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Survey paper

From model based to learned regularization in medical image registration: A comprehensive review

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ABSTRACT

Image registration is fundamental in medical imaging applications, such as disease progression analysis or radiation therapy planning. The primary objective of image registration is to precisely capture the deformation between two or more images, typically achieved by minimizing an optimization problem. Due to its inherent ill-posedness, regularization is a key component in driving the solution toward anatomically meaningful deformations. A wide range of regularization methods has been proposed for both conventional and deep learning-based registration. However, the appropriate application of regularization techniques often depends on the specific registration problem, and no "one-fits-all" method exists. Despite its importance, regularization is often overlooked or addressed with default approaches, assuming existing methods are sufficient. A comprehensive and structured review remains missing. This review addresses this gap by introducing a novel taxonomy that systematically categorizes the diverse range of proposed regularization methods. It highlights the emerging field of *learned regularization*, which leverages data-driven techniques to automatically derive deformation properties from the data. Moreover, this review examines the transfer of regularization methods from conventional to learning-based registration, identifies open challenges, and outlines future research directions. By emphasizing the critical role of regularization in image registration, we hope to inspire the research community to reconsider regularization strategies in modern registration algorithms and to explore this rapidly evolving field further.

1. Introduction

Image registration is crucial in many clinical applications, e.g., in radiation therapy or disease monitoring (Rueckert and Schnabel, 2010; Sotiras et al., 2013). Its primary objective is to accurately identify the deformation between two or more images, typically by minimizing an optimization problem. In recent years, learning-based registration methods have become state-of-the-art. Unlike conventional methods that iteratively solve an optimization problem for each image pair, learning-based approaches use neural networks to parameterize the transformation model and to learn the registration with training data. Once trained, these models can register unseen image pairs in real time.

A key challenge in image registration lies in its ill-posed nature: Mathematically, multiple solutions exist, but only few are anatomically or physiologically feasible. Achieving such plausible solutions is crucial for accurate intra-patient registration in clinical settings, where the deformation should reflect the true motion of the physical structure. For instance, when deformation causes image regions to overlap, this is called folding (see Fig. 3), which is physically impossible for soft tissue and thus should not be present in its deformation.

The key to achieving a unique and realistic solution to a registration problem is the regularization of the optimization problem. Regularization constrains the solution space and incorporates deformation characteristics into the process. It is an essential element in almost every registration algorithm, forming a *fundamental building block* of a successful registration algorithm – alongside the (dis-)similarity measure, transformation model, optimization procedure, and validation protocol as outlined in (Rueckert and Schnabel, 2010).

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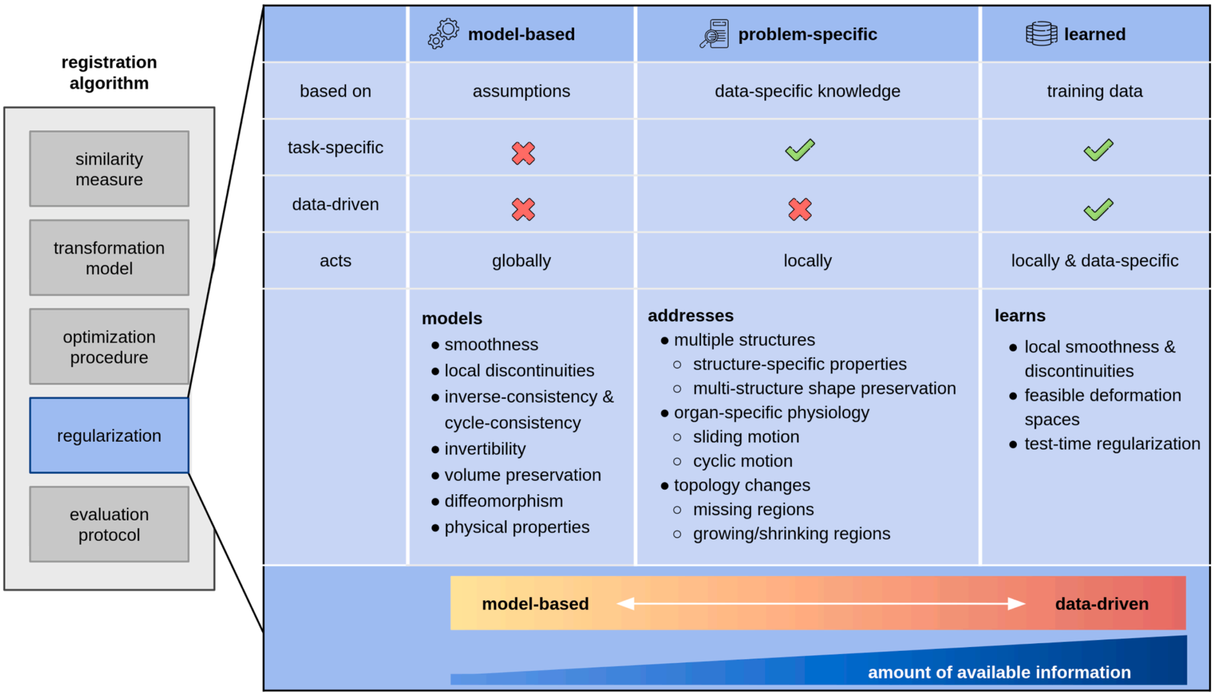

Fig. 1. Regularization is an essential building block of successful registration algorithms. We identify three main categories of regularization methods: (I) Model based regularization that imposes prior assumptions on the deformation; (II) problem specific regularization that takes into account additional knowledge about the data, such as spatial information in the form of segmentation maps or physiological information; and (III) Learned regularization, which derives deformation properties from training data with a machine or deep learning model. The amount of prior information included in the regularization increases from category I to III. Most problem specific and learned regularization methods have their origin in model based regularization.

