Strain Energy Decay Predicts Elastic Registration Accuracy from Intraoperative Data Constraints

Jon S. Heiselman and Michael I. Miga

Abstract-Image-guided intervention for soft tissue organs depends on the accuracy of deformable registration methods to achieve effective results. While registration techniques based on elastic theory are prevalent, no methods yet exist that can prospectively estimate registration uncertainty to regulate sources and mitigate consequences of localization error in deforming organs. This paper introduces registration uncertainty metrics based on dispersion of strain energy from boundary constraints to predict the proportion of target registration error (TRE) remaining after nonrigid elastic registration. These uncertainty metrics depend on the spatial distribution of intraoperative constraints provided to registration with relation to patient-specific organ geometry. Predictive linear and bivariate gamma models are fit and cross-validated using an existing dataset of 6291 simulated registration examples, plus 699 novel simulated registrations withheld for independent validation. Average uncertainty and average proportion of TRE remaining after elastic registration are strongly correlated (r =0.78), with mean absolute difference in predicted TRE equivalent to 0.9 ± 0.6 mm (cross-validation) and 0.9 ± 0.5 mm (independent validation). Spatial uncertainty maps also permit localized TRE estimates accurate to an equivalent of 3.0 ± 3.1 mm (crossvalidation) and 1.6 ± 1.2 mm (independent validation). Additional clinical evaluation of vascular features yields localized TRE estimates accurate to 3.4 ± 3.2 mm. This work formalizes a lower bound for the inherent uncertainty of nonrigid elastic registrations given coverage of intraoperative data constraints, and demonstrates a relation to TRE that can be predictively leveraged to inform data collection and provide a measure of registration confidence for elastic methods.

Index Terms—Accuracy, deformation, error estimation, image guidance, registration, target registration error, uncertainty.

I. INTRODUCTION

REGISTRATION of medical images finds application at every stage of clinical intervention. Fundamentally, registration determines a transformation that intends to most accurately map patient anatomy between coordinate spaces given data

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The landmark paper by Fitzpatrick, West, and Maurer [1] established rigorous theory for rigid point-based registration that accurately predicts average target registration error (TRE) from the spatial configuration of target locations and the measurable fiducial points used to calculate the registration. Fitzpatrick and West [2] soon extended this work to estimate the spatial distribution of TRE surrounding these fiducials at any location of interest. These seminal works were later expanded to account for the case of anisotropic [3] and heterogeneous [4, 5] fiducial localization errors. These contributions have become profoundly important in the domain of image-guided surgery, wherein these error distributions steer the placement of fiducial markers and provide feedback on the accuracy of intraoperative guidance in rigid body scenarios suitable for point-based registration. However, these descriptions of registration error become invalid in the presence of underlying soft tissue deformation, which cannot be explained by models of fully rigid systems.

To achieve more accurate registrations in the presence of deformation, numerous registration approaches have been proposed, which are reviewed thoroughly in [6]. Of these, registration techniques based on linear elastic mechanics have become common for image guidance purposes where the data available to registration algorithms are limited [7–11]. Such methods that rely on physics to constrain the registration problem can obtain more realistic and accurate solutions especially in scenarios of sparse data [12, 13]. Although this paper will focus on the application of image-guided liver surgery, the same principles extend to elastic registration methods for other organ systems.

Previous empirical work has shown that average TRE of deformable elastic methods tends to be related to the extent of data made available for registration [9, 14, 15]. More recently, it has been shown that TRE at any location in the organ is

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correlated with distance between the target and the nearest data point driving the registration [11]. The objective of this paper is to establish a framework that explains how the spatial distribution of incomplete data driving a nonrigid elastic registration consequently affects the spatial distribution of TRE throughout the material domain. Similar to the foundational work by Fitzpatrick et al. [1, 2], this paper will consider both the average and the spatial distribution of error based on patient-specific organ shape and intraoperative patterns of data. Whereas rigid registration benefits from explicit mathematical expressions that explain error patterns and guide best practice, no counterpart yet exists for deformable registration methods. This paper aims to close this gap by introducing a metric for registration uncertainty based on the dispersal of boundary condition energy as information from data constraints propagates through an elastic material. This uncertainty metric can be computed in a fraction of a second from the spatial pattern of data available for registration and is demonstrated in this paper to be correlated with registration fidelity. In addition, a bivariate statistical model is introduced for constructing predictive spatial distributions of registration error from this metric. Predictive accuracies of the error models are tested on an extensive existing dataset of 6291 registrations, plus a novel dataset of 699 additional registrations created for independent validation. Finally, a clinical evaluation is performed on three patients.

The structure of this paper is organized as follows. Section II derives two metric variants for estimating spatially localized and total registration uncertainty from the spatial coverage of intraoperative data that can be instantly computed either before initiating or after completing registration. Section III describes the experimental framework used to evaluate the predictive capability of these metrics. Finally, the remaining sections discuss and conclude the work.

II. A MODEL FOR ELASTIC UNCERTAINTY

A. The Elastic Registration Problem

Deformable registration in the context of image guidance aims to update a preoperative model of the organ to match an intraoperative deformation state described by sparsely measured data. Fig. 1 illustrates some examples of data that can be obtained for liver registration. Biomechanically elastic registrations usually treat the preoperative model as a continuum bounded by the domain $\mathcal{M} \in \mathbb{R}^3$ that satisfies the following three conditions [16]:

I. The static equilibrium condition

$$\nabla \cdot \bar{\sigma} + F = 0 \tag{1}$$

II. The linear elastic condition

$$\bar{\bar{\sigma}} = \mathbb{C} : \bar{\bar{\varepsilon}} \tag{2}$$

III. The linear strain-displacement relation

$$\bar{\varepsilon} = \frac{1}{2} (\nabla u + (\nabla u)^T)$$
(3)

where $\overline{\sigma}$ and $\overline{\varepsilon}$ are second-order stress and strain tensors, u is displacement, F is applied force, \mathbb{C} is the fourth-order material tensor, and (:) is the double tensor inner product. Under the condition of isotropic stiffness, these equations simplify to the Navier-Cauchy equations for linear elasticity [16],

$$\mu \nabla^2 u + (\lambda + \mu) \nabla (\nabla \cdot u) + F = 0 \tag{4}$$

where λ and μ are the Lamé parameters. These equations represent a classic boundary value problem that requires knowledge about behavior on the boundary $\partial \mathcal{M}$ before a specific solution over the entire domain \mathcal{M} can be solved, for example using the finite element method. During registration, intraoperative data can be measured from the organ and combined with anatomical knowledge to either directly or indirectly enforce boundary conditions over the domain of the organ with the goal of accurately matching deformation between the intraoperative anatomy and an image-derived preoperative model. It should be noted that while the present description assumes isotropic and homogeneous linear elasticity, the same arguments may be extended to anisotropic, heterogeneous, and fully nonlinear representations on the overarching premise of strain energy decay.

