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3D Measurements of Acceleration-Induced Brain Deformation via Harmonic Phase Analysis and Finite-Element Models

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Abstract

Objective: To obtain dense spatiotemporal measurements of brain deformation from two distinct but complementary head motion experiments: linear and rotational accelerations.

Methods: This study introduces a strategy for integrating harmonic phase analysis of tagged magnetic resonance imaging (MRI) and finite element models to extract mechanically representative deformation measurements. The method was calibrated using simulated as well as

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experimental data, demonstrated in a phantom including data with image artifacts, and used to measure brain deformation in human volunteers undergoing rotational and linear acceleration.

Results: Evaluation methods yielded a displacement error of 1.1 mm compared to human observers, and strain errors between $0.1 \pm 0.2\%$ (mean $\pm$ std. dev.) for linear acceleration and $0.7 \pm 0.3\%$ for rotational acceleration. This study also demonstrates an approach that can reduce error by 86% in the presence of corrupted data. Analysis of results shows consistency with 2D motion estimation, agreement with external sensors, and the expected physical behavior of the brain.

Conclusion: Mechanical regularization is useful for obtaining dense spatiotemporal measurements of in-vivo brain deformation under different loading regimes.

Significance: The measurements suggest that the brain's 3D response to mild accelerations includes distinct patterns observable using practical MRI resolutions. This type of measurement can provide validation data for computer models for the study of traumatic brain injury (TBI).

Keywords

tagged MRI; harmonic phase analysis; finite strain; finite element method; brain biomechanics

I. INTRODUCTION

MEASUREMENTS of brain deformation and skull displacement are important for TBI research. TBI is a significant problem worldwide, causing disability and lingering repercussions [1]–[4]. Acceleration-induced brain deformation is a key causal factor in TBI, and preventive strategies often aim at reducing deformation caused by sudden accelerations [5]. Because the design of preventive strategies often depends on computer simulations, experimental observations are useful for evaluation, and to better understand the link between different forces and injury [6]. However, associating specific accelerations with the resulting deformation fields is quite difficult [7]. MRI-based displacement measurement constitutes a leap forward to investigate human brain motion noninvasively [8]. observations in human volunteers involve accelerations well below injury levels, and have proved useful for studying deformation variability and modeling as well as postulating injury mechanisms [9], [10]. But observations have been limited to individual slices [8]–[10].

Motion estimation using MRI has been studied extensively, mostly for cardiac applications [11], [12]. Displacements have been obtained with motion-sensitive pulse sequences [13], [14] and by integrating velocity fields [15]. Motion also can be obtained by registering CINE images, but areas lacking texture give rise to the aperture problem [16]. Since registration is mathematically ill-posed, different regularization schemes are used to produce stable solutions [17]–[21]. Artificial patterns or “tags” may be used to introduce texture that deforms with the tissue, allowing tracking [22]. Tag tracking methods include intensity-based methods [23]–[25] and phase-based methods such as harmonic phase (HARP) analysis [26]–[29] and displacement encoding with stimulated echoes (DENSE) [30]. Displacements can also be obtained via feature recognition in CINE or tagged data [31], [32]. These methods have been demonstrated in other organs, including skeletal muscles [33], the tongue [34], the liver [35], and the brain [9].

However, the study of 3D dynamic brain deformation includes additional challenges compared to cardiac motion estimation. Periodic deformation is natural in the heart; however, in the brain, dynamic observations employ specialized devices (Figs. 1 and 2), and acquisitions [36]. Acquisition for motion estimation requires several motion repeats to complete a single slice. Image artifacts, such as tag blurring and ghosting, can occur if the variability in the repeated motion becomes large. Additionally, small variations in the motion profile between neighboring slices can introduce the appearance of deformation [37]. This, combined with the fact that brain deformation from in vivo experiments is also relatively small (with strains below 6% compared to over 30% in the heart) [8], [38], has prevented the application of existing methods, limiting the analysis of brain deformation to 2D (or 2.5D, when multiple slices are available) [5], [8], [10], [38].

The specific nature of brain motion estimation data requires special considerations for defining the strain tensor in 4D (volume and time). Volumetric results are also necessary to study strain while considering specific structures (obtained from tissue labeling [39], [40]). While it is possible to interpolate sparse displacement data from slice data [29], [41], [42], interpolation and smoothing have their disadvantages, such as introducing arbitrary relationships between neighboring particles causing artificial boundary tractions (or other non-physical behavior). Physically realistic displacements and strains that represent a mechanically representative process are particularly applicable to studying the brain, because subcortical structures and axonal connections are sensitive to shear [43], [44] and can also improve motion estimation in other organs.

II. HARP-FE: HARMONIC PHASE ANALYSIS WITH FINITE-ELEMENT MODELS

The goal of this paper is to give a complete description of harmonic phase analysis with finite-element models (HARP-FE) and show how it can be used for brain and skull motion estimation in vivo (Fig 3). A preliminary description of the algorithm was introduced in a conference paper [45].

A. Phase Images and Tissue Tracking

HARP analysis was designed for measuring cardiac motion with the goal of solving the aperture problem by attributing a unique harmonic phase vector to any given material tissue point [11], [27]. The phase vector $\Phi = [\phi_1 \ \phi_2 \ \phi_3]^T$, combines three tagged images with orthogonal tagging directions. Each image contains harmonic peak information extracted using a direction-specific multiplicative filter in the Fourier domain. In the experiments, we used conjugate highpass filters tuned at the tagging frequency in each direction. Applying the inverse Fourier transform to the filtered image results in complex harmonic images $\mathbf{I}(\mathbf{x}, t) = D(\mathbf{x}, t)e^{i\phi(\mathbf{x}, t)}$ with a magnitude $D(\mathbf{x}, t)$, and a phase vector field $\Phi(\mathbf{x}, t)$. Letting $\mathbf{X}$ represent the reference, or *material*, configuration and $\mathbf{x}$ denote a current, or *spatial*, configuration, the tracking problem can be formulated as follows: Given an initial phase vector $\Phi(\mathbf{x}, t_0)$, find the location $\mathbf{x}$ at a later time t , such that

$$\phi(X, t_0) = \phi(x, t), \quad (1)$$

suggests a type of conservative principle.