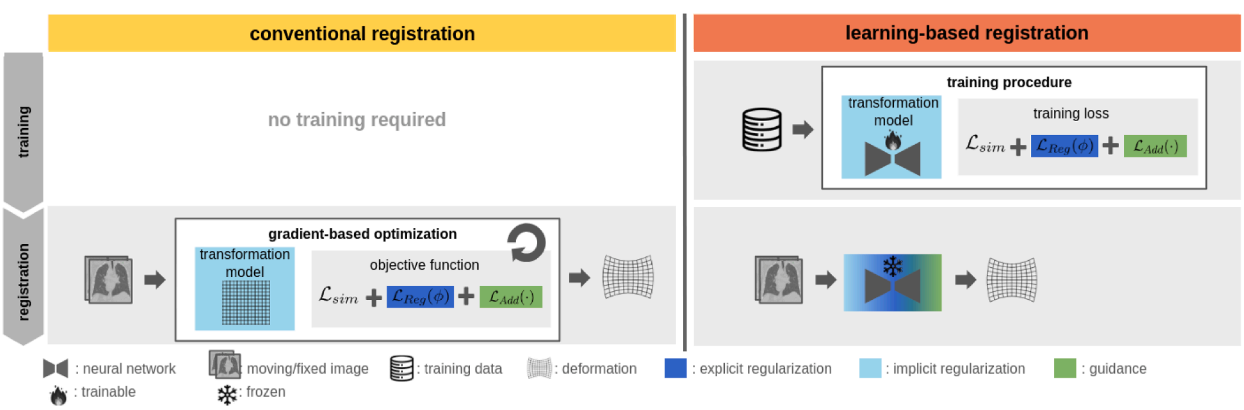

Fig. 2. Explicit vs. implicit regularization: Overview of approaches to integrating regularization in conventional (left) and learning-based (right) medical image registration. In both, regularization can be achieved explicitly with a regularizing loss term (dark blue) or implicitly with the parameterization of the transformation model (light blue). Additionally, guiding loss terms (green) can drive the registration toward a desired solution. For learning-based registration, the regularization applied during training is inherently captured in the network parameters at inference time.

A wide variety of regularization methods has been proposed with different aims. These range from enforcing general properties such as spatial smoothness and invertibility to addressing more complex ones, including modeling organ specific motion or handling missing regions. While most of these methods originate in conventional registration, several have already been successfully adapted to learning-based registration (Hering et al., 2023). However, despite the widely acknowledged importance of regularization, its role is often neglected in practice, and many state-of-the-art registration frameworks rely on standard techniques, such as $\mathcal{L}_2$-norm smoothing, which may not fully address real-world deformations. Furthermore, regularization approaches often seem handcrafted, and a 'one-fits-all' method does not exist.

The lack of a comprehensive taxonomy that organizes the diverse landscape of regularization techniques hinders the potential method transfer across different image registration applications and limits progress in the field. Several general review papers exist on conventional and deep learning-based medical image registration methods (Viergever et al., 2016; Haskins et al., 2020; Fu et al., 2020; Chen et al., 2024) as well as targeted reviews on specific registration building blocks like deformation models (Wang and Li, 2019) or registration error estimation (Bierbrier et al., 2022), and application-specific areas

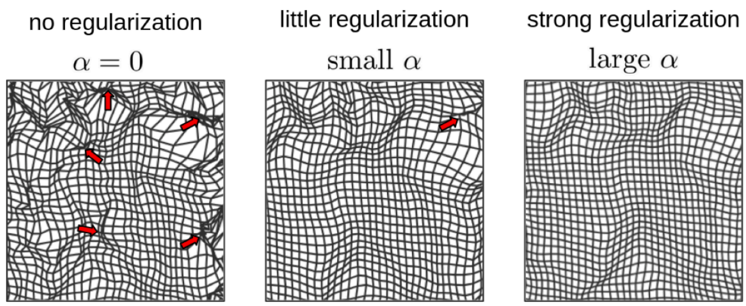

Fig. 3. Model based regularization – Smoothness and folding: Different levels of smoothness regularization, controlled with the regularization parameter α (see Eq. 1). The pink arrows indicate regions of folding. With increasing α, more smoothing is applied and less folding is observed.

(Ferrante and Paragios, 2017; Matl et al., 2017). While some of these reviews briefly cover prominent regularization methods, no structured review exists that fully explores the many proposed regularization techniques in both conventional and learning-based medical image registration algorithms.

In this review, we address this gap by providing the first comprehensive overview of regularization techniques in conventional and deep learning-based image registration. We identify three main categories (see also Fig. 1): Regularization, which is (I) model based and takes prior assumptions into account (Section 3.1), (II) problem specific and incorporates additional knowledge (Section 3.2), and (III) learned from a training dataset using machine or deep learning models (Section 3.3).

The goals of this review are three-fold. First, we intend to give researchers a structured overview of existing regularization techniques. Second, we aim to facilitate the transfer of regularization methods across different registration techniques and applications. To this end, we examine to what extent regularization techniques have been transferred to learning-based registration and highlight the emerging field of learned regularization. Moreover, we discuss open challenges and promising future directions. Finally, we hope to inspire the research community to further explore regularization in deep learning-based image registration, encouraging innovation in this rapidly evolving field.

The review includes articles published up to October 2024 that contribute novel methodologies for regularization in pairwise medical image registration. We searched for papers in Scopus, PubMed and GoogleScholar using combinations of the keywords "medical image registration", "regulariz(s)ation", "regulariz(s)er", and the terms presented in Fig. 1. As our focus lies on the regularization aspect, the proposed taxonomy targets the *regularization* only, independent from the *registration* (where possible). We do not intend to give an overview of deep learning-based registration methods (refer to the reviews mentioned above). However, for a better overview, we mention whether the regularization techniques were initially proposed for conventional or learning-based registration. A collection of valuable code resources connected to the presented regularization methods can be found at https://github.com/annareithmeir/regularization-in-medical-image-registration. The remainder of this review is structured as follows:

- **Section 2**: Brief background on medical image registration and regularization. The mathematical notation used in this review is presented here;
- **Section 3**: Presentation and discussion of the three main categories of regularization methods found in the literature; The method transfer from conventional to learning-based registration is also examined;
- **Section 4**: Discussion of open challenges and future directions in the field;
- **Section 5**: Concluding remarks.