B. Transduction of Boundary Information

A crucial insight to be made is that any set of boundary conditions applied to a linear elastic domain can be decomposed into a superposition of a linearly independent basis of boundary conditions [16]. These basis functions can be constructed pointwise so that the boundary interface $\partial \mathcal{M}$ consists of superposed independent point sources. This principle of domain decomposition is often used within the context of matrix condensation to facilitate real-time computation for *in silico* simulators that use finite element methods [17]. With this idea, consider the propagation of energy from any point source *i* located on $\partial \mathcal{M}$. At static equilibrium, the strain energy $U_i(r)$ stored in the domain at distance greater than *r* from the applied load is bounded by the Toupin-type decay [18]:

$$U_i(r) \le U_i^{\ 0} e^{-k_i r} \tag{5}$$

where U_i^{0} is the total energy of perturbation and k_i is a rate constant associated with the point source. This relationship is a fundamental result from the field equations of elasticity and describes an upper bound on the amount of energy transmitted from any source in the domain to the region of the domain beyond distance r. In (5), three assumptions are made. First, the material properties of \mathcal{M} are considered homogeneous so that the decay rate k_i equals the same constant k for any choice of *i*; however, heterogeneity can be incorporated by integrating the decay rate over distance [18]. Second, \mathcal{M} must be either convex or subject to mild concavity constraints so the region within distance r from position x_i of point source iis connected, namely the set $\{x \in \mathcal{M} : ||x - x_i||_2 < r\}$ is a connected region [18]. Third, elastic modulus is assumed to be isotropic and linear; however, analogous decay relationships have been derived for anisotropic media [19] and nonlinear elasticity [20] that can be directly substituted here.

0278-0062 (c) 2020 IEEE. Personal use is permitted, but republication/redistribution requires IEEE permission. See http://www.ieee.org/publications_standards/publications/rights/index.html for more information. Authorized licensed use limited to: Vanderbilt University Libraries. Downloaded on January 20,2021 at 22:24:01 UTC from IEEE Xplore. Restrictions apply. By this decay relationship, deformation energy at static equilibrium will be attenuated over space due to the spatial accumulation of stress and strain in response to an applied load. Whereas lossless transduction of energy from the boundary of a finite domain would be described by $U_i(r) =$ U_i^0 , this scenario can only be satisfied by rigid motion where the total strain energy must necessarily equal zero. Instead, under deformation, the distribution of strain energy decays exponentially with distance from the applied perturbation. Based on the Shannon information of this distribution, the uncertainty S_i of information provided by this point source measures the reduction in boundary energy that reaches any location in \mathcal{M} given specified behavior from source *i* on $\partial \mathcal{M}$,

$$S_i(r) = -\ln(U_i(r)) \ge kr - \ln(U_i^{0}).$$
 (6)

By this metric, a lower bound on the uncertainty in energetic behavior given a known boundary condition increases linearly with distance away from that condition and logarithmically with the total energy of deformation imposed by the boundary condition. While the previous equation describes information theoretic as opposed to thermodynamic information, a thermodynamic resemblance does exist. Any mechanical excitation applied at the boundary contains directionally ordered information that randomizes, disperses, and attenuates as it propagates into the domain.

Using the principle of domain decomposition through superposition, any configuration of loading on the domain can be considered as a linear combination of local point effects. Let α be a vector of linear coefficients for any basis of stress and strain tensors $\overline{\sigma}_i$ and $\overline{\varepsilon}_i$. Then, the total strain energy U_i^0 for each source is

$$U_i^{\ 0} = \frac{1}{2} \int_{\mathcal{M}} \bar{\sigma}_i : \bar{\varepsilon}_i \, dV \tag{7}$$

and the total strain energy for the full superposed state is

$$U^{0} = \frac{1}{2} \int_{\mathcal{M}} \left(\sum_{i} \alpha_{i} \overline{\overline{\sigma}}_{i} \right) : \left(\sum_{i} \alpha_{i} \overline{\overline{\varepsilon}}_{i} \right) dV = \sum_{i} \alpha_{i}^{2} U_{i}^{0}.$$
(8)

Incorporating the decay relationship from (5), the superposed strain energy U(x) that reaches any point $x \in \mathcal{M}$ is

$$U(x) \le \sum_{i} \alpha_i^{2} U_i^{0} e^{-k\delta_i}$$
(9)

where $\delta_i = ||x - x_i||_2$ is the Euclidean distance from x to each point source. This equation can be simplified by considering the predominant contribution from the nearest point source x_j to x such that $\delta_j \leq \delta_i$ for all *i*. The sum can then be rewritten as

$$U(x) \le \left(\alpha_j^2 U_j^0 + \sum_{i \ne j} \alpha_i^2 U_i^0 \Delta_{ij}\right) e^{-k\delta_j}.$$
 (10)

The term $\Delta_{ij} = e^{k(\delta_j - \delta_i)} \le 1$ and therefore using (8) it is also the case that

$$U(x) \le U^0 e^{-k\delta} \tag{11}$$

where $\delta = \min(||x - x_i||_2)$ is the shortest distance from x to any boundary condition located at $x_i \in \partial \mathcal{M}$ and U^0 is the total strain energy added to the system regardless of any need for explicit domain decomposition. Compared with the tighter bound of (9), due to Δ_{ij} the bound in (11) supposes that all energy sources decay only up to a distance of δ_j instead of to their actual interaction distances δ_i ; however, the looser bound eliminates the need for determining α and regains tightness when multiple boundary conditions are collocated at similar interaction distances. From (11), the energetic uncertainty of the deformation state now can be obtained from the positions of active boundary conditions in any loading configuration by

$$S(x) \ge k\delta - \ln(U^0). \tag{12}$$

During soft tissue registration, the true set of boundary conditions that induces a deformed state is unknown. Instead, all information provided to the system originates from a set of intraoperative data points Π and an optional set of known anatomical constraints Λ . Typically, elastic registrations use data points directly as boundary conditions or as sampled locations against which error is minimized to reconstruct deformation through optimization of a deformation basis. In any elastic registration, the total strain energy required to match all constraints reaches a minimum at static equilibrium. To incorporate the relationship between uncertainty and data distribution, direct boundary conditions that globally minimize strain energy could be considered localized around each data point regardless of how the data point constraints are implemented, because the uncertainty of this minimum energy state will always be greater than any higher energy configuration that could otherwise be reconstructed to satisfy the same constraints. For a set of intraoperative data points Π and preoperative constraints Λ , the constraint uncertainty $S_{\Pi,\Lambda}$ of the internal elastic response based on direct boundary conditions at Π and Λ becomes

$$S_{\Pi,\Lambda}(x) \ge k\delta' - \ln(U^0) \tag{13}$$

where $\delta' = \min\{||x - x_{\Pi}||_2, ||x - x_{\Lambda}||_2\}$ now represents the shortest distance to the set of data points at $x_{\Pi} \in \Pi$ or to the predetermined boundary conditions at $x_{\Lambda} \in \Lambda$ already known to constrain the system.

Finally, the constraint entropy $H_{\Pi,\Lambda}$ is defined to be the average uncertainty over \mathcal{M} given the data:

$$H_{\Pi,\Lambda} = \frac{1}{V_{\mathcal{M}}} \int_{\mathcal{M}} S_{\Pi,\Lambda}(x) \, dV \ge \frac{k}{V_{\mathcal{M}}} \int_{\mathcal{M}} \delta' \, dV - \ln(U^0) \tag{14}$$

for $V_{\mathcal{M}}$ the volume of the domain.

Equations (13) and (14) are the main relationships introduced in this paper that measure a lower bound for the positional and average energetic uncertainty in registration

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given a spatial distribution of constraints that drive the registration. Since the uncertainty is inversely related to the strength of constraint energy that reaches a particular location in the domain, uncertainty can be conceived as the susceptibility of this location to be affected by additional forces acting on or within the domain that influence the true deformation state, though are not represented by the current constraints of the system. These unknown forces could represent additional loads placed on an organ, or effective changes to internal stresses for example related to linear elastic or material assumptions compared to the behavior and structure of real tissue. The first term of the uncertainty metric relates to the spatial coverage of constraints throughout the domain, while the second term relates to the amount of energy required to match the observed deformation state. While computations of the rate constant k and the strain energy U^0 require more description, these steps will be the focus of the following two sections. It is important to note that these quantities can be computed for a registration algorithm regardless of whether a basis for superposed boundary conditions has been explicitly defined as regarded in (8)–(10).