B. Conservation of Harmonic Phase

HARP-FE assumes that the phase vector is associated with the tissue mass from which the MRI signal originates. In particular, ϕ can be expressed as a vectorial angular quantity per unit mass (i.e., phase density), which is subject to the conservative transport processes

$$\frac{D}{Dt} \int_{\mathcal{R}} \phi \rho \, dV = \int_{\mathcal{R}} \frac{\partial(\phi \rho)}{\partial t} dV + \int_{\mathcal{S}} \rho \phi \otimes \mathbf{v} \cdot \mathbf{n} \, dS, \quad (2)$$

where the left-hand side represents the net change in phase density across an arbitrary volume $\mathcal{R}$ in $\mathbb{R}^3$ (and ρ represents mass density), and right-hand side represents phase generation and flux (with velocity $\mathbf{v}$ across the boundary surface $\mathcal{S}$ with normal $\mathbf{n}$, respectively [46]. ($\otimes$ denotes the outer product.) Invoking mass conservation after the application of Gauss' theorem allows obtaining two equivalent expressions for conservation of phase. The spatial description is the phase equivalent to the equation used for intensity-based registration [16] or pixel-wise tracking [47]. The material description is

$$\frac{D\phi(X, t)}{Dt} = 0, \quad (3)$$

which is used in HARP-FE. To enable ϕ to be defined across the extent of $\mathcal{R}$, tagged images are interpolated onto a volume using a cubic spline kernel. Therefore, the method enables calculating 3D strains based on multiple 2D slices.

C. Phase Conservation and Momentum Balance

In the material frame, $\mathbf{x} = \mathbf{x}(X)$ and (1) is equivalent to a finite-difference approximation of (3), which allows practical implementation of phase conservation using imaging data acquired at two different times. Specifically, the conservative relationship is applied as a numerical constraint for application in the classic static momentum balance equation.

$$\int_{\mathcal{R}} P : \delta \mathbf{F} \, dV - \int_{\mathcal{R}} \mathbf{f}_0 \cdot \delta \mathbf{v} \, dV + \int_{\mathcal{S}} \mathbf{t}_0 \cdot \delta \mathbf{u} \, dS = 0, \quad (4)$$

where body forces $\mathbf{f}_0$ and boundary forces $\mathbf{b}_0$ equilibrate with material and deformation-dependent stresses quantified through the first Piola-Kirchhoff stress tensor, $\mathbf{P}(\mathbf{F})$ [48]. (The deformation gradient is denoted by $\mathbf{F} = \frac{d\mathbf{x}}{d\mathbf{X}}$, and the over dot denotes a time derivative.)

Notice that (4) arises from elastic energy minimization, and can be also written as

$$\delta W(x, \delta v) = \delta W_{\text{int}}(x, \delta v) + \delta W_{\text{ext}}(x, \delta v), \quad (5)$$

with W_{int} being equivalent to the internal (stress) contribution and W_{ext} referring to the net external forces (second and third terms in (4)). The boundary problem arising from (4) is used to simulate deformation, but here it provides mechanical regularization to the tracking problem minimizing

$$\varepsilon = \phi(X, t_0) - \phi(x(X), t), \quad (6)$$

producing the error-minimization constraint

$$\delta W_{\text{harp}}(x, \delta v) = \int_{\mathcal{R}} \lambda(t) (\phi(X, t_0) - \phi(x(X), t)) \cdot \delta v \, dV, \quad (7)$$

which is added to the momentum balance (4) or (5) and includes the penalty parameter $\lambda(t)$. The tracking constraint (7) converts harmonic phase image information in to a pseudoforce field (i.e., image-based pseudoforces rather than physical loads) that drives a model from a reference state to a deformed state according to the motion in the images. Thus, the HARP-FE results are more akin to regularized registration than a mechanical simulation.

Solving (4) subject to (7) is a nonlinear problem that requires an incremental-iterative numerical solution strategy [48], [49]. Nonlinear behavior arises intrinsically from (4) and also from the harmonic phase quantities. Linearization is an implementation requirement for the solver, and the specifics are included in the Appendix.

D. Solution Strategy

HARP-FE was implemented as a plug-in for the FEBio finite-element software [50]. Two strategies for equilibrating tracking forces against material stresses were implemented: the penalty method and Lagrangian augmentation [51], [52]. The penalty method consists of letting λ act as penalty parameter, which applies globally. This value is associated with a load curve $\lambda(t)$. The experiments herein assume linear load curves with $\lambda(0) = 0$ and a maximum value of λ_{max} . The Lagrangian augmentation method is an iterative approach for calculating local Lagrange coefficients [53]. The value λ_{tol} denotes the fractional change in local coefficients needed to terminate the augmentation algorithm.

HARP-FE can be applied between any two images. We used an incremental approach where the phase values from the initial frame were kept, but nodal coordinates were updated every frame. The logic is to reduce registration errors by tracking small displacements, and discard stress fields from previous iterations to improve solver convergence.