2. Background

In this section, we cover the relevant mathematical background, notation, and definitions for image registration, as well as its regularization. **Image registration:** Given two images $M, F : \Omega \subset \mathbb{R}^N \to \mathbb{R}$ with $N \in \{2, 3\}$, deformable image registration aims to find an optimal spatial deformation $\phi : \mathbb{R}^N \to \mathbb{R}^N$, so that $F \approx M \circ \phi$. Generally, this deformation is obtained by minimizing the following optimization problem:

$$\mathcal{L}(F, M, \phi) = \mathcal{L}_{Sim}(F, M \circ \phi) + \alpha \mathcal{L}_{Reg}(\phi). \tag{1}$$

Here, $\mathcal{L}_{Sim}$ is a dissimilarity measure that quantifies how well the deformed moving image $M \circ \phi$ matches the fixed image F. Common choices for $\mathcal{L}_{Sim}$ include the sum of squared distances (SSD) and the negative normalized cross-correlation (NCC) (Haskins et al., 2020). The regularization term $\mathcal{L}_{Reg}$ constrains the solution space. This is necessary since the optimization problem is inherently ill-posed, i.e., multiple solutions can exist. With this term, the registration can be driven towards a solution with desired properties.

Both terms are balanced by the regularization weight $\alpha \in \mathbb{R}^+$, which is a hyperparameter that is typically tuned manually. For high values of α, the deformation properties are given more importance than the image alignment. In contrast, for low values, the intensity alignment is given more weight, and the deformation is more flexible (see Fig. 3 for an example). For more details on medical image registration in general, see, e.g., (Rueckert and Schnabel, 2010).

The displacement field Jacobian and its determinant: In deformable image registration, the spatial deformation ϕ is typically parameterized as a discretized displacement field $\mathbf{u} \in \mathbb{R}^{H \times W (\times D) \times N}$ where a displacement vector is assigned to each voxel position x. The Jacobian matrix $\mathbf{J}$ of $\mathbf{u}$ is defined as

$$\mathbf{J} = \begin{bmatrix} \frac{\partial u_x}{\partial x} & \frac{\partial u_x}{\partial y} & \frac{\partial u_x}{\partial z} \\ \frac{\partial u_y}{\partial x} & \frac{\partial u_y}{\partial y} & \frac{\partial u_y}{\partial z} \\ \frac{\partial u_z}{\partial x} & \frac{\partial u_z}{\partial y} & \frac{\partial u_z}{\partial z} \end{bmatrix} \in \mathbb{R}^{H \times W (\times D) \times N \times N} \tag{2}$$

and contains the first-order partial derivatives of $\mathbf{u}$. An important concept is the Jacobian determinant $det\mathbf{J} \in \mathbb{R}^{H \times W (\times D)}$. It indicates local volume and orientation change within a small neighborhood of x:

$$\text{local} \begin{cases} \text{tearing} & \text{if } det\mathbf{J}(x) \to \infty, \\ \text{volume increase} & \text{if } det\mathbf{J}(x) > 1, \\ \text{volume preservation} & \text{if } det\mathbf{J}(x) = 1, \\ \text{volume decrease} & \text{if } det\mathbf{J}(x) < 1, \\ \text{singularity/folding} & \text{if } det\mathbf{J}(x) < 0. \end{cases} \tag{3}$$

Folding means that after the deformation is applied, multiple image regions overlap, as visualized in Fig. 3. In this case, the deformation locally lacks invertibility and orientation preservation. The Jacobian determinant plays an important role not only in the analysis of deformation fields, e.g., to assess their smoothness, but also for the regularization of registration techniques.

Explicit vs. implicit regularization and guidance: We differentiate two kinds of regularization:

- *Explicit regularization*, which operates on the deformation and comes in the form of a loss term, and
- *Implicit regularization*, which arises from the parameterization of the deformation model.

In conventional registration, explicit regularization is achieved by a regularizing loss term $\mathcal{L}_{Reg}(\phi)$ in the objective function Eq. 1 (Fig. 2, left). In contrast, implicit regularization is achieved, for instance, with the B-Spline-based transformation parameterization in free-form deformations (FFD) (Rueckert, 1999) and coarse-to-fine multiresolution approaches, as in (Mok and Chung, 2020). They naturally enforce smoothness without requiring explicit constraints. In learning-based registration, explicit and implicit regularization is applied during network training (Fig. 2, top right). At inference time, the regularization is inherently incorporated in the trained network weights. (Fig. 2, bottom right). In the context of learning-based registration, this review focuses on regularization strategies that constrain the deformation space during training.

Beyond explicit regularization loss terms, additional *guiding loss terms* $\mathcal{L}_{Add}(\cdot)$, such as segmentation overlap measures (Balakrishnan et al., 2019), can indirectly encourage plausible solutions and drive the registration toward a desired result. Since such guiding terms do not operate on the deformation field, they are, strictly speaking, not a type of regularization. However, we believe that guidance approaches can be equally important in obtaining plausible registration solutions as "real" regularization, and thus include some widely adopted methods in this review.

3. Regularization techniques in medical image registration

Within the medical image registration literature, three main categories regarding regularization methods can be identified:

- Category I: *Model based regularization with prior assumptions* (Section 3.1). This type of regularization models user-defined assumptions about the deformation properties, such as smoothness, inverse-consistency, invertibility, diffeomorphisms, volume preservation, or based on physical principles. It is applied globally, i.e., the same regularization is applied similarly at every location of the image.
- Category II: *problem specific regularization with prior data knowledge* (Section 3.2). This type of regularization enriches the registration process with a priori available knowledge about the data. On the one hand, this can be spatial information about the image content, which allows for modeling structure specific deformation properties and preserving intra-organ topology. On the other hand, this can be information about the clinical context of the data or the physiology of the organ in focus. For example, the knowledge that the data consists of pre- and post-operative images indicates the presence of missing regions, and the knowledge that the images are inhale-exhale lung image pairs suggests to model sliding motion of the lung. Problem specific regularization is spatially adaptive, meaning that it depends on the image location and can adapt to local properties.
- Category III: *Learned regularization* (Section 3.3). This type of regularization is data-driven and learns the deformation properties directly from a training dataset. It is often spatially adaptive and is learned either independently before being applied in the registration or jointly alongside the registration. Learned regularization is typically parameterized as a deep learning model.

As becomes clear, the amount of prior information included in the regularization increases from category I to III. An overview of the proposed taxonomy is shown in Fig. 1, and the three categories are presented in the following.

3.1. Model based regularization with prior assumptions

In this section, we present and discuss model based regularization techniques, organized by the deformation properties they enforce. Model based regularization imposes a user-defined model on the deformation properties and is governed by prior assumptions, such as deformation invertibility or physical principles. These regularization methods are uniformly applied across the image domain. Tab. 1 summarizes the most prominent model based techniques.