C. Rate of Information Decay

Under the assumptions of a homogeneous and isotropic material domain, the rate of information decay k is a constant that depends on geometry and material parameters. In general, the rate constant takes the form $k = \gamma/s$, where s is a characteristic length and γ is a constant that has analytical solutions in 2-D rectangular [21] and 3-D cylindrical [22] coordinate systems. While s can be determined as functions of width or diameter in toy coordinate systems, in the case of arbitrary geometry [18] the characteristic length takes the form

$$s = \sqrt{\frac{\mu^*}{\rho \omega_0^2}} \tag{15}$$

where $\mu^* = {\mu_M}^2/{\mu_m}$ for which ${\mu_M} = 2\mu + 3\lambda$ is the largest and ${\mu_m} = 2\mu$ is the smallest eigenvalue of \mathbb{C} [16], ρ is the material density, and ω_0 is the lowest characteristic frequency of free vibration. Vibration theory lets this frequency be estimated from the Rayleigh quotient, which can be derived from setting the maximum potential energy of any static nonzero displacement field that satisfies (1–3) equal to the maximum kinetic energy of its undamped oscillation:

$$\omega_0^2 = \frac{\mu^* \int_{\mathcal{M}} \bar{\varepsilon} : \bar{\varepsilon} \, dV}{\rho \int_{\mathcal{M}} u \cdot u \, dV}.$$
 (16)

If a deformation basis or a candidate set of admissible deformations u_i and ε_i have been created, then the frequency estimate can be obtained from $\omega_0^2 = \min(\omega_{0,i}^2)$, where $\omega_{0,i}^2$ is identical to (16) except for substituting $u = u_i$ and $\overline{\varepsilon} = \overline{\varepsilon}_i$.

For the purpose of describing the rate of energy decay, the characteristic length is scaled by the ratio of shear to longitudinal wave speed $1/\chi$ due to the observation that displacements applied to the boundary generate excitation that is not purely dilatational. In fact, it has been shown in the case of $\nu = 1/4$ that the amount of power radiated by a single

boundary condition acting in the normal direction of a semiinfinite medium is approximately 3.7 times greater in the shear mode than the longitudinal mode of wave transmission [23]. The longitudinal wave speed $c_L = \sqrt{(\lambda + 2\mu)/\rho}$ and the shear wave speed $c_S = \sqrt{\mu/\rho}$ represent the maximum rate at which information can be propagated through the material in each mode, which gives a ratio

$$\chi = \frac{c_L}{c_S} = \sqrt{\frac{\lambda + 2\mu}{\mu}} = \sqrt{\frac{(2 - 2\nu)}{(1 - 2\nu)}}$$
(17)

where ν is the Poisson ratio. In this way, the characteristic length s/χ now considers the dissipation of energy through the dominant shear mode and leads to the rate constant

$$k = \frac{\gamma \chi}{s} = \gamma \sqrt{\frac{(2 - 2\nu) \int_{\mathcal{M}} \bar{\varepsilon} : \bar{\varepsilon} \, dV}{(1 - 2\nu) \int_{\mathcal{M}} u \cdot u \, dV}}.$$
 (18)

If a set of basis or candidate deformations u_i and $\overline{\overline{\varepsilon}}_i$ are known, then $k = \min(k_i)$ as if using the lowest estimate of fundamental frequency from (16). The rate factor γ is estimated experimentally by optimizing a root mean square (RMS) correlation coefficient described in section III-B.

D. Energy of Deformation

The final quantity needed to compute $S_{\Pi,A}$ and $H_{\Pi,A}$ is the total energy of deformation U^0 . Algorithmically, two variants of these uncertainty metrics are proposed depending on how U^0 and k are computed. These variants lead to retrospective metrics S_r and H_r that utilize measurements of deformation and strain energy obtained after registration has completed, and prospective metrics S_p and H_p that use alternative estimates computed prior to initiating registration.

The retrospective metrics S_r and H_r assume the most reliable estimate for the energy of deformation from the total internal strain energy of the registration solution,

$$U^{0} = \frac{1}{2} \int_{\mathcal{M}} \bar{\sigma} : \bar{\varepsilon} \, dV.$$
⁽¹⁹⁾

Substitution of (18)–(19) into (13)–(14) leads to generalized metrics for uncertainty S_r and entropy H_r that can be obtained after the completion of any elastic registration method from the solved displacement, stress, and strain fields, organ volume, the Poisson ratio, and the distribution of constraints provided to the registration. Computation of these retrospective metrics is summarized in Algorithm I.

Whereas the generalized retrospective metrics can only be computed after registration has completed, a fully predictive metric that can be computed in real time during data collection would be invaluable for actively assisting image-guided surgical applications. A fully predictive metric can be constructed if two conditions are met: if the rate constant is pre-computed from a known basis of boundary conditions or from simulating admissible displacements to estimate the Rayleigh quotient in (16), and if the internal energy of deformation is estimated from external work. The total external work W can be approximated from the mean squared This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TMI.2021.3052523, IEEE Transactions on Medical Imaging

Input: Π – Point cloud of intraoperatively deformed organ features Λ – Positions of other known anatomical constraints, if any M – Initial organ model rigidly registered to Π , Λ V_M – Volume of M $u(M,\Pi,\Lambda)$ – Displacement field of elastic reg. from M to Π,Λ $\varepsilon(M,\Pi,\Lambda)$ – Strain field of elastic registration from M to Π,Λ $\sigma(M,\Pi,\Lambda)$ – Stress field of elastic registration from M to Π,Λ $\boldsymbol{\nu}$ – Poisson ratio 1: For each point in M, 2: Compute distance $\delta(M; \Pi, \Lambda)$ to the nearest point in Π, Λ $ssu = \sum_{i=1}^{3} u_i^2$ $sse = \sum_{i=1}^{3} \sum_{j=1}^{3} \varepsilon_{ij}^2$ 3: 4: $sed = \sum_{i=1}^{3} \sum_{j=1}^{3} \sigma_{ij} \varepsilon_{ij}$ (strain energy density) 5: 6: $I\delta = \int \delta dV_M$ 7: $Iu = \int ssu \, dV_M$ 8: $I\varepsilon = \int ss\varepsilon \, dV_M$ 9: $U_0 = (1/2) \int sed \, dV_M$ 10: $\boldsymbol{\omega} = \boldsymbol{I}\boldsymbol{\varepsilon}/\boldsymbol{I}\boldsymbol{u}$ 11: $\chi = (2 - 2\nu)/(1 - 2\nu)$ 12: $\gamma = 1.08$ (optimized from Section III-B) 13: $\mathbf{k} = \gamma \sqrt{\chi \omega}$ 14: $S_r = k\delta - \ln(U_0)$ 15: $\boldsymbol{H}_r = (\boldsymbol{k}/\boldsymbol{V}_M)\boldsymbol{I}\boldsymbol{\delta} - \ln(\boldsymbol{U}_0)$ Output: S_r – Uncertainty of constraints at each vertex of **M** H_{r} – Entropy of constraints over **M**

error between data points and a rigidly aligned model from the Hookean relationship

$$W = \frac{1}{N_{\Pi}} \sum_{j=1}^{N_{\Pi}} \frac{1}{2} \kappa \|u_j\|^2 = \frac{\kappa}{2N_{\Pi}} \sum_{j=1}^{N_{\Pi}} \|u_j\|^2$$
(20)

where N_{Π} is the number of data points, κ is an effective spring constant, and $||u_j||$ is the magnitude of displacement between data point *j* and the corresponding position on a rigidly aligned model, for which the closest point is the most conservative estimate. Then the energy of deformation can also be approximated as

$$\ln(U^0) \approx \ln(W) = \ln\left(\frac{1}{2N_{\Pi}}\sum_{j=1}^{N_{\Pi}} \|u_j\|^2\right) + C$$
 (21)

for $C = \ln(\kappa)$ representing a constant shift that can be ignored for the purpose of establishing a correlation between uncertainty and registration error. Equations (13), (14), (18), and (21) then lead to fully predictive uncertainty metrics S_p and H_p that can be computed prior to registration from precomputed examples of candidate deformations as summarized in Algorithm II.