III. EXPERIMENTS AND RESULTS

A. Evaluation

To our knowledge, open-access calibration databases for impact-induced motion estimation are not yet available. Thus, the method was evaluated using: (1) a cardiac-motion benchmarking database for displacement error calculation and comparison to other methods, and (2) simulations of brain deformation for displacement and strain error calculation.

1) Cardiac phantom MRI: The open-access benchmarking database included tagged MRI acquisitions from a phantom under combined torsion and inflation, a T_1 image, and the ground truth. The ground truth consisted of expert visual tracking of 8 landmark points across 23 frames [12]. We evaluated HARP-FE results twice, with a voxels-based mesh (simpler to generate), and with a surface-based mesh (which requires more manual intervention). Both meshes were created by delineating T_1 images (Seg3D, University of Utah, Salt Lake City, USA) (Fig. 4(a–b)). The voxel-based mesh comprised 33,000 hexahedral elements, and surface-based mesh consisted of 26,000 tetrahedral elements (via TetGen, WIAAS, Berlin, USA). Because tagged data was not available across the entire volume, the meshes were subdivided into a tracking domain within the MRI slices, and a support domain where boundary conditions were applied—the bottom surface nodes were allowed only to rotate. The domain was assumed to be a hyperelastic solid with strain energy density [54], [55]

$$\Psi = C_1(\tilde{I}_1 - 3) + C_2(\tilde{I}_2 - 3) + \kappa \ln(J)^2, \quad (8)$$

with stiffness defined by $C_1 = 1.0$ kPa, $C_2 = 0$ kPa, and bulk modulus $\kappa = 100$ kPa. In (9), $\tilde{I}_1$ and $\tilde{I}_2$ are the invariants of the deviatoric component of the Cauchy-Green strain tensor $\tilde{C} = \tilde{F}^T \tilde{F}$ ($\tilde{F} = J^{-1/3} F$), and J is the determinant of F . Note that the constitutive contribution in (4) arises from $P = \frac{\partial \Psi}{\partial F}$ which equilibrates image-based pseudoforces from (8). HARP-FE was performed with $\lambda_{\max} = 0.5 \times 10^{-2}$ mN/rad and $\lambda_{\text{tol}} = 0.5$ (found by trial-and-error). Displacement error ϵ_d was defined as the Euclidean distance between HARP-FE and the ground truth. ϵ_d was averaged in all time frames, at maximum deformation, and at the final frame.

Results via HARP-FE compared well to the ground truth in the both experimental and simulated data. In the open database experiment, the median displacement error at the final time frame (Fig. 5) was 1.19 mm when tracking using the surface-based mesh, and 1.10 mm when using the voxel-based mesh. The voxel-based mesh had a lower median error only when averaging all frames, but more variability. At maximum deformation, and in the final frame, the surface-based mesh yielded a slightly better median than the voxel-based mesh. For reference, intra-observer variability was 0.77 [12].

2) Simulated Brain MRI: To mimic brain motion, simulated tagged MRI was created using a subject-specific mechanical simulation detailed in [56]. The simulated image

sequence (10 frames) was produced by pushing forward a static tagged MRI using the inverse deformation field from the simulation and cubic spline interpolation. The simulated images were oriented and tagged in the same manner as experiments in volunteers (described in later sections). Thus, the resulting simulated images represented an ideal acquisition of a rotational acceleration experiment (RAE) and a linear acceleration experiment (LAE). The RAE consisted of a 32° rotation of the head towards the subject's left shoulder that imparts an acceleration of $\sim 250 \text{ rad/s}^2$. The LAE is a 10 mm drop that impacts the posterior of the head, imparting 2–6 g of acceleration. An adult-human head mesh (described in [57]) was used in HARP-FE. The mesh, shown in Fig. 4(c), was adapted to subject-specific anatomy by matching the contour of the cerebrospinal fluid surrounding the brain via affine registration [58]. Intracranial tissue was deformable according to (9) with the same coefficients. Fully integrated tetrahedral elements were used to avoid locking in all experiments [59]. The boundary of the extracranial tissue (the support domain) was assumed to be rigid, and motion was constrained with 4 spring elements of $1 \times 10^{-3} \text{ N/m}$ on opposite sides of the mesh. The tracking parameters were $\lambda_{\max} = 1.5 \times 10^{-2} \text{ mN/rad}$ and $\lambda_{\text{tol}} = 0.3$ (found by trial-and-error). In this experiment, strain error ϵ_s was defined within the volume covered by MRI slices as the difference in maximum shear strain (*MSS*) between the ground truth and measured strain fields.

$$MSS = E_1 - E_3, \quad (9)$$

where E_1 and E_3 are the first and third eigenvalues of $\tilde{C}$.

By visual inspection of Fig. 6, the strain maps produced by HARP-FE were very similar to the ground truth. This was true of the axial and sagittal slices. During the simulated LAE ϵ_s ranged from $0.1 \pm 0.2\%$ (mean $\pm$ std. dev.) at the first frame to $0.7 \pm 0.3\%$ at the last time frame. During the simulated RAE ϵ_s ranged from $0.3 \pm 0.7\%$ (mean $\pm$ std. dev.) at the first frame to $0.6 \pm 0.9\%$ at the frame with peak deformation. The maximum error values represent 11% and 9% of the largest strain in each of the experiments. Displacement error ϵ_d was $0.2 \pm 0.1 \text{ mm}$ for both experiments (13% of the in-plane resolution). Despite the similarities between the ground truth and measured strain fields, some differences can also be seen, particularly slightly elevated magnitude near the edges of the brain and differences in smoothness, which contributed to ϵ_s . Magnitude differences were more pronounced outside the range of slice coverage of some slices (sagittal in the LAE, and axial the RAE). The HARP-FE solution also tends to smooth scattered patterns, and this effect can be seen in the latter frames of the simulated rotation (Fig. 6(b)).