3.1.1. Smoothness

A spatially smooth deformation changes gradually across the image, where neighboring image locations deform similarly and no abrupt changes or folding are present (see Fig. 3). This property is particularly desirable, as most biological tissues deform smoothly. Among the various methods for enforcing smoothness, explicit diffusion regularization is perhaps the most widely used method in image registration. It promotes smoothness by penalizing the L_2-norm of the spatial deformation gradient. Originating from the optical flow estimation of Horn and Schunck (1981), it is found in many state-of-the-art registration frameworks, including, e.g., VoxelMorph (Balakrishnan et al., 2019). Alternatively, smoothness regularization can be achieved using a Gaussian kernel, as demonstrated in the well-known Demons algorithm (Thirion, 1998). While diffusion regularization considers first-order derivatives, curvature regularization (Fischer and Modersitzki, 2004) leverages second-order derivatives to approximate the curvature of the displacement components. Recently, Song et al. (2023) proposed using average pooling layers within registration networks to enforce smoothness, encouraging voxel displacements to align with the mean displacement in their neighborhood.

Smoothness can also be imposed implicitly through the transformation model. For instance, free-form deformation (FFD) registration (Rueckert, 1999) parameterizes the deformation with cubic B-splines, which are inherently smooth. Extensively applied in conventional registration, FFD registration has also been successfully adapted to learning-based frameworks, such as in Qiu et al. (2021). Moreover, multiresolution registration strategies, which derive high resolution deformations from coarser levels, impose smoothness implicitly and are widely regarded as state-of-the-art, particularly in learning-based registration. Training strategies range from separately training each resolution level (de Vos et al., 2019; Hering et al., 2019; Mok and Chung, 2020; Gu et al., 2021) to end-to-end training across all levels (Fu et al., 2018; Wodzinski et al., 2021; Yang et al., 2022; Ma et al., 2023). Beyond image resolution, multiresolution schemes have been extended to feature resolution Wang et al. (2023b). For spatio-temporal 4D (3D + t) data, smoothness can be extended to the temporal dimension. Examples include spatio-temporal Gaussian filters (Shen et al., 2005), B-spline transformation models (Perperidis et al., 2005), and multiresolution schemes (Aggrawal et al., 2020).

3.1.2. Invertibility

Most biological tissue deformations observed in the human body are inherently reversible. According to the inverse function theorem, a deformation is locally invertible if the Jacobian determinant $det\mathbf{J}$ is positive, indicating the absence of folding. One of the first methods to ensure local invertibility involves monitoring $det\mathbf{J}$ throughout the registration process and re-gridding the image whenever it approaches zero, followed by restarting the optimization (Christensen et al., 1996). Explicit invertibility regularization includes applying penalties to areas that locally collapse to zero volume (Edwards et al., 1998), to very small values of $det\mathbf{J}$ (Christensen and Johnson, 2001), or constraining $det\mathbf{J}$ to remain within a pre-defined positive range (Haber and Modersitzki, 2007).

Invertibility of FFD B-spline deformations can be achieved by constraining $det\mathbf{J}$ at the control points to be above a positive threshold while penalizing large displacement derivatives between control point locations (Sdika, 2008). Alternatively, the difference between neighboring

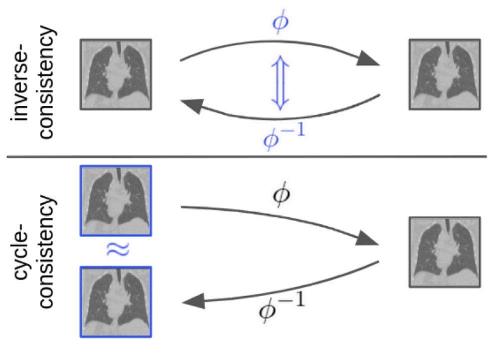

Fig. 4. Model based regularization – Inverse- vs. cycle-consistency: Inverse-consistency ensures that the forward and backward deformations are inverses of each other. Cycle-consistency ensures that a forward-backward deformed image resembles the original image.

spline coefficients can be constrained, as proposed in Chun and Fessler (2008). Recently, Huang et al. (2024) introduced a topology-preserving regularization using Beltrami coefficients, which quantify local distortions.

Explicit invertibility regularization has also been effectively incorporated into learning-based registration. For instance, folding can be mitigated by applying a rectified linear unit (ReLU) activation function to $-det\mathbf{J}$ (Mok and Chung, 2021b; Zhu and Lu, 2022) or by penalizing the sum of negative $-det\mathbf{J}$ values within the training loss function (Estienne et al., 2021). Pal et al. (2022) eliminate folding by reconstructing the predicted deformation from the matrix exponential of its Jacobian. This reconstruction inherently ensures positive $det\mathbf{J}$, and the reconstruction loss is seamlessly integrated as an explicit regularization term in the training loss function.

3.1.3. *Inverse-consistency and cycle-consistency*

The existence of an inverse deformation does not necessarily guarantee its plausibility. To ensure meaningful results, the forward deformation $\phi_{M\to F}$ (from M to F) should be the exact inverse of the backward deformation $\phi_{F\to M}$ (from F to M), making the registration independent of the order in which the two images are processed (see Fig. 4). This property, called inverse-consistency (IC), can be explicitly enforced by penalizing deviations between the identity and the composed forward-backward deformation. Originally proposed for conventional registration in Christensen and Johnson (2001), Leow et al. (2005), it has since been adapted to learning-based registration (Zhang, 2018; Shen et al., 2019a; Estienne et al., 2021; Greer et al., 2021). Moreover, IC regularization can be found in symmetric registration, which simultaneously optimizes both registration directions, e.g., in the registration network of Sha et al. (2024). While some symmetric methods calculate the IC loss with the inverses of the estimated deformations (Zhang, 2018; Shen et al., 2019a), Leow et al. (2005) model the backward deformation by inverting the forward deformation to reduce computational effort.