In the next sections, correlations of the uncertainties S_r and S_p are computed with respect to the error capacity E, which represents the proportion of TRE remaining after deformable registration relative to initial error, defined as the percentage

$$E = \frac{TRE_d}{/TRE_r} \times 100\%$$
(22)

at each target where TRE_d is the final target registration error after deformable registration and $\overline{TRE_r}$ is the average target registration error after initial rigid registration of the organ.

ALGORITHM II: PRE-REGISTRATION (PROSPECTIVE) UNCERTAINTY

```
Input: \Pi – Point cloud of intraoperatively deformed organ features
            \Lambda – Positions of other known anatomical constraints, if any
            M – Initial organ model rigidly registered to \Pi, \Lambda
           V_M – Volume of M
           \overset{\sim}{u_1, u_2, \dots, u_n} – Displacement fields of candidate deformations \varepsilon_1, \varepsilon_2, \dots, \varepsilon_n – Strain fields of candidate deformations
            \nu – Poisson ratio
  Pre-compute:
        1: For k = 1 to n
        2:
                For each point in M,
                    ssu_{k} = \sum_{i=1}^{3} u_{k,i}^{2}
ss\varepsilon_{k} = \sum_{i=1}^{3} \sum_{j=1}^{3} \varepsilon_{k,ij}^{2}
        3:
        4:
                Iu_k = \int ssu_k \, dV_M
        5:
                I\varepsilon_k = \int ss\varepsilon_k \, dV_M
        6:
        7: \boldsymbol{\omega} = \min(\boldsymbol{I}\boldsymbol{\varepsilon}_k/\boldsymbol{I}\boldsymbol{u}_k)
        8: \chi = (2 - 2\nu)/(1 - 2\nu)
        9: \gamma = 6.62 (optimized from Section III-B, method-specific)
      10: \mathbf{k} = \gamma \sqrt{\chi \omega}
  Intraoperatively:
        1: For each point in M,
                 Compute distance \delta(M; \Pi, \Lambda) to the nearest point in \Pi, \Lambda
        2:
        3: I\delta = \int \delta dV_M
        4: For each point in I,
                 Compute distance d(\Pi; M) to the nearest corresponding feature
        5:
                 point in M
        6: W = 1/(2N_{\Pi}) \sum_{i=1}^{N_{\Pi}} d_i^2
        7: S_p = k\delta - \ln(W)
        8: H_p = (k/V_M)I\delta - \ln(W)
Output: \overline{S_p} – Uncertainty of constraints at each vertex of M
            H_p – Entropy of constraints over M
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Furthermore, the entropy metrics H_r and H_p are correlated against \overline{E} , the average error capacity across domain \mathcal{M} . For evaluation in this paper, elastic registrations are computed using the linearized iterative boundary reconstruction method described in [11] and all variables are defined in m-kg-s units.

E. Spatial Distributions of Predicted TRE

Pointwise spatial estimation of error capacity at each vertex of \mathcal{M} is enabled by fitting joint bivariate gamma (bigamma) distributions relating E to S_r and E to S_p . Bivariate gamma distributions excel at describing recurring attenuation of signal due to multipath propagation or partial obstructions, and have found applications modeling fading channels in radiofrequency analysis [24] and the relationships between rainfall and runoff in hydrology [25]. The shape of the gamma distribution is highly flexible and generalizes many common distributions including the chi-square, exponential, Rayleigh, and Maxwell distributions. If the directional components of TRE are independent and normally distributed in three dimensions as presented in [2], then the magnitude of TRE is by definition Maxwell-distributed and the sum of squares chisquared. These characteristics make the bigamma distribution exceptionally pertinent to the present application of describing the relationship between the dispersive propagation of boundary energy and the reduction in TRE. The bivariate gamma distribution used in this paper is a six-parameter adaptation of [26] and its formulation and parameter estimation are described in Appendix A. Bigamma distributions $P(S_r, E \mid \hat{\theta}_r)$ and $P(S_p, E \mid \hat{\theta}_p)$ are computed by fitting distribution parameters $\hat{\theta}_r$ and $\hat{\theta}_p$ to data described in section III using the method of Appendix A. After these distributions are fit, the probability distribution of error

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Fig. 1. Data available for registration in hepatic image guidance. Deformable registration updates the preoperative model (parenchyma - gray; portal vein - red; hepatic vein - blue) to match intraoperative data while predicting internal displacements as accurately as possible. (a) Organ shape from intraoperative CT (green) indicates the full deformed surface of the liver. (b) In the surgical setting, points on the anterior surface of the liver (black) can be measured using tracked tools or computer vision. (c) A tracked intraoperative ultrasound plane allows localization of intrahepatic vessels and the posterior surface of the liver.

ALGORITHM III: PREDICTION OF TARGET REGISTRATION ERROR CAPACITY
Input: S – Constraint uncertainty at each vertex of organ model
H – Constraint entropy of organ model given data
Pre-compute:
1: Set bivariate gamma parameters $\hat{\theta}_r$ and $\hat{\theta}_p$ (see Appendix A)
2: Compute lookup tables $P(S, E \mid \hat{\theta}_r)$ and $P(S, E \mid \hat{\theta}_n)$ from (A3)
Intraoperatively:
1: If S , H are post-registration (retrospective) metrics:
2: $P(S, E) = P(S, E \hat{\theta}_r)$
3: $\alpha = 14.1; \beta = 19.0$ (see linear model Section III.B)
4: Else if S , H are pre-registration (prospective) metrics:
5: $P(S, E) = P(S, E \hat{\theta}_p)$
6: $\alpha = 5.1; \beta = 40.0$ (see linear model Section III.B)
7: Set \boldsymbol{p} as percentile of interest (e.g. 0.5 or 0.05 and 0.95)
8: For each value in S
9: Interpolate $P(E S)$ from joint distribution $P(S, E)$
10: $F(E S) = \int_0^x P(E S) dE$ (cumulative distribution function)
11: $E_p = F^{-1}(p)$ (<i>p</i> -quantile function)
12: $\overline{E} = \alpha H + \beta$
Dutput: $E_p - p^{th}$ quantile of error capacity at each vertex of organ model

capacity is predicted at every spatial location from the conditional distributions $P(E|S_r, \hat{\theta}_r)$, $P(E|S_p, \hat{\theta}_p)$ and new values of S_r and S_p computed across \mathcal{M} . These pointwise probability distributions can be summarized into a spatial uncertainty map from distribution medians or confidence intervals. Algorithm III outlines this process for predicting error capacity E from retrospective and prospective uncertainty metrics S_r and S_p .

 \overline{E} – Average error capacity across organ model after registration

III. EXPERIMENTAL SIMULATIONS

A. Data

The proposed metrics are evaluated on a dataset of 6291 registration scenarios (dataset A, previously reported in [11]) derived from three patient-specific liver geometries (Livers 1, 2, and 3) each subjected to three unique liver deformations of mobilization from the left triangular ligament, no ligaments, or right triangular ligament (L, N and R) and mapped from the profile of 147 target displacements in a silicone phantom after it was subjected to these deformations inside a laparoscopic simulator. For each of the nine deformed organs, a sparse pattern of anterior surface data and 16 simulated ultrasound (US) planes were generated. These data were assembled into combinatorial configurations of intraoperative data for registration, consisting of:

- i. Anterior surface data only, n = 9;
- ii. Anterior surface data plus one US plane, n = 144;
- iii. Anterior surface data plus two US planes, n = 1080;