B. Reconstruction with Partially Corrupted Data

This experiment involved tracking in datasets with slices affected by image artifacts. To achieve sufficient temporal resolution to capture brain deformation, the subject must repeat the motion multiple times [36], and artifacts can result from variability between motion repetitions. These artifacts can lead to tracking errors, which propagate to strain measurements. This effect was reproduced using a silicone phantom (Fig. 7). Tagged MRI

data was acquired using the apparatus in Fig 2, which is outfitted with an encoder to measure the rotation of the cradle (the moving component). The phantom was imaged while following an ideal motion profile and while adding resistance to the apparatus, slowing motion (Fig. 8(a)) and corrupting half the frequency data in two complementary tagged slices (Figs. 7(c) and 8(d–e)). The slower motion profile had a lower peak than the mean peak of the ideal profiles (more than 2 standard deviations), which was the criterion for excluding the defective slice. We evaluated ways to deal with the missing slice by comparing tracking results using the intact data (the ground truth), and by:

- 1) Including the corrupted slice and tracking cross the entire mesh (i.e. no correction);
- 2) including the corrupted slice, and removing image-based forces in part of the mesh (Fig. 7(a)); and
- 3) replacing the corrupted slice with interpolated data from adjacent slices.

Error was measured using ϵ_s as previously defined.

Tracking via HARP-FE and the approaches above shared the same material model and tracking parameters, as in the previous section. The phantom mesh consisted of 4,250 quadratic brick elements (Fig. 4(c)), which was constructed from T_1 acquisitions of 1 mm isotropic resolution. As boundary conditions, the nodes at the surface affixed to the phantom's enclosure were only allowed to rotate about the z direction (Fig. 7(c)) and to move in the x and y directions. The tagged slices were interpolated onto a volume of 1.5 mm isotropic resolution. The tracking parameters $\lambda_{\max}$ and λ_{tol} were 2×10^2 mN/rad, and 0.3, respectively. Tagged MRI acquisitions were performed in a Siemens Biograph mMR 3T scanner (Siemens, Munich, Germany). The multislice imaging protocol consisted of 13 axial slices (x - y plane, with tagging in the x and y directions), and 7 sagittal slices (y - z plane tagged along the z direction) during 13 frames (SPAMM sequence 18 ms TR, 3 ms TE, 160×160 pixel matrix, 1.5×1.5 mm in-plane resolution for axial and sagittal slices).

The strain distribution in the phantom appears in Fig. 9. The peak deformation resulted in principal strain of 6%. As motion was slower at the corrupted slice, it induced artifactual relative motion, resulting in strain error. The error ϵ_s was the largest when no correction is applied (Fig. 9(a)) near the corrupted slice, measuring $0.21 \pm 0.32\%$ (or 7% of the largest deformation). Mitigating the influence of the defective slice with a tracking-insensitive subdomain reduced error to $0.11 \pm 0.21\%$. Using an interpolated slice yielded an average error of $0.03 \pm 0.01\%$ (or 1% of the largest deformation). The application of an interpolated slice resulted in a reduction of mean error of 85.7%.

C. Measurement of Skull Rotation and Brain Deformation under Linear and Rotational Loading

The goal of this experiment was to demonstrate HARP-FE for studying brain deformation resulting from mild accelerations induced by the devices in Figs. 1 and 2. We investigated linear and rotational loads (i.e., LAE and RAE) on two healthy human volunteers. Informed consent was obtained from each participant, and the experimental protocol was approved by

institutional ethical committees in accordance with the latest revision (2013) of the Helsinki Declaration and other appropriate ethical guidelines.

Each experiment was repeated—in two separate imaging sessions for each subject—yielding a total of four sets of images (2 LAEs in one subject and 2 RAEs in the other, as opposed to both LAE and RAE in each subject). Encoders mounted to the device were used to measure the motion profile associated with the head cradle (about 150 motion repeats were needed for each 3D acquisition). Slices with visible defects or more than 2 standard deviations in terms of peak encoder motion were removed and replaced by interpolated images from spatially adjacent slices. The LAE #1 had 1 slice replaced, and RAE #2 had 2 slices replaced. No slices were replaced for LAE #2 and RAE #1.

To address motion inconsistency between neighboring slices, all temporal sequences were aligned using the mean 2D rigid transformation from any given frame to the initial time frame. That is, if $\mathbf{M}_i^t$ represents the 2D rigid transformation from time t to the initial time frame across $i = 1, 2, \dots, N$ slices, and $\bar{\mathbf{M}}^t$ is the mean over all the slices, then each image underwent $(\bar{\mathbf{M}}^t)^{-1} \mathbf{M}_i^t$. To obtain this small transformation (between -0.1° and 0.1°), tag lines were removed from each image using a notch filter at the location of the spectral peaks shown in Fig 3.

In terms of data acquisition, the motion resulting from each of the loading regimes was fundamentally different; therefore, slices for tagged acquisition were oriented differently for the LAE when compared to the orientation for the RAE. Tagged MRI acquisitions were performed in a Siemens Biograph mMR 3T scanner (Siemens, Munich, Germany). The multislice imaging protocol consisted of a 13-frame time sequence acquired over multiple slices (SPAMM sequence 18 ms TR, 3 ms TE, 160×160 pixel matrix, 1.5×1.5 mm in-plane resolution, 8 mm thick with square profile). The slices were separated by 10 mm to cover the whole brain while minimizing the total motion repetitions in a 35-minute scan session and were oriented as follows:

- 1) *LAE*. Ten sagittal slices were encoded separately in the anteroposterior and inferosuperior directions, and 12 axial slices were encoded in the left-to-right direction.
- 2) *RAE*. Twelve Axial slices were encoded in the anteroposterior and left-to-right directions, and six radially oriented slices were encoded in the inferosuperior direction. The radially oriented slices varied from the sagittal plane to the coronal plane in increments of 30° .