Recent advancements extend inverse-consistency regularization to learning-based registration. Zhang et al. (2023) introduce a robust IC loss that averages the predicted forward and inverted backward deformations, while Duan et al. (2023a) relax the IC constraint proportionally to the deformation magnitude. The GradICON regularization (Tian et al., 2023) departs from previous methods by explicitly penalizing deviations of the *gradient* of the forward-backward composition from the identity deformation. This maintains good IC properties while showing much better training convergence. Multiresolution registration networks with built-in IC and symmetry properties have been recently proposed (Greer et al., 2023; Honkamaa and Marttinen, 2024).

While IC considers the deformation space, the same effect can be achieved by posing constraints in image space instead, a concept called cycle-consistency (CC). Here, an image should remain unchanged after the combined forward-backward deformation is applied (Fig. 4). This is typically achieved with a guidance loss that penalizes deviations between the original and the forward-backward deformed image. CC guidance is commonly incorporated in the training loss of a registration network, e.g., in Lu et al. (2019), Kim et al. (2021), Nazib et al. (2021), Huang et al. (2021), Zhou et al. (2023), and incorporated in advanced network architectures such as cycle-GANs (Mahapatra et al., 2018; Zheng et al., 2022), symmetric attention layers (Gao et al., 2022), and cycle-consistent implicit neural representations (van Harten et al., 2024).

3.1.4. *Diffeomorphisms*

A diffeomorphic deformation is not only smooth but also constitutes a one-to-one mapping with a smooth inverse. As a homeomorphic transformation, it preserves the underlying topology, which is essential given that anatomical structures generally maintain their topology during deformation. As it equally ensures smoothness, invertibility, and topology preservation, diffeomorphism regularization can be useful.

A common approach for achieving diffeomorphisms is implicit regularization via the transformation model. The space of diffeomorphisms forms a Riemannian manifold, and the registration problem can be viewed as the search for the shortest geodesic (which can be considered as identifying the least distorted diffeomorphic deformation). This geometric optimization is typically formulated as ordinary differential equations (ODEs) based on smooth stationary velocity fields (SVF) (Arsigny et al., 2006) or time-dependent velocity fields, as in the large deformation diffeomorphic metric mapping (LDDMM) (Beg et al., 2005; Ashburner and Friston, 2011). To ensure the necessary SVF smoothness, the diffusion regularizer or constraints on $det\mathbf{J}$ can be additionally applied (Dupuis et al., 1998; Beg et al., 2005). The optimized SVF is then integrated over time to obtain the displacement field, e.g., with the scaling-and-squaring method (Arsigny et al., 2006).

The optimization on the manifold of diffeomorphisms is computationally demanding. Thus, the log-Euclidean framework (Arsigny et al., 2006) performs the optimization in the Euclidean tangent space of the manifold. Several well-established conventional registration methods leverage diffeomorphisms, such as symmetric normalization (SyN) (Avants et al., 2008), which optimizes both images towards the mean image, and diffeomorphic Demons (Vercauteren et al., 2009). A geodesic shooting approach was proposed in Ashburner and Friston (2011), which optimizes only the initial momentum SVF and an IC regularization within diffeomorphic registration is found in Beg and Khan (2007).

Diffeomorphic registration has been well transferred to learning-based registration. For instance, the registration networks in Krebs et al. (2018), Dalca et al. (2019), Mok and Chung (2020) predict SVFs and integrate them with a differentiable scaling-and-squaring integration layer. Learning-based adaptations have furthermore been developed for, e.g., the mean-image approach of SyN (Mok and Chung, 2021b; Ma et al., 2023) and geodesic shooting (Shen et al., 2019a; Ramon-Julvez et al., 2024). Recent advancements include imposing inverse-consistency within diffeomorphic registration with a vision transformer architecture (Xu et al., 2023), employing Lipschitz-continuous ResNet blocks to numerically approximate the flow field ODE (Joshi and Hong, 2022), and leveraging time-embedded networks (Matinkia and Ray, 2024).

3.1.5. *Volume preservation and incompressibility*

Many biological tissues are (nearly) incompressible, meaning they maintain their volume under pressure. This applies particularly to organs with high water or blood content, such as cardiac muscle (Bistoquet et al., 2008) and the liver (Hinkle et al., 2009). Volume changes of deformations are quantified by the Jacobian determinant $det\mathbf{J}$ where perfect volume preservation is achieved for $det\mathbf{J} = 1$. (see Eq. 3). A straightforward method to enforce volume preservation explicitly is to penalize deviations of $det\mathbf{J}$ from unity (Haber and Modersitzki, 2004). To equally penalize both expansion ($det\mathbf{J} > 1$) and compression ($det\mathbf{J} < 1$), Rohlfing et al. (2003) use the logarithm of $det\mathbf{J}$. Extensions to the above

Table 1
Model based regularization: Overview of model based regularization with prior assumptions about the deformation properties. The type of regularization (■ = explicit, ■ = implicit, ■ = guidance) and registration framework in which the respective approach has been *originally* proposed (■ = conventional, ■ = deep learning-based) are given. For simplicity, we omit $\int_\Omega \cdot \, dx$. Notation: exp = matrix exponential, $||\cdot||_F$ = Frobenius norm, $\partial_{ij}\mathbf{u} = \partial_{x_i}\mathbf{u}_j$, $\partial^2_{ij}\mathbf{u} = \partial^2_{x_i x_j}\mathbf{u}$, $\mathrm{len}(\mathbf{u}) = ||\nabla\mathbf{u} - I||_F^2$, cof = cofactor, $\mathrm{surf}(\mathbf{u}) = (||\mathrm{cof}\nabla u||_F^2 - 3)^2$, $\mathrm{vol}(\mathbf{u}) = ((det\mathbf{J} - 1)^2/det\mathbf{J})^2$, $\mathrm{div}(\mathbf{u})$ = divergence component, $\mathrm{curl}(\mathbf{u})$ = curl component.