Fig. 2. RMS Pearson correlation coefficient plotted against rate factor γ for retrospective and prospective information metrics H_r and H_p , respectively. As γ grows large, H depends only on the first distance term and as γ approaches zero, H depends only on the second energy of deformation term. The existence of prominent optima suggests that both terms contribute complementary information towards predicting registration performance. At small γ , the average correlation coefficient is considerably lower for H_n than H_r because the prospective formulation approximates energy of deformation less accurately than achievable with internal strain energy. At large γ , the difference relates to rate constant computation, where the prospective metric estimates the fundamental frequency by the lowest mode response from a series of candidate deformations, whereas the retrospective metric computes a fundamental frequency from the actual activation of deformation modes in the system. An empirical characterization of the rate factor γ affords leniency in the approximations made for the prospective metric without sacrificing substantial predictive value relative to the complete retrospective approach.

- iv. Anterior surface data plus three US planes, n = 5040;
- Anterior surface data plus all 16 US planes, n = 9; v
- vi. Ground truth position of the complete surface plus the complete intrahepatic vessel structure, n = 9.

A representative subset of examples from these data configurations is shown in Fig. 1. TRE is measured as the Euclidean distance between the registered and ground truth positions of each vertex in the volumetric liver mesh, creating 27,218 (Liver 1), 31,044 (Liver 2), and 18,821 (Liver 3) total targets per registration instance. In total, over 161 million individual target samples are considered in this first dataset, from which model parameters are fitted and correlations between the uncertainty metrics and registration error are cross validated in a leave-one-out experimental design.

A novel dataset was also created for independent validation using the same data-generative method of [11]. In this case, a displacement field was obtained from the motion of 159 target positions embedded in a silicone liver phantom imaged before and after the phantom was placed in an open surgical configuration with deformation created by perihepatic packing placed beneath the posterior surface of the liver. This

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Fig. 3. Linear regressions between constraint entropy H_p and average error capacity \overline{E} with each point representing one registration to a specific configuration of intraoperative data from dataset A. (a) Correlations of H_p and \overline{E} for each of the nine deformation conditions of dataset A. Axes same as (b). (b) All 6291 registrations from dataset A and total regression line (black) plotted with the 699 registrations from the separate validation dataset B (red). Legend indicates the extent of intraoperative data provided to each registration.

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PREDICTION OF AVERAGE REGISTRATION ERROR FROM BOUNDARY INFORMATION ENTRO	ρPY

Deformation	Mean Rigid TRE (mm)	Difference in Predicted Average TRE (mm), H_r	Difference in Predicted Average TRE (mm), H_p	Difference in Predicted Average Error Capacity (%), H_r	Difference in Predicted Average Error Capacity (%), H_p
1-L	12.4	$0.9(0.7\pm0.5)$	$0.8 (0.6 \pm 0.5)$	$7.0(5.9 \pm 3.8)$	$6.3(4.9 \pm 4.0)$
1-N	15.3	$1.5(1.4 \pm 0.7)$	$2.0(1.8\pm0.8)$	$10.0(9.0 \pm 4.4)$	$13.1(11.9 \pm 5.5)$
1-R	14.9	$0.9(0.7\pm0.5)$	$1.1 (0.8 \pm 0.7)$	$5.7(4.5 \pm 3.6)$	$7.3(5.5 \pm 4.8)$
2–L	10.9	$0.7 (0.5 \pm 0.4)$	$0.7 (0.5 \pm 0.4)$	$6.2(4.9\pm3.8)$	$6.4(5.0 \pm 4.1)$
2–N	16.9	$1.5(1.3 \pm 0.7)$	$1.0(0.8\pm0.5)$	8.6 (7.7 ± 3.9)	$5.6(4.7 \pm 3.2)$
2–R	12.5	$1.0(0.7\pm0.7)$	$1.1 (0.8 \pm 0.8)$	$8.1(5.8\pm5.7)$	$8.8(6.1\pm6.4)$
3–L	12.8	$1.2(1.1 \pm 0.6)$	$1.2(1.1 \pm 0.6)$	$9.5(8.5 \pm 4.3)$	$9.6(8.4 \pm 4.7)$
3–N	13.9	$0.6 (0.5 \pm 0.3)$	$0.8 (0.6 \pm 0.4)$	$4.0(3.4 \pm 2.1)$	$5.4(4.6 \pm 2.9)$
3–R	15.1	$1.2(1.1 \pm 0.6)$	$1.6(1.4 \pm 0.8)$	8.2 (7.2 ± 3.9)	$10.9(9.6 \pm 5.3)$
Total	_	$1.1 (0.9 \pm 0.6)$	$1.2 (0.9 \pm 0.8)$	$7.7(6.3 \pm 4.4)$	8.5 (6.7 ± 5.3)
Validation	5.4	1.1 (0.9 ± 0.5)	0.5 (0.4 ± 0.3)	<i>19.7 (17.6</i> ± <i>8.8)</i>	10.2 (8.4 ± 5.9)

Predictive errors reported as RMSE (MAE ± STD): RMSE root mean square error; MAE mean absolute error; STD standard deviation.

displacement field was mapped using an affine and elastic transformation onto a novel patient-specific liver geometry consisting of 25,905 mesh vertices. Each vertex is treated as a target location for computing TRE. Intraoperative data were simulated combinatorially as previously described. This validation dataset (dataset B) represents 699 additional registration scenarios based on a novel liver geometry and novel deformation profile.

B. Prediction of Average Error Capacity

For each of the nine deformed organs in dataset A, Pearson correlation coefficients were computed between H_r and \overline{E} , and H_p and \overline{E} as represented by Fig. 3a. The RMS value of these correlation coefficients was maximized to determine the rate factor γ in Fig. 2, from which optima were found at $\gamma_r = 1.08$ and $\gamma_p = 6.62$. These values were used for the rest of the analysis in this paper. Fig. 3a shows strong linear relationships that suggest registration error may be minimized in each instance of organ deformation by supplying a configuration of intraoperative data that minimizes constraint entropy. Furthermore, a linear regression may be used to predict the average amount of elastic correction achievable from a provided pattern of intraoperative data coverage.

To assess general predictive capability across multiple deformations and organ shapes, prediction errors were crossvalidated in a leave-one-out fashion. Linear regressions were fit to registrations from eight of the nine deformations in dataset A, then predictions for \overline{E} , the average error capacity, were made from the values of each entropy metric H_r and H_n for each registration in the left-out deformation. Table 1 shows the differences between the average registration errors as reported in [11] and the predicted average registration errors using H_r and H_p . With respect to quantitative predictive value, if the average rigid TRE values reported in Table I were known, the RMS error in predicted average TRE after elastic registration would be 1.1 mm for the retrospective metric H_r and 1.2 mm for the prospective metric H_p across all nine leave-one-out cross-validations. These values suggest that the proposed constraint entropy metrics predict overall registration performance quite accurately. This prediction accuracy was achieved over the range of average TRE values reported in [11], from 2.8 ± 0.5 mm when registering to complete data to 11.4 ± 2.2 mm when registering to the sparsest data configurations. Although the actual value of average rigid TRE is typically unknown, in practice a value could be inferred or conservatively estimated for an organ if

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Fig. 4. Empirical joint distributions of paired observations between error capacity E and uncertainty S_p . (a) Empirical distributions drawn from all registrations of each of the nine deformation conditions of dataset A, plotted on the same axes as (b); (b) The total empirical joint distribution using all targets in dataset A. TABLE II

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Deformation	Mean Rigid TRE (mm)	Difference in Median Predicted TRE (mm), S_r	Difference in Median Predicted TRE (mm), S_p	Difference in Median Predicted Error Capacity (%), <i>S_r</i>	Difference in Median Predicted Error Capacity (%), S_p
1–L	12.4	$3.4(2.6 \pm 2.3)$	$3.5(2.5\pm2.4)$	$27.7(20.8 \pm 18.3)$	28.3 (20.5 ± 19.5)
1-N	15.3	$5.7(3.8 \pm 4.3)$	$5.9(3.8 \pm 4.5)$	$37.3(24.8 \pm 27.9)$	38.5 (25.1 ± 29.2)