Interpolation of the radially oriented slices onto the dense grid was achieved using scattered interpolation (MATLAB, MathWorks, Natick, MA). The mesh, material model, boundary conditions, and HARP-FE parameters were derived from the evaluation experiment with synthetic brain deformations $\lambda_{\max} = 1.5 \times 10^{-2}$ mN/rad and $\lambda_{\text{tol}} = 0.3$.

The output measurements included strain, head rotation, and volume fraction. Strain fields were quantified using MSS per (9) and the direction and magnitude of the first principal strain E_1 . Head rotation was approximated by fitting extra-cranial displacements with a

rotation matrix, and extracting Euler angles about the main axis of rotation. Volume fractions (ratio of element volume) were averaged across the cranial cavity.

The LAE resulted mostly in anteroposterior skull displacement (Fig. 10 (a)), the displacements in the superiormost part of the head exhibited a slight arch, which is consistent with the experimental setup. Displacement results of the RAE (Fig. 10(b)) are centered about the spine, which agrees with the fact that the volunteer rotated their head to face their left shoulder. From the images, the LAE yielded a rotation of less than 4° , but resulted in a peak displacement of 10 mm. The RAE resulted in rotations above 32° with maximum displacements of 6 mm (Fig. 11). (Note that the reference image was acquired after the subject rotated 29°).

Comparing image-based head motion results with the builtin encoders shows general agreement and some key differences. As shown in Fig. 11, all the signals reach their maximum value after a nearly linear ramp-up, and level off after a small “bounce.” The overall head motion estimate from the images (via HARP-FE) and from the encoders are similar in overall magnitude. However, the HARP-FE solution shows smoother features compared to the encoder. The image-based result has a noticeable lag in terms of bounce and settling time in both experiments. The encoder shows maximum rotation values at 67 ± 9 ms for the LAE, and 39 ± 7 ms for the RAE (combined for across all repeats, in both acquisition sessions). Maximum rotation values obtained from HARP-FE were 84 ± 9 ms and 45 ± 9 ms, respectively. Additional encoder values for maximum velocity acceleration for each acquisition are shown in Table 1.

MSS strains were heterogeneously distributed, featuring maximum deformation at 81 ms in the linear acceleration experiment (Fig. 12), and 45 ms in the rotational experiment (Fig. 13). In both of the experiments the peak deformation occurred *after* the peak mean cradle acceleration (Table 1).

During the LAE, the peak deformation resulted in an MSS of approximately 3%, with concentrations as high as 6% near the basal pons, which were observed in both repetitions (Fig. 12). The axial slice at 81 ms shows elevated strain near the posterior brain cortex and at the level of the lateral ventricles, but lower strain values near the center of the anterior (frontal) brain. After the peak deformation, strain decreases and remains fairly consistent thereafter at approximately 1% with some localized regions near 2%. The peaks occur near the center of the brain, which can be seen the axial slices, and near the superior edges of the brain, which can be seen in the sagittal slices. The direction of the first principal strain E_1 (supplementary Fig. 1) indicates that the strain concentration near the basal pons at between 45 and 81 ms occurs in the inferosuperior axis. During this time, both repetitions exhibit a similar pattern of directionality, including areas near the brainstem and the parietal and occipital lobes, as well as parts of the cerebellum. In these areas, deformation seems to follow the curvature of the skull inward and posteriorly. While the aforementioned strain patterns were consistent in the two acquisitions, some differences could also be seen. Note that LAE #2 in Fig. 12(a) included a corrected sagittal slice near the middle. Differences in strain patterns included the overall strain values (which were 1% higher near the ventricles and around the superior part of the skull at 81 ms in LAE #2), and striated strain left-to-right

patterns on the axial slices. Although the striated patterns appeared in both of the acquisitions, they were more visible in the first (Fig. 12(a)). The directional pattern of E_1 was less consistent in the latter time frames compared to peak deformation (supplementary Animation 1). The RMS MSS difference between LAE repeats was $1.5 \pm 1\%$.

Compared to the linear acceleration experiment, rotational acceleration results (Fig. 13) were less consistent between the two acquisitions. Note that the RAE #1 in Fig. 13(b) included 2 corrected slices near the cerebellum. Both acquisitions resulted in peak deformation occurring at 45 ms, with a maximum of approximately 6% in the first acquisition (Fig. 13(a)) and 3% in the second. The peak occurred in the front of the brain towards one side. Other localized strain concentrations within the volume covered by the axial slices occurred near the center of the brain, which is visible in both axial and sagittal slices. Temporally, both acquisitions resulted in a peak-reduction-rebound pattern with respect to strain magnitude. After the peak strain (45 ms), strain was reduced to values near 1% around 117 ms, and then increased towards the end of the sequence near 189 ms. The RMS MSS difference between RAEs across all time points was $3.5 \pm 3\%$. The direction of E_1 (in supplementary Fig. 2) followed a spiraling pattern at peak deformation, and a similar pattern—but in the opposite direction—a few time frames after that at 99 ms. The results from the second acquisition appeared smoother with respect to the first and had fewer striated patterns, which run from the anterior to the posterior edges in the sagittal slices. Strain values outside the slice coverage region at the bottom of the cerebellum resulted in relatively large values, which increased as a function of time (supplementary Animation 2).