deformation property	reference	type	approach	regularization term	registration framework
smoothness	(Horn and Schunck, 1981)	explicit	diffusion/L_2-norm	$\sum_i^N \|\|\nabla\mathbf{u}_i\|\|_2^2$	conventional
	(Thirion, 1998)	explicit	Gaussian kernel		conventional
	(Fischer and Modersitzki, 2004)	explicit	curvature	$\sum_i^N (\nabla\mathbf{u}_i^2)^2$	conventional
	(Song et al., 2023)	explicit	average pooling layer		deep learning-based
	e.g. in (Mok and Chung, 2020)	implicit	multiresolution registration		conventional
	(Rueckert, 1999)	implicit	B-spline FFD		conventional
invertibility	(Christensen and Johnson, 2001)	explicit	avoid negative $det\mathbf{J}$	$(1/det\mathbf{J})^2$	conventional
	(Christensen et al., 1996)	implicit	monitor $det\mathbf{J}$ & re-grid		conventional
	(Mok and Chung, 2021b)	explicit	penalize negative $det\mathbf{J}$	$\mathrm{ReLU}(-det\mathbf{J})$	deep learning-based
	(Estienne et al., 2021)	explicit	penalize negative $det\mathbf{J}$	$\max(0, -det\mathbf{J})$	deep learning-based
	(Pal et al., 2022)	explicit	matrix exp. reconstruction	$\sum_i^N \|\|\exp(\mathbf{J}) - \mathbf{J}_i\|\|_2^2$	deep learning-based
inverse consistency	(Christensen and Johnson, 2001)	explicit	forward-backward loss	$\|\|\mathbf{u}_{M\to F}\circ\mathbf{u}_{F\to M} - \mathbf{I}\|\|^2$	conventional
	(Tian et al., 2023)	explicit	GradICON	$\|\|\nabla(\mathbf{u}_{M\to F}\circ\mathbf{u}_{F\to M}) - \mathbf{I}\|\|_F^2$	deep learning-based
	e.g. in (Lu et al., 2019)	guidance	cycle-consistency loss	$\|\|M - M\circ\mathbf{u}_{M\to F}\circ\mathbf{u}_{F\to M}\|\|$	deep learning-based
diffeomorphism	(Arsigny et al., 2006)	implicit	stationary velocity field (SVF)		conventional
	(Beg et al., 2005)	implicit	time-dependent velocity field		conventional
	(Ashburner and Friston, 2011)	implicit	momentum-based SVF		conventional
volume preservation	(Rohlfing et al., 2003)	explicit	penalize $det\mathbf{J} \neq 1$	$\|\|\log(det\mathbf{J})\|\|$	conventional
	(Haber and Modersitzki, 2004)	explicit	penalize $det\mathbf{J} \neq 1$	$det\mathbf{J} - 1$	conventional
	(Saddi et al., 2007)	implicit	divergence-free deformations		conventional
	(Bistoquet et al., 2008)	implicit	divergence-free basis functions		conventional
	(Fidon et al., 2019)	implicit	divergence-conforming B-splines		conventional
local discontinuities	(Chumchob, 2013)	explicit	anisotropic TV/L_1-norm	$\sum_i^N \|\|\nabla\mathbf{u}_i\|\|_1$	conventional
	(Vishnevskiy et al., 2017)	explicit	isotropic TV	$\sqrt{\sum_{i,j}^N \nabla_i\mathbf{u}_j}$	conventional
	(Duan et al., 2023b)	explicit	higher-order TV	$\sqrt{\sum_{i,j}^N \|\nabla_i^n\mathbf{u}_j\|^2}$	conventional
	(Nie and Yang, 2019)	implicit	bounded deformations		conventional
physics inspired	(Rueckert, 1999)	explicit	bending energy	$\sum_i^N (\partial^2_{ii}\mathbf{u})^2 + \sum_{i,j}^N 2(\partial^2_{ij}\mathbf{u})^2$	conventional
	(Bookstein, 1989)	implicit	bending energy		conventional
	(Broit, 1981)	explicit	linear elasticity	$\frac{\mu}{4}\sum_{i,j}^N(\partial_{ij}\mathbf{u} + \partial_{ji}\mathbf{u})^2 + \frac{\lambda}{2}(\mathrm{div}\ \mathbf{u})^2$	conventional
	(Christensen, 1994)	explicit	viscous fluid	$\frac{\mu}{4}\sum_{i,j}^N(\partial_{ij}\mathbf{v} + \partial_{ji}\mathbf{v})^2 + \frac{\lambda}{2}(\mathrm{div}\ \mathbf{v})^2$	conventional
	(Burger et al., 2013)	explicit	hyper-elasticity	$\mathrm{len}(\mathbf{u}) + \mathrm{surf}(\mathbf{u}) + \mathrm{vol}(\mathbf{u})$	conventional
	(Arratia López et al., 2023)	explicit	hyperelastic PINN		deep learning-based
	(Yang et al., 2022)	explicit	compressed regularization		deep learning-based
	(Tzitzimpasis et al., 2024)	explicit	divergence-curl regularization	$\|\|\nabla\mathrm{div}(\mathbf{u})\|\|^2 + \|\|\|\nabla\mathrm{curl}(\mathbf{u})\|\|^2$	deep learning-based

constraints include a relaxed volume preserving regularization that allows volume shrinking and growth within a certain range (Li et al., 2024) and spatiotemporal volume preservation constraints (Zhao et al., 2016).

A different explicit approach to enforcing incompressibility is constraining deformations to be divergence-free. This implies volume preservation since the vector field divergence measures the extent to which each voxel behaves as a source. Divergence-free deformations can be achieved with the Helmholtz decomposition, which splits deformations into curl- and divergence-free components (Saddi et al., 2007; Mansi et al., 2011). Alternatively, transformation parameterizations using divergence-free radial basis functions (Bistoquet et al., 2008) or divergence-conforming B-splines (Fidon et al., 2019) can be employed for implicit regularization.

While incompressibility regularization is well studied in conventional registration, it is less frequently applied in learning-based registration. A notable exception is the physics-informed neural network (PINN, see Section 3.1.7) of Arratia LÃ³pez et al. (2023), which penalizes deviations of $det\mathbf{J}$ from unity in the training loss function.

3.1.6. Discontinuities

While many regularization techniques aim to enforce spatial smoothness, there are scenarios where allowing locally discontinuous deformations is more appropriate. Discontinuities are, for example, observed at organ boundaries (Nie and Yang, 2019). A popular method that models local discontinuities is total variation (TV) regularization, which originates from works on image noise removal (Rudin et al., 1992) and optical flow estimation of overlapping objects (Sun et al., 2010). TV regularization, based on the L_1-norm of the deformation gradient, smoothens regions with little variation while preserving edges and discontinuities. However, its non-differentiability at zero poses a challenge for gradient-based optimization. To address this, smooth approximations (Sun et al., 2010) or duality-based optimization schemes (Pock et al., 2007) have been proposed.