1–R	14.9	$4.5(3.3\pm3.1)$	$4.6(3.3 \pm 3.2)$	$30.2(22.0\pm20.7)$	$30.9(22.1 \pm 21.5)$
2–L	10.9	$3.4(2.4 \pm 2.4)$	$3.4(2.4 \pm 2.5)$	$30.9(21.6 \pm 22.0)$	$31.5(21.7 \pm 22.9)$
2–N	16.9	$5.4(3.6 \pm 4.0)$	$5.2(3.6 \pm 3.8)$	$32.0(21.3 \pm 23.9)$	$30.7 (21.0 \pm 22.4)$
2–R	12.5	$4.5(3.0\pm3.3)$	$4.6(3.1\pm3.4)$	$35.6(24.3 \pm 26.0)$	$36.3(24.6 \pm 26.7)$
3–L	12.8	$3.2(2.4 \pm 2.0)$	$3.2(2.4\pm2.0)$	$24.7(19.1 \pm 15.6)$	$24.7(18.9 \pm 15.9)$
3–N	13.9	$3.5(2.7\pm2.3)$	$3.6(2.7\pm2.3)$	$25.1(19.1 \pm 16.3)$	$25.5(19.4 \pm 16.6)$
3–R	15.1	$3.6(2.8\pm2.3)$	$3.6(2.8\pm2.3)$	$24.0(18.4 \pm 15.3)$	$24.1(18.8 \pm 15.1)$
Total	_	$4.3(3.0\pm3.1)$	$4.4(3.0\pm 3.2)$	30.7 (21.6 ± 21.9)	31.1 (21.7 ± 22.4)
Validation	5.4	2.0 (1.6 ± 1.2)	$2.0~(1.4 \pm 1.4)$	37.0 (29.4 ± 22.5)	36.9 (26.3 ± 25.9)

Predictive errors reported as RMSE (MAE ± STD): RMSE root mean square error; MAE mean absolute error; STD standard deviation.

an interpretation with spatial length scale is needed. Differences in the predicted and actual average error capacity \overline{E} are shown in the last two columns of Table I, with total RMS prediction error of 7.7% (H_r) and 8.5% (H_p) across the leave-one-out experiments, meaning that the metric-estimated percentage of TRE remaining after elastic registration was accurate to approximately $\pm 8\%$ of the underlying magnitude of rigid error.

Combining all 6291 registrations from dataset A leads to total linear regressions between \overline{E} and H with 95% confidence intervals and correlation coefficients

$$\overline{E} = [14.1 \pm 0.3]H_r - [19.0 \pm 1.3]; r = 0.78$$

$$E = [5.1 \pm 0.1]H_p - [40.0 \pm 2.0]; r = 0.73$$

where the difference between strength of correlation for H_r and H_p may be attributed to loss of precision when prospectively approximating energy of deformation and rate of information decay as conjectured in Fig. 2. However, Table 1 suggests that quantitative prediction accuracies are similar between both metrics.

Independent evaluation of predicted average error estimation was performed with validation dataset B using the total regressions to dataset A. Fig. 3b plots the total regression of H_p and \overline{E} from dataset A compared to the values of H_p and \overline{E} from all registrations in dataset B, illustrating consistent

alignment of the metric regression across disparate cases. The final row of Table I provides numerical results for the accuracy of TRE prediction from retrospective and prospective entropy metrics. While the length scales of prediction errors are in agreement between both datasets, it is expected that the error capacities become less stable when the total energy of deformation is small, such as in the case of validation dataset B for which the average rigid TRE was only 5.4 mm due to smaller underlying deformations in the mapped displacement field. For increasingly rigid systems, \overline{E} becomes more sensitive and the uncertainty bound becomes degenerate as U_0 approaches zero and ω_0 emerges from a state approaching zero displacement and zero strain. It is intuitive that a degenerate case is reached in the limit of zero deformation because no energetic information is introduced to the system. However, as shown by the alignment of predicted values in Fig. 3b, the validation dataset shows that the method for error prediction is still effective outside the specific range of deformation magnitudes in dataset A.

C. Prediction of Pointwise Error Capacity

To analyze pointwise TRE predictions, the bivariate distributions were fit and evaluated using a similar leave-one-deformation-out approach from dataset A, plus independent validation from dataset B. After registration, the 161 million

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Fig. 5. Predicted TRE from median error capacity (top) and measured TRE (bottom) after elastic registration. (a,d) Error profiles of registration to surface data pattern (black). (b,e) Error profiles after data from one additional US plane is added to registration. (c,f) Error profiles with data from three US planes provided. The distributions of predicted remaining error can guide additional data collection to areas of poor expected performance for improving registration fidelity.

target samples in dataset A provide paired observations of the uncertainty metrics S and error capacities E. These target samples are separated into nine groups respective to the underlying liver geometry and deformation profile. The joint relationships of these paired observations S and E are shown for each deformation condition in Fig. 4a. Bigamma probability distributions P(S, E) are alternately fit to all target samples from eight of the nine groups, and samples from the last group are withheld for evaluation. For evaluation, the median predicted values of $E_{0.5}$ are obtained for the withheld group using the conditional distribution P(E|S). The predicted median $E_{0.5}$ and the actual value of E are compared in Table II for predictions based on the post-registration retrospective metric S_r and the pre-registration prospective metric S_p . If the average rigid TRE were to be known or estimated for each registration, then both the prospective and retrospective registration uncertainty metrics could predict pointwise elastic TRE from the distribution median to less than 4.5 mm RMS error across all cross-validated samples in dataset A. However, the absolute difference between the predicted and actual error capacity at each target was approximately 30% RMS.

All 161 million target samples from dataset A were combined into an empirical distribution (Fig. 4b) and bigamma distribution parameters $\hat{\theta}_r$ and $\hat{\theta}_p$ were estimated for S_r and S_p metrics as reported in Appendix A. From these distributions, median values of E were predicted from S_r and S_p computed on dataset B and were compared against their corresponding measured values. Prediction errors for these pointwise estimates from dataset B are displayed in the final row of Table II and agree in magnitude with errors obtained from the leave-one-out study on dataset A. While the results of Fig. 4 and Table II are informative, Fig. 5 further exhibits predictive capability. Fig. 5a-c illustrate spatial distributions of TRE predicted from median error capacity in comparison to spatial distributions of TRE measured with respect to the ground truth deformation in Fig. 5d-e as the amount of data provided to the registration is incremented by adding sparse features from tracked intraoperative ultrasound planes.

D. Clinical Verification

Pointwise estimates of uncertainty and registration errors were evaluated in three patients undergoing image-guided open liver resection with tracked intraoperative ultrasound. In all patients, intraoperative anterior surface data points were collected with an optically tracked stylus. In addition, two ultrasound image planes of the portal and hepatic vein features, respectively, were acquired at distances 3.4-8.3 cm apart (Fig. 6a). These data were previously reported in [11] and were collected with approval by the institutional review board at Memorial Sloan Kettering Cancer Center. The error capacity at each feature was computed as the ratio between the maximum closest-point error of the feature after deformable elastic registration and the maximum closest-point errors of both features after rigid registration. For each patient, three elastic registrations were performed, first to the anterior surface data after which uncertainties and error were measured at both venous features, second to the anterior surface data plus portal vein feature with evaluation at the hepatic vein feature, and third to the anterior surface data plus hepatic vein feature with evaluation at the portal vein feature. In total, 12 evaluations were obtained. The estimated distributions of error capacity were inferred from the average uncertainty computed across each feature through the conditional distributions $P(E|S_r, \hat{\theta}_r)$ and $P(E|S_p, \hat{\theta}_p)$. In Fig 6b–c, the measured error capacity of each evaluated feature is shown plotted against its computed uncertainty and the empirical distribution of P(S, E)from dataset A. Fig. 6d shows an example of the measured error from one evaluated feature with respect to the predicted error distributions conditional on its uncertainties. For the retrospective and prospective uncertainty metrics, the clinically measured error capacities were not significantly biased around their estimated distribution medians (p = 0.15, sign test), and 100% of samples fell within the 98% confidence intervals of the respective conditional distributions. Accounting for the initial magnitude of rigid error, the difference in measured error and median predicted TRE at the centroids of the vessel features was 4.6 mm RMS (3.4 ± 3.2)