The volume fraction at the time of peak deformation in the LAE#1 was $1.00 \pm 1 \times 10^{-4}$ with a maximum of 1.01, or a maximum of 1% change in volume. Volumetric changes were less than 1% were in all motion fields, which was a direct result of enforcing incompressibility via the material model.

IV. DISCUSSION

Dynamic analysis of acceleration-induced brain motion has been largely limited to 2D analysis, because precise observations of displacement and strain in 3D are challenging. We have shown a methodology to obtain these measurements based on a conservative principle via (4), which is associated with a mechanical process in (5). This method was evaluated against several evaluation approaches. The results indicate that displacement tracking accuracy (Fig. 5) compares well with state-of-the-art techniques, even in meshes that can be obtained automatically. We reported final-frame errors of 1.19 and 1.1 mm, while other tracking methods result in errors ranging from 3.3 to 0.8 mm in this open-source cardiac motion benchmarking dataset [12]. (The performance of the voxel-wise mesh was below the manually generated mesh, likely due to stress concentrations in the domain edges.)

In the ideal scenario, as shown in Fig. 6, HARP-FE is sensitive to small deformations, such as those expected when the brain is subjected to small accelerations. This evaluation experiment using synthetic data provided the parameters used to demonstrate the technique using experimental data. The experiment also shows that, as expected, extrapolation outside the acquisition area leads to increased error in the estimated strains. It also shows some

tendency to over smooth and induce minor edge artifacts, which perhaps could be reduced by modifying the shape and constitutive model of the support domain. Note that, unlike a complete dynamic simulation [56], HARP-FE does not include neither a realistic material model, boundary conditions, or dynamic modeling. This confirms the theoretical principle that deformation is mostly associated with the imaging information, rather than a mechanical simulation of the process. However, the ability to use a mechanical framework can produce displacements that are diffeomorphic, incompressible (as demonstrated by the volume fraction measurements), rigid (as in the support domain, where the skull is located), or a combination of these, if necessary.

A significant experimental challenge is motion inconsistency during MR acquisition, which can introduce image artifacts, such as those seen in Fig. 8, and lead to erroneous strain fields between neighboring slices. The phantom results in Fig. 9 show that the introduction of image artifacts to the data results in incorrect strain measurement. Here, detection of defective slices was retrospective using the signal from the position encoders and visual inspection. This can also take place online, although the relationship between encoder signals and artifacts is nonlinear, with the lower spatial frequencies being much more sensitive than the rest of the image. Nevertheless, we show that error can be reduced if the defective data is discarded and replaced by interpolated slices. Error reduction via interpolation was substantial (at 86%), which assumes a smooth strain distribution. This suggests that improvements at the image level are effective in the slice spacing in the study (10 mm), which was derived based on the number of motion repetitions [36]. However, future research is needed to further optimize the spatial slice coverage and slice spacing in light of all experimental considerations.

Experimental measurements in the brain of volunteers (Figs. 10—13) were logically coherent with respect to the mechanical processes taking place. Displacement measurements agreed with the motion produced by the apparatuses, as shown in Fig. 10. The lag between device's head cradle and the image-based measurement of head rotation shown in Fig. 11 is likely associated with the fact that the head is not perfectly attached to the device's cradle. Hence, head motion follows a slightly different trajectory. This is a useful finding because it shows that our approach can be used to generate boundary conditions to improve physical simulations of the mechanical impact—a predictive model should ideally agree with the experimental data given the same boundary conditions.

In terms of strain measurement, the experiments showed consistency between the repeated experiments. The strain patterns observed during the LAE indicate that brain deformation (Fig. 12) occurs approximately 20 ms after the peak acceleration of the cradle (Table 1). The delay was shorter in the RAE, where the difference was approximately 5 ms (Fig. 13). Both cases can be related to an elastic process, where brain deformation results from cumulative inertial loading. This is also substantiated by the directional distribution or the first principal strain (in the supplementary materials) where the deep brain tissue “wants” to continue moving due to inertia, creating relative displacement with respect to the skull (which rotates slightly in the opposite direction). Interestingly, the opposite occurs later in time, which results in a spiraling pattern in the opposite direction. However, strain is lower during this time, which likely reflects energy dissipation. The lag also suggests intrinsically slower

dynamic response (as described in [5]). The RAE showed a bounce in terms of strain magnitude, and the same was not seen in the LAE; this can be associated to loading, but it may also suggest differences in geometrical or structural stiffness. The brain deformation maps show consistency with previous studies in 2D during similar acceleration regimes [8], [10]. In particular, the deformation pattern during peak acceleration, i.e., the directional distribution of the first principal strain seen in supplementary Fig. 1 (81 ms) was previously seen in a similar “head drop” study (Fig. 5c in [8]). Likewise, the strain magnitude distribution in supplementary Fig. 2 is similar to that shown in [10], featuring relatively high strains near the skull with two lower regions at the center of each half of the brain, near the lateral ventricles. Compared to these previous studies, the overall deformation magnitudes are lower in this study, likely due to differences in the experimental setup. The LAE also features strain concentration between the pituitary gland and the basal pons (Fig. 12), which is likely associated fluid motion [30] and some stretching of the anterior brainstem structures. Additional research is needed confirm the overall strain patterns in a larger number of volunteers.