In its standard formulation, TV regularization treats each gradient direction independently, which is why it is also referred to as *anisotropic* TV regularization (Chumchob, 2013; Vishnevskiy et al., 2017). In contrast, *isotropic* TV regularization (Zhang et al., 2016; Vishnevskiy et al., 2014, 2017) couples the gradient directions, making it better suited for non-axis aligned motion. Higher-order TV regularization can be found in Duan et al. (2023b).

Unlike the explicit approaches above, Nie and Yang (2019) implicitly model local discontinuities by parameterizing the transformation with functions of bounded deformations (Nie and Yang, 2019). Overall, global discontinuity-preserving regularization has limited application in conventional and learning-based registration. However, it is foundational for many spatially adaptive extensions that accommodate sliding motion (see Section 3.2.2).

3.1.7. Physics and biomechanics inspired properties

Human organs conform to physical and biomechanical principles, inspiring various regularization approaches that constrain deformations to align with these properties. Physics inspired regularization typically models the moving image M as a physical object to which external forces are applied at every location. The resulting deformation depends on the material properties of the object. This is often modeled as a metal sheet, an elastic object, or a viscous fluid.

The original implicit bending energy (BE) regularization in the 2D thin-plate splines registration (Bookstein, 1989) models M as a thin metal sheet and minimizes the energy required for bending it based on keypoint correspondences. Its explicit 3D equivalent has been formulated in the FFD registration (Rueckert, 1999). Alternatively, M can be modeled as an elastic object (Broit, 1981) or viscous fluid (Christensen, 1994) with explicit regularization. The linear elastic regularization introduced by Broit (1981) assumes a linear relationship between the strain (relative deformation) and stress (internal force). Recently, Ringel et al. (2023) proposed regularized Kelvinlet functions as an implicit method to model linear elasticity. Kelvinlet functions are analytical solutions to the linear elastic partial differential equation (PDE), and for registration, their optimal superposition is identified. Hyperelastic regularization relaxes the linearity assumption and allows more flexibility (Rabbitt et al., 1995; Burger et al., 2013).

While suitable for small deformations, elasticity regularization accumulates energy with increasing external forces. In comparison, viscous fluid regularization (Christensen, 1994) does not accumulate internal energy, making it suitable for large deformations. Both elastic and fluid regularization are based on the Navier-Stokes/Navier-Cauchy PDEs, with elastic regularization operating on displacement fields $\mathbf{u}$ and fluid regularization on velocity fields $\mathbf{v}$. The elasticity and viscosity properties are governed by two physical parameters $\lambda, \mu \in \mathbb{R}$ (see Tab. 1). Typically, isotropy and homogeneity of the material are assumed, meaning the material properties are independent of location and direction.

Several learning-based registration frameworks have incorporated physics inspired regularization. Examples include analytical hyperelasticity equilibrium gap regularization, which penalizes deviations from equilibrium during training (Alvarez and Cotin, 2024), and using physics-informed neural networks (PINNs), which learn data-driven solutions to PDEs. In the context of registration, PINNs have been employed to model linear elasticity (Min et al., 2023) and hyper-/nonlinear elasticity (Arratia LÃ³pez et al., 2023; Min et al., 2024). They are optimized for each image pair individually. Apart from that, Yang et al. (2022) introduced a compressed regularization approach based on fluid mechanics. This method suppresses folding in regions of high compression, by treating deformation grid intersections as fluid molecules. Recently, Tzitzimpasis et al. (2024) have proposed a divergence-curl regularization that enforces smoothness in the divergence and curl components of the deformation individually, adhering to the physical principles of fluid flow.

3.1.8. Discussion

Model based regularization forms the foundation of many image registration techniques. The primary goal of most methods – including smoothness, invertibility, inverse-consistency, cycle-consistency, and diffeomorphic regularization – is to ensure global smoothness, prevent folding, and preserve the overall topology. Yet, their successful application requires careful consideration.

Smoothness regularization can improve the robustness and speed of the registration, for instance, in multiresolution registration. Yet, excessive regularization may lead to over-smoothing, compromising alignment precision. To balance the trade-off between smoothness and registration accuracy, precise tuning of the regularization weight α (see Eq. 1, Fig. 3) is essential. Invertibility constraints have been shown to effectively mitigate folding artifacts without affecting registration metrics like the Dice score (Estienne et al., 2021; Pal et al., 2022). While inverse-consistency is computationally demanding due to the inversion operation in every optimization iteration, cycle-consistency provides a more efficient alternative in terms of time and memory (Zhou et al., 2023).

Despite the theoretical guarantees of diffeomorphic regularization, minor folding may still occur in practice due to numerical errors (Avants et al., 2008; Ashburner and Friston, 2011; Dalca et al., 2019; Mok and Chung, 2021b). While the differentiable scaling-and-squaring layer of (Dalca et al., 2019) facilitates the incorporation of diffeomorphic registration into learning-based registration approaches, the computational cost of velocity field integration remains challenging. As a result, downsampling of the velocity field is often used, for instance, in (Dalca et al., 2019), which can reduce the accuracy of high-resolution registration. Recent approaches, such as ResNet-based methods (Joshi and Hong, 2023b) or time-embedded networks (Matinkia and Ray, 2024), avoid scaling-and-squaring altogether and offer full-resolution integration without substantial computational overhead.

TV regularization, while effective for local discontinuities, faces the challenge of non-differentiability at zero, complicating its integration in gradient-based optimization and neural network training. Physics inspired regularization methods offer a theoretically grounded approach; however, these methods assume isotropic and homogeneous tissue properties, which may not hold for complex biological structures. Furthermore, the selection of values for the physical parameters λ, μ (Tab. 1) is arbitrary and frequently lacks justification, limiting both interpretability and generalizability (Christensen et al., 1996; Min et al., 2023). Overall, some general properties like smoothness, invertibility, and inverse-consistency are widely applicable across different anatomic structures. However, more specialized constraints, such as incompressibility or physics inspired regularization, are best suited for targeted applications where some high level information about the data is given. For example, global incompressibility can benefit the registration of contrast-enhanced images to prevent lesions of interest from shrinking during the registration process (Tanner et al., 2000; Rohlfing et al., 2003).