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Fig. 6. Results from clinical evaluation. (a) Vascular features from three patients located at the hepatic vein (blue) and portal vein (red) were measured with tracked intraoperative ultrasound. (b) Joint distribution of retrospective uncertainty metric $P(S_r, E)$ with overlaid clinical measurements of error capacity and computed uncertainty for each registered feature. (c) Joint distribution of prospective uncertainty metric $P(S_p, E)$ with overlaid clinical feature measurements of error capacity and computed uncertainty. (d) Conditional distributions $P(E|S, \theta)$ for both metrics, with measured error capacity from clinical data in solid red compared to the predicted distribution medians as vertical lines.

mm) for the retrospective uncertainty metric and 5.8 mm RMS $(4.4 \pm 3.9 \text{ mm})$ for the prospective uncertainty metric. These results suggest that the constraint uncertainty and error distributions established in simulated data agree with clinical expectation.

IV. DISCUSSION

A. Prospective Application

This paper demonstrates that uncertainty in elastic registration is inherent when incomplete information is provided, and that an uncertainty metric that correlates with the proportion of TRE remaining after registration can be computed from the spatial coverage of data constraints. Registration uncertainty was found to depend on two crucial variables, firstly the distance from a target within an organ to the closest intraoperative constraint that most strongly informs its motion, and secondly the total amount of deformation described by the intraoperative data. These relationships substantiate a trend for data collection that aims to maximize registration performance: data should be collected as broadly as possible, with special focus placed near interventional targets and in regions of greatest organ deformation.

However, practical constraints often make intraoperative data collection time intensive and encumbering to personnel. While sparse organ surface measurements can be obtained through digitization of tracked tool positions or computer vision, more thorough geometric measurements from intraoperative imaging often require manual or semi-automatic segmentation before becoming usable. These real-world limitations inspire a need for new approaches that inform and allow optimization of the data collection process. The entropy and uncertainty metrics proposed in this paper address this need in several ways. First, a monotonic decrease in total registration error over the domain is expected as entropy decreases. Subsequently, the summary number H_n can be computed and monitored in real time during data collection to potentially reveal local saturation of data coverage that ceases to improve overall registration quality. Second, the effectiveness of elastic registration at any target of interest can be estimated based on a confidence interval or average value of predicted error capacity inferred from the pointwise registration uncertainty S. Third and foremost, as illustrated in Fig. 5, a spatial map of the predicted TRE distribution can be constructed to indicate expected regions of poor registration performance. These maps can suggest regions that require improvements to data coverage or qualify localization accuracy after registration has completed to mitigate guidance errors. Although registration to partial data fundamentally prevents exact prediction of TRE because a specific unknown underlying organ deformation must be selected from many potentially valid solutions, this paper contributes a means by which data sufficiency can be estimated in an average and distributional sense through correlation to measured results.

B. Prediction Quality

Only a small number of prior studies have aimed to experimentally validate TRE predicted by rigid registration theory. In [27], the difference between measured and estimated average TRE predicted by the method of [1] was found to be 1.3 ± 1.2 mm. In [28], pointwise measurements and estimates of TRE predicted by [5] were reported to be 3.1 ± 1.2 mm. The results reported in Table I and Table II indicate that the constraint entropy and uncertainty metrics proposed in

this work for nonrigid elastic registration are able to achieve a similar range of TRE prediction errors, with average error predictions equivalent to 0.9 ± 1.6 mm and pointwise error predictions equivalent to 3.0 ± 3.1 mm if baseline average rigid TRE could be identified or anticipated. Further, the clinical experiment achieved pointwise error predictions equivalent to 3.4 ± 3.2 mm with the retrospective constraint uncertainty metric. However, it should be stressed that S and H are regressed to the proportion of uncorrected error that remains after elastic registration instead of to the final magnitude of TRE. This approach provides superior correlation that normalizes relative variation in initial error to indicate the proportionate capacity for error in the system after elastic registration terminates. Additionally, it must be recognized that because S and H are lower bounds as opposed to strict equalities, residual variance still remains within the regression models for error capacity. It is possible that incorporating tighter energetic bounds could further improve predictive quality.

C. Relation to Rigid Body Registration

In rigid body registration, fiducial registration error (FRE) represents the external alignment accuracy of fiducials after rigid registration. Although rigid theory has demonstrated that FRE and TRE are only related through distribution averages while individual samples are uncorrelated [29–31], the bigamma distribution that estimates pointwise error capacity from uncertainty in the deformable case does empirically model statistical deviation. However, care must be taken in both rigid and deformable TRE estimation to correctly interpret distributional predictions based on measured samples not as quantitative certainty, but instead as quantitative tendency.