The measurements show some unexpected patterns. For instance, the strain magnitudes do not return to zero as time progresses. This can be explained by a combination of the relatively short imaging window (given the delay between the dynamics of the apparatus and the head, Figure 11), the change in relative direction of gravity [60], fluidic motion via pulsatile cardiac pressurization [30], and image artifacts. Also, the strain maps showed some striated patterns that may be associated with the HARP filtering process, and artifacts induced by slice coverage. Introducing interpolated slices resulted in no visible artifacts, but these acquisitions contain less actual experimental data may smooth over some details. The LAE acquisitions were relatively consistent with respect to cradle motion (Table 1), and the resulting strain. In contrast, the RAE resulted in different strain magnitudes. The second acquisition (Fig. 13 (b)) had the appearance of being blurred; this can be due to a larger standard deviation in cradle motion, which according to Table 1 is almost twice as the first acquisition (explaining the inconsistencies in the strain maps).

One limitation of this study is the lack of evaluation against an experimental strain ground truth (as opposed to the displacement ground truth, or simulated strains). This task will be useful to define uncertainty limits of the measurement with respect to imaging and tracking parameters, such as the slice placement and thickness (which introduces blurring), or the tracking penalty. Note that a drastic change in material assumptions would require recalibration of the tracking parameters. Lastly, the ideal termination criteria would be associated with the phase error (7), which determines tracking performance in the absence of artifacts [27]. In practice, this approach would require the formulation of harmonic phase similarity metrics having into account phase image quality, and it is currently being investigated.

V. CONCLUSION

This paper described HARP-FE analysis of brain and head displacement under linear and rotational acceleration. Unlike a forward simulation of head acceleration, the tracking process is highly constrained (by the image data), and will produce consistent results with

balance of tracking penalties; thus, it can be considered an image-based measurement rather than an inertia-based simulation. (The experimental kinematic characterization preserves nonlinearities associated with the physical process.) HARP-FE was used to observe skull rotation and brain deformation under two different loading regimes (linear and rotational acceleration). These novel 3D results were consistent with previous 2D research and revealed distinct patterns of motion, including directional arrangements of principal strain and lagged response (in motion and deformation). The results can be used for model validation and improved extraction of boundary conditions for modeling in investigational use. In the future, head rotation measurements can also be used to observe energy transmission dynamics between the head and the apparatus, to place strain results from different individuals in a common mesh template, or for stress analysis (if accurate constitutive modeling is available).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

A. Linearization and Discretization of Tracking Constraint

In a displacement-based formulation $x(X, t) = X + u(X, t)$ (u denotes displacement), the directional derivative of a test function $f(\mathbf{x})$ takes the form $Df(x)[u] = \left. \frac{d}{d\epsilon} \right|_{\epsilon=0} f(x + \epsilon U)$.

When applied to the constrained version of (6), linearization results in geometric and material stiffness terms, which form the basis of traditional implementations, and

$$Df(x, \delta v)[u] = \int_{\mathcal{R}} \lambda(t) \nabla \phi(x(X), t) \delta v \cdot \delta u \, dV, \quad (10)$$

which is a second-order tensor equivalent to the stiffness contribution derived from the phase conservation constraint.

The approximate solution to the general motion estimation problem is found using a finite element discretization scheme, which has been thoroughly documented in the context of intensity-based registration [19], [61]. Although the same theoretical underpinnings are applicable here, we note two fundamental distinctions. First, the definitions of phase-based tracking force (8) and stiffness (10) involve fundamentally different quantities and dimensionality. Second, vectorial operations such as difference and interpolation must be robust to phase wrapping. This is necessary so that a reasonable gradient estimate of the real-valued *true* phase ϕ can be recovered from the *harmonic* phase $a \in [-\pi, \pi)$ obtained in practice. These quantities are related by

$$a(x, t) = \mathcal{W}(\phi(x, t)), \quad (11)$$

where $\mathcal{W} = \text{mod}(\phi + \pi, 2\pi) - \pi$ is known as the nonlinear wrapping function [27]. In HARP-FE phase gradients are employed in two contexts: to convect harmonic phase values defined on the imaging grid onto mesh nodes by vectorial interpolation, and for evaluating the gradient term in (10). Both of these situations require definition of a *corrected* gradient operator,

$$\nabla^* a = \begin{bmatrix} \nabla^* a_1 \\ \nabla^* a_2 \\ \nabla^* a_3 \end{bmatrix}, \quad (12)$$

where

$$\nabla^* a_i \begin{cases} \nabla a_i, & \|\nabla a_i\| \leq \|\nabla \mathcal{W}(a_i + \pi)\| \\ \nabla \mathcal{W}(a_i + \pi), & \text{otherwise} \end{cases} \quad (13)$$

which ensures that $\nabla^* a = \phi(x, t)$. The effectiveness of this correction approach is limited to the gradient, meaning that the temporal matching (tracking) of harmonic phase values is not unique in an absolute sense, but in a local sense instead. The extent of local uniqueness is related to the tag period and the magnitude of motion; in particular, a large displacement may result in phase values being displaced outside a given unique region yielding spurious displacements. This produces a motion artifact known as “tag jumping” [62]. Although it has shown that mechanical regularization is generally robust to this artifact [45], its effects can be avoided by improving the temporal resolution, increasing the tag period, using tracking refinement [62], or applying global phase unwrapping [63].

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Fig. 1.

MRI-compatible head motion apparatus (linear). The apparatus (A) fits inside the bore of the imaging instrument and guides voluntary head motion in the direction of the arrow towards a rubber stop (S), which acts as a receiver. Sudden contact with the stop results in a mild acceleration spike. Although the head cradle (B) rotates about a center of rotation near the shoulders (marked with a cross), the acceleration is mostly linear and in the range of 2–6 g in magnitude ($1g = 9.81 \text{ m/s}^2$).

Fig. 2.