Many model based regularization methods have been effectively adapted to learning-based registration. The most prominent approaches include explicit regularization in the training loss function, as well as implicit smoothness regularization via multiresolution schemes and B-spline parameterization. However, methods for discontinuity preservation, incompressibility, and physical properties remain underexplored in learning-based settings despite their extensive development in conventional registration.

In conclusion, model based regularization methods provide a powerful framework for enforcing deformation properties based on prior assumptions. However, they require careful tuning and only have limited flexibility due to their global application. As we will see in the following sections, model based regularization serves as the basis for problem specific and learned regularization, and maintains its essential role in the ongoing advancements of medical image registration.

3.2. Problem specific regularization with prior knowledge

This section presents regularization tailored to particular registration problems, organized according to the corresponding registration tasks. While model based regularization (Section 3.1) imposes global deformation properties based on user *assumptions*, the methods in this section enrich the registration process with data-specific *knowledge*. Often, this includes spatial information, which makes the regularization spatially varying and adaptive to local characteristics. Additionally, knowledge about the clinical context and physiology of the anatomical structures can be used.

We divide problem specific methods into three categories of registration problems that require specific regularization: Registration of images with (i) multiple structures (Section 3.2.1), (ii) organs that exhibit special motion properties (Section 3.2.2), and (iii) changing topologies (Section 3.2.3). These are presented in the following and visualized in Fig. 5.

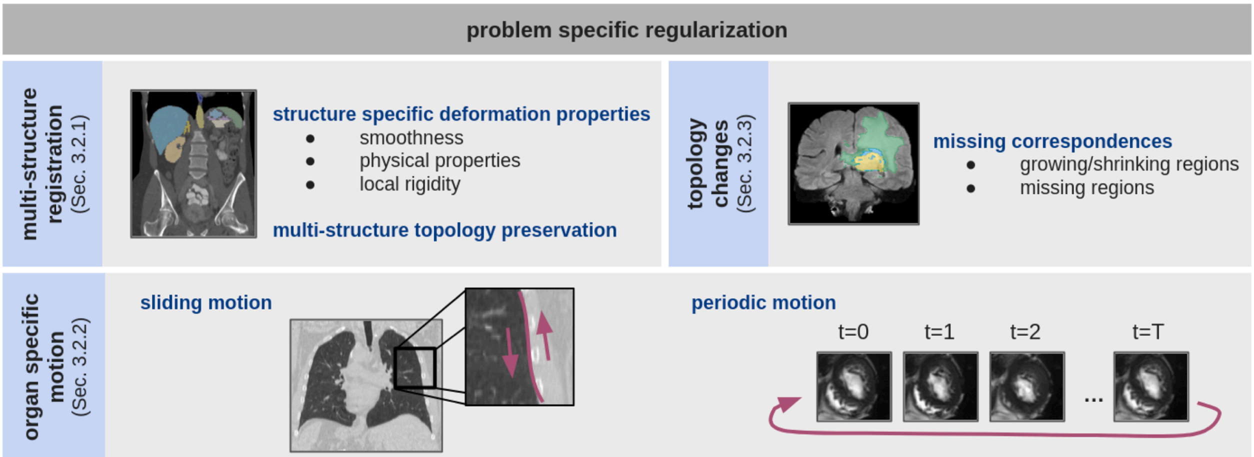

Fig. 5. Problem specific regularization: Depending on the registration problem and data, different deformation properties may arise. With data-specific information, such as segmentation maps, regularization can locally account for suitable deformation properties. Images are taken from the Learn2Reg abdominal CT (Xu et al., 2016), NLST (National Lung Screening Trial Research Team (2011)), BraTS (Baid et al., 2021), and ACDC (Bernard et al., 2018) datasets.

3.2.1. *Multi-structure registration*

Multi-structure registration aims to accurately align multiple anatomical structures within one image (see Fig. 5, top left). This is commonly encountered at the organ level, as in abdominal and chest registration, or at the sub-organ level, such as in brain registration. Two key challenges arise in these scenarios: The variability of deformation properties of individual structures and overall topology preservation of the structures, including their relative positions within the body and individual shapes. An overview of the methods discussed in this section is shown in Table 2.

Structure specific deformation properties: To address varying deformation properties across different structures, regularization can be employed that enforces structure specific smoothness, physical properties, or rigidity. *Spatially adaptive smoothness* is concerned with locally adapting the amount of smoothness. This can be achieved with a Gaussian smoothing kernel that adapts its size and shape to local image properties, such as the eigenvalues and -vectors of the image structure tensor (Forsberg et al., 2010) or the uncertainty of the local displacement magnitude (Wei et al., 2022). Freiman et al. (2011) derive local anisotropic smoothing from local affine transformations. Neighboring transformations with minimal differences are smoothed more since they are considered to belong to the same structure. Similarly, locally adaptive Gaussian filters have been proposed that only target areas with folding, indicated by negative values of $det\mathbf{J}$ (Wang et al., 2023d).

Apart from adapting the regularization, another possibility is to extend the scalar regularization weight α in Eq. 1 to a location dependent weight map $\mathbf{A}(x) \in \mathbb{R}^{H\times W(\times D)}$. Stefanescu et al. (2004) derive a map from local intensity variations and apply more smoothing to regions with small variations. Learning-based registration methods have adopted spatially adaptive regularization weights, e.g. in Ye et al. (2023), where a weight map is based on the predicted deformation during the training process. More smoothing is applied to image locations at which small displacements are predicted. Beyond smoothness, structure dependent incompressibility and anti-folding constraints have been proposed within the training loss of a registration network (Wei et al., 2022).

Moreover, it may be beneficial to model *structure specific physical properties*. Physical properties, such as elasticity, not only vary across structures but also between healthy and pathological tissues. For example, increased stiffness is observed for fibrotic lung and liver tissue (Talwalkar, 2008; Haak et al., 2018). A straightforward approach to model local physical properties involves using location dependent physical parameters $\lambda(x), \mu(x)$ within physics inspired regularization (see tab. 1). This has been proposed for linear elastic (Kabus et al., 2005; Risholm et al., 2010; Drakopoulos et al., 2014) and viscous fluid regularization (Lester et al., 1999). An alternative approach registers each structure individually using global model based linear elastic regularization. The obtained local deformations are