x_0 = 14$  cm for selected values of TI and  $V_s$ . The upper panels display the transverse distribution of SNR averaged over all TI and  $V_s$ , while the side bar graphs report SNR values averaged spatially across the canal and over all stroke volumes.

decreases. Thus, while PC-MRI provides useful complementary information about the steady-streaming component under the present conditions, Time-SLIP enables a more direct and complete characterization of the net Lagrangian displacement. An additional practical advantage of Time-SLIP is its short acquisition time, on the order of seconds, compared with the 3–4 minutes required for PC-MRI.

Good qualitative agreement between the Time-SLIP images and the corresponding numerical predictions is demonstrated in Fig. 5. The MR technique accurately captures the shape of the progressively distorted bolus of tagged fluid over the six cardiac cycles shown, although visual comparison becomes more challenging at higher inversion times due to reduced image contrast. As shown, the caudally directed Lagrangian motion in the narrower region of the canal is characterized by a nearly parabolic displacement profile, whereas the flow in the wider region exhibits a more complex structure, as expected given the larger local Womersley number.

While the images in Fig. 5 provide clear qualitative evidence of Time-SLIP's ability to track Lagrangian motion, the reduced contrast between the tagged and background fluids complicates accurate quantification of fluid-particle displacements at large inversion times. Using the semi-automated quantification procedure employed in our analysis, the results obtained for TI = 1000, 2000, and 3000 ms show strong internal consistency and good agreement with the numerical predictions across

most of the canal, independent of axial location and stroke volume. In contrast, images acquired at larger inversion times ( $TI \geq 4000$  ms) lack this level of consistency, with some measured displacements failing to exhibit the expected trends. For this reason, the systematic evaluation of the Lagrangian displacement in Fig. 6 is limited to three oscillatory cycles.

The results reveal several flow features that are consistent with previous theoretical predictions<sup>3,4</sup>. In particular, the magnitude of the Lagrangian displacement increases with increasing stroke volume, with an approximately quadratic dependence. This behavior is demonstrated in Fig. 6 by plotting the variation of the medial-axis displacement on both sides of the spinal cord after one ( $\delta_1$ ), two ( $\delta_2$ ), and three ( $\delta_3$ ) cycles as a function of the local stroke volume  $V_s$ , together with curves showing the corresponding parabolic fits.

This quadratic scaling can be understood by noting that all experiments are conducted at the same frequency (1 Hz), so the oscillatory velocity that dominates motion in the spinal-canal phantom scales linearly with stroke volume. In contrast, the small steady secondary velocity that drives the mean Lagrangian drift is proportional to products of the oscillatory velocity and its spatial derivatives<sup>4</sup>, and therefore scales with the square of the stroke volume. This trend is clearly reflected in the mean Lagrangian displacements for all three inversion times shown in the figure.

As expected, the Lagrangian displacement of the fluid increases with the number of cycles, i.e.  $\delta_3 > \delta_2 > \delta_1$ . An estimate of the displacement per cycle,  $\delta_c$ , at a given axial location can be obtained by dividing the displacement measured for a given inversion time by the corresponding number of cycles, i.e.  $\delta_c = (\delta_1, \delta_2/2, \delta_3/3)$ , with results shown in Fig. 6b.

The results exhibit non-negligible differences among the estimated cyclic displacements, particularly for experiments with relatively large stroke volumes. Specifically, on the wider side of the canal,  $\delta_c$  tends to increase with the number of cycles, whereas the opposite trend is observed on the narrower side. This behavior can be attributed to axial non-uniformity in the canal geometry. On the wider (narrower) side, each cycle advects a fluid particle closer to (farther from) the entrance, placing it in a region where the local stroke volume is slightly higher (lower), so that subsequent cyclic displacements increase (decrease) in magnitude. This effect, which is clearly significant in the phantom measurements owing to the relatively large stroke volumes, is expected to be negligibly small for *in vivo* measurements of the human spinal canal, where the cyclic displacements have been estimated to be a fraction of a millimeter.

The quantitative information on signal-to-noise ratio presented in Fig. 7 allows us to assess several important aspects of Time-SLIP relevant to its potential use as a tool to quantify Lagrangian drift in clinical settings. These include confidence in tagged-fluid detection near walls, uncertainty in displacement measurements and its dependence on stroke volume, and the choice and comparison of inversion times (TI). The detailed color maps showing the spatial distributions of SNR for different inversion times and stroke volumes, summarized in the top and lateral panels, lead to the following conclusions: (i) The signal quality degrades near the bounding walls, particularly near the flexible tube, where consistently low SNR values are observed regardless of TI and  $V_s$ . (ii) The SNR peaks for the smallest stroke volume considered,  $V_s = 2.9$  mL. (iii) As expected, the SNR is directly linked to the bolus-to-background contrast, which peaks at approximately 2500 ms (see Fig. 2a). Correspondingly, the SNR reaches its largest values at  $TI = 2000$  and  $3000$  ms. As shown in the logarithmic bar graphs on both sides of Fig. 7, for larger inversion times the SNR decreases sharply, accounting for less consistent displacement estimates at those longer inversion times.

The phantom study has demonstrated the capability of Time-SLIP to reliably identify the cyclic displacements of a tagged fluid region over successive oscillatory cycles. Uncertainties associated with the application of this method in clinical settings arise primarily from differences between the phantom and the human spinal canal. In particular, the smaller width of the latter (approximately 2–4 mm, compared to  $R_o - R_i = 6$  mm in our annular tube), together with the presence of microanatomical features such as nerve roots, denticulate ligaments, and trabeculae, is expected to hinder the quantification of tagged-bolus displacements. These limitations are anticipated to be most pronounced near the walls, where the SNR has been shown to be small.

The experimental conditions studied here can be compared to the physiological conditions in the human spinal canal in terms of the dimensionless stroke volume  $\varepsilon = V_0/V_{\text{canal}}$ , which characterizes the relative magnitude of the mean Lagrangian velocity with respect to the oscillatory velocity. Representative human values of  $V_0 \sim 1$  mL and  $V_{\text{canal}} \sim 50$  mL yield  $\varepsilon \sim 0.020$ , with associated peak velocities of  $\sim 10$  cm/s. In the present phantom,  $V_{\text{canal}} \simeq 84$  mL and  $5.8 \leq V_0 \leq 23.5$  mL, yielding  $0.069 \leq \varepsilon \leq 0.279$ , with associated peak velocities ranging from 6 to 24 cm/s. The investigated dimensionless stroke volumes were therefore larger than representative physiological values. This lower bound reflected a limitation of the pumping system rather than of Time-SLIP: below approximately 5 mL, the pulsatile pump could not reliably produce the prescribed stroke volume, and the flow-rate waveform was no longer reliably sinusoidal.

Our *in vitro* Time-SLIP study has successfully quantified Lagrangian displacements for inversion times up to  $TI = 3000$  ms, corresponding to three cardiac cycles. The expected Lagrangian displacements in the human spinal canal are on the order of  $\delta_3 \sim 1$  mm<sup>6</sup>, so characterizing such small displacements will be challenging and will likely require improvements in both imaging and post-processing techniques beyond those implemented here. A key limitation in characterizing such small displacements is spatial resolution: with the  $0.379 \text{ mm} \times 0.379 \text{ mm}$  pixel size employed here, displacements spanning only

one or two pixels cannot be characterized reliably. Increasing the inversion time would allow small cyclic displacements to accumulate over more cycles, but the tag-to-background contrast deteriorates at longer inversion times. Measurements at physiological stroke volumes therefore involve a practical trade-off between displacement magnitude and image contrast. As shown in Fig. 7, the peak signal-to-noise ratio (SNR) occurs for the smallest local stroke volume considered,  $V_s = 2.9$  mL, indicating that reducing the stroke volume did not degrade image contrast within the investigated range. Nevertheless, favorable SNR does not ensure that the much smaller displacements associated with physiological conditions can be spatially resolved. Taken together, these limitations indicate that the present experiments should be regarded as a proof-of-concept study rather than a demonstration of Time-SLIP under fully physiological conditions. Increasing the magnetic field strength of the scanner—these experiments were conducted using a 3-Tesla MRI system—could further enhance tag-to-background contrast at longer inversion times, thereby enabling the use of larger TI values and the characterization of displacements over a greater number of cycles.

It is also worth noting that the phantom experiments presented here have focused on Lagrangian flow driven by the cardiac cycle. In contrast, motion in the lumbar region—which is responsible for the initial spreading of intrathecal drugs injected at the L2–L3 level—is known to exhibit a significant contribution from respiratory effects<sup>10</sup>. These effects should be addressed in future studies, bearing in mind that, given the inversion times currently available, Time-SLIP is expected to be able to track the tagged bolus over at least a complete respiratory cycle.

## Conclusion

The phantom experiments presented here demonstrate that Time-SLIP MRI can be used to reliably characterize cyclic Lagrangian displacements over multiple oscillatory cycles, yielding results in close agreement with MRI-informed numerical simulations. The study clarifies the conditions under which quantitative displacement measurements are robust, including the choice of inversion time, stroke volume, and number of cycles, and highlights the key limitations associated with signal-to-noise ratio and spatial resolution. Together, these results provide a quantitative foundation for future *in vivo* Time-SLIP investigations aimed at assessing mean Lagrangian motion in the human spinal canal.

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## Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## Author contributions statement

Conceptualization: SS, WC, ALS; Methodology: OC, SS, VM, MM, MV, WC, CG-M, CM-B, GP, ALS; Investigation: OC, JA-Q, SS, VM, MM, MV, WC, CG-M, CM-B, GP, ALS; Interpretation: OC, JA-Q, WC, CG-M, CM-B, GP, ALS; Supervision: GP, ALS; Writing-original draft: OC, WC, ALS; Writing-review & editing: JA-Q, SS, VM, MM, MV, CG-M, CM-B, GP.

## Additional information

The authors declare no competing interests.