MRI-compatible head motion apparatus (rotational). A volunteer initiates a rotation from a forward-facing position (A) to a slight rotation (B). In this case (unlike Fig. 1), the axis of rotation passes through the head. Acceleration is mostly rotational and in the order of 250 rad/s^2 . Using a phantom allows a controlled acquisition in terms of motion consistency. As with all experiments, motion is repeated multiple times for the acquisition of several slices.

Fig. 3. Measurement of multidimensional brain deformation via HARP-FE. Tracking of tagged MRI, and strain calculation occurs in a FE domain. However, preprocessing steps, including interpolation and filtering for tagged MRI and diffusion tensor MRI reconstruction, occur in an imaging grid. Imaging information is convected onto the mesh through interpolation.

Fig. 4. Meshes for Evaluation Experiments: The meshes were divided into a tracking domain (where the tracking constraint was enforced) and a support domain. Two meshes were created for evaluation against the open-access benchmarking database: A tetrahedral, surface-based mesh (a) and a hexahedral, voxel-based mesh (b). Boundary conditions (B.C.) were applied on the support domains. The human head mesh (c) was based on [57].

Fig. 5. Tracking performance using open benchmarking database. At the frame with peak deformation, the displacement field (a) exhibits torsion and expansion. (arrow density was reduced to 20% for clarity). The comparison against the ground truth (b) indicates Tukey box plots. Observer variability appears as a dotted line.

Fig. 6.

Evaluation results against synthetic data: The top rows show axial (ax) slices for the linear acceleration (a), and rotational acceleration experiment (b). Sagittal slices (sag) are shown in the bottom rows. The arrows show the approximated direction of motion using the devices in Figs 1 and 2. The dotted line shows the sagittal slice coverage in (a), and the axial coverage in (b).

Fig. 7.

Deformable phantom. The phantom (a) was affixed by the enclosure onto the rotational apparatus (see Fig. 2 (b)). The enclosure (b) rotates with the apparatus in the direction of the arrow, and inertial forces cause the silicone body to deform. The surfaces of the silicone body (which is attached to the enclosure's base, but free otherwise) were modeled as traction-free surfaces in the HARP-FE mesh (c). The rear surface of the mesh was constrained to act as a rigid body. The shaded area in (c) represents the domain where no tracking forces were active for one of the experiments.

Fig. 8.

Motion inconsistency in tagged MRI acquisition. In the absence of motion inconsistency, 'the phantom's enclosure will rotate along the ideal rotation profile (a). In the corrupted slices, half of the frequency data were acquired while following the ideal profile, but the other half followed a suboptimal rotation profile. In contrast to the uncorrupted images (b-c), the corrupted slices (d-e) exhibited motion artifacts including ghosting due to aliasing, and tag blurring (inside the dotted rectangles).

Fig. 9.

Phantom deformation and error due to incomplete data. The strain results using intact imaging data (top row) shows strain concentrations toward the base that increase in volume and magnitude as time progresses. Error due to motion inconsistency (bottom row) depends on the reconstruction approach: (a) no correction, (b) correction via elastic interpolation, and (c) correction with an interpolated slice.

Fig. 10.

3D rendering of displacement field results. Both of the displacement fields exhibit some rotation, but the linear acceleration apparatus (a) has an axis of rotation far away from the brain; thus, displacements tend to point in the same direction. The rotational acceleration apparatus (b) yields a displacement field with a larger directional change. (For clarity, arrow density was 5% of the original).

Fig. 11.

Comparison between head rotation estimates. Mean head cradle encoder readings (solid) appear next to image-based head rotation estimates via HARP-FE (squares). The dashed lines represent each of the motion repeats (r1 and r2) for the linear (a) and in the rotational (b) acceleration experiment. HARP-FE resulted in similar traces in (b).

Fig. 12.

Deformation fields from analysis of images acquired in the linear acceleration apparatus in Fig. 1. The color maps represent maximum shear strain (MSS), resulting from HARP-FE analysis in a complete dataset (a), as well as a dataset where an additional sagittal (sag) slice was generated via interpolation of adjacent slices. The arrow in the axial (ax) slices shows the direction of motion, and the line shows the approximate location of the missing slice. The slice at 63 ms (insert, left) corresponds to an axial view near the base of the brain, where concentrated strain appears near the brainstem. The slice at 81 ms (insert, right) shows the direction of the first principal strain (E1), with the arrow pointing at similarities in directional arrangement.

Fig. 13.

Deformation fields from analysis of images acquired in the rotational acceleration apparatus in Fig 2. The maximum shear strain (MSS) color maps indicate the HARP-FE results using a complete set of images (a), and using a set with two interpolated slices (b). The arrow in the axial slices (ax) shows the approximate direction of motion. The dotted line in the sagittal (sag) slices shows the slice coverage. solid lines indicate the location of the interpolated slices. The inserts show the direction of the first principal strain (E_1), which exhibits a clockwise arrangement at peak deformation (insert at 45 ms), and a counterclockwise arrangement 4 frames later (insert at 99 ms).

TABLE I**MAXIMUM ACCELERATION MEASUREMENTS FROM BUILT-IN ENCODERS**

	velocity (rad/s)	time (ms)	acceleration (rad/s²)	time (ms)
LAE #1	1.98 ± 0.3	56.8 ± 10	-340 ± 48	64.5 ± 9.0
LAE #2	1.69 ± 0.2	58.0 ± 10	-312 ± 47	68.1 ± 10
RAE #1	2.28 ± 0.2	20.8 ± 3.0	-171 ± 47	39.5 ± 4.0
RAE #2	2.18 ± 0.4	18.0 ± 7.0	-193 ± 40	34.0 ± 8.5

Averages (and standard deviations) of the maximum readings and their timing across motion repetitions during image acquisition. LAE = Linear acceleration experiment, RAE = Rotational acceleration experiment