Another relation between rigid FRE and deformation is the external work W where alternatively $W = (\kappa/2) FRE^2$. Fig. 2 shows that as $\gamma \to 0$, a logarithmic transformation of the energy of deformation, i.e. the total energetic information content, is indeed correlated with the average deformable error capacity \overline{E} . This transformation reveals that rigid FRE is proportional to the observed quantity of information carried in the deformation energy. Although the external energy measure W is a weaker approximation to the actual internal energy U^0 , both uncertainty bounds reflect a loss of energetic information depending on the total amount of observed deformation and a propagation distance δ' . In the limiting case of perfect information that would minimize energetic uncertainty, either data must be collected everywhere so that $\delta' \rightarrow 0$, or deformation must vanish as $U^0 \rightarrow 0$ to leave behind a rigid body system. In the case of deformation and sparse measurement where $U^0 > 0$ and $\delta' > 0$, the amount of propagated constraint energy is restricted and prediction becomes possible from the Toupin upper bound for energy decay. While rigid body registration is a limiting case where no energy from the boundary is communicated into the domain, external error measurements with respect to rigid body motion still provide partial information about limits on internal error in the deforming case, which develop through energetic propagation and dispersal governed by the relationship between boundary conditions and elastic field conservation.

D. Limitations

In this work, a simulation framework is leveraged to allow for a comprehensive prediction of registration error throughout a variety of organ shapes and deformations with known ground truth. Although these deformations are derived from organ phantom displacement fields that only approximate real tissue behavior, this approach enables a more statistically sound avenue for evaluation that does not introduce sampling biases typically encountered when measuring sparse clinical targets. Additional verification with clinical data demonstrates feasibility and suggests that the proposed models for constraint uncertainty and error estimation are directly translatable to elastic image-to-patient registration.

Although evaluation on alternative methods of elastic registration would be desirable, no openly available methods yet exist that are capable of registering geometric features to sparse intraoperative patient data. It should be noted that free form, spline-based, and deep learning image registration techniques do not necessarily produce mechanically elastic deformations that follow physical elastic conservation laws. While the proposed uncertainty measures are derived directly from the field equations of elasticity through the Toupin bound for energetic propagation of data constraints, no assumptions are made that restrict viability in applications with other purely elastic registration methods. Although some assumptions are made so that a general form can be readily employed, additional terms could be introduced to the uncertainty model to produce a more exact bound based on specialized implementation of data constraints, constraint distances, or material heterogeneity and anisotropy. Additionally, considering that error distributions were fit based on registration results using the linearized iterative boundary reconstruction method in [11], error inference for alternative methods may require reoptimization of parameters such as θ and γ to account for differences in accuracy between registration approaches.

Finally, while it is beneficial that the datasets used for evaluation contain large variation in data coverage for characterizing behavior across a wide range of inputs, it is possible that sensitivity of registration to marginal changes in data content may not be easily detected if other sources of registration noise such as mesh discretization, material and linearity assumptions, and instrumentation errors are large in comparison to more limited datasets with smaller constraint variation. These factors make it possible that some customization could be needed on a method-to-method basis. However, this work provides a framework with which to evaluate susceptibility to elastic registration errors using energetic bounds on intraoperative data constraints, to optimize intraoperative data collection and achieve a mechanism for assessing intraoperative risk during imageguided localization and navigation.

V. CONCLUSION

This paper presents a method for estimating the spatial distribution of elastic registration uncertainty using an information-theoretic approach to characterize the dissipation of boundary condition energy as it propagates from data constraints into the volume of an organ. Proposed metrics for This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TMI.2021.3052523, IEEE Transactions on Medical Imaging

registration uncertainty can be rapidly computed for any linear elastic registration method. Regressions are fit and evaluated on over 6000 total simulated registrations consisting of over 160 million individual targets to infer remaining TRE from registration uncertainty using a standard linear model and spatial covariation of variables through bivariate gamma statistics. The results illustrate that the proportion of TRE remaining after elastic registration can be accurately predicted from the spatial distribution of data provided to the registration.

APPENDIX A: BIVARIATE GAMMA DISTRIBUTION

A six-parameter bivariate gamma distribution used in this work is extended from the five-parameter mixed effects model by G. C. Ghirtis [26] by adding one location parameter S_0 to allow translation. Suppose q, r, and s are gamma-distributed random variables. Then the uncertainty S and the error capacity E are defined to be a weighted sum of the underlying random variables so that

$$S = \xi(q+r) + S_0 \tag{A1}$$

$$E = \eta(q+s) \tag{A2}$$

where ξ and η are scale parameters of the distribution. Then the joint distribution provided shape parameters *a*, *b*, and *c* is

$$P(S, E \mid \theta) = \frac{e^{-\left(\frac{S-S_0}{\xi} + \frac{E}{\eta}\right)}}{\lambda^b \mu^c \Gamma(a) \Gamma(b) \Gamma(c)} I_q$$
(A3)

where $\theta = \{S_0, \xi, \eta, a, b, c\}, \Gamma(\cdot)$ is the gamma function, and

$$I_q = \int_0^m q^{a-1} (S - S_0 - \xi q)^{b-1} (E - \eta q)^{c-1} e^q dq \qquad (A4)$$

for $m = \min\left(\frac{S-S_0}{\xi}, \frac{E}{\eta}\right)$.

From a set of paired observations (S, E), parameter estimates \hat{S}_0 , $\hat{\xi}$, $\hat{\eta}$, \hat{a} , \hat{b} , and \hat{c} can be obtained by the method of moments with

$$\begin{cases} \hat{S}_0 = \min(S) \\ \hat{\xi} = \operatorname{var}(S - \hat{S}_0)/\operatorname{mean}(S - \hat{S}_0) \\ \hat{\eta} = \operatorname{var}(E)/\operatorname{mean}(E) \\ \hat{a} = \frac{\operatorname{mean}(S - \hat{S}_0)\operatorname{mean}(E)\operatorname{cov}(S - \hat{S}_0, E)}{\operatorname{var}(S - \hat{S}_0)\operatorname{var}(E)} \\ \hat{b} = \operatorname{mean}(S - \hat{S}_0)^2/\operatorname{var}(S - \hat{S}_0) - \hat{a} \\ \hat{c} = \operatorname{mean}(E)^2/\operatorname{var}(E) - \hat{a} \end{cases}$$
(A7)

as derived in [26]. These initial parameters are further optimized using the Nelder-Mead downhill simplex method by minimizing the squared Hellinger distance defined as,

$$h^{2}(P,Q) = 1 - \sum_{(S,E)} \sqrt{P(S,E)Q(S,E)}$$
(A8)



Fig. 7. (a) Quantile-quantile plot between joint cumulative distributions of $P(S_r, E \mid \hat{\theta}_r)$ and $Q(S_r, E)$ from post-registration metric. (b) Quantile-quantile plot between joint cumulative distributions of $P(S_p, E \mid \hat{\theta}_p)$ and $Q(S_p, E)$ from pre-registration metric.

where P(S, E) is given by (A3) and Q(S, E) is an empirical probability distribution constructed from the set of paired observations.

The optimized parameter estimates $\hat{\theta} = \{\hat{S}_0, \hat{\xi}, \hat{\eta}, \hat{a}, \hat{b}, \hat{c}\}$ for S_r and S_p from all samples in dataset A are:

$$\theta_r = \{2.5268, 0.5024, 20.2834, 1.3712, 2.8348, 0.9045\}$$

 $\hat{\theta}_n = \{9.0537, 2.3825, 20.2154, 1.2164, 2.0696, 1.0654\}.$

The quality of the distribution regressions are illustrated in Fig. 7, which shows close agreement in quantile-quantile plots between the cumulative distributions of P(S, E) and Q(S, E) for S_r and S_p .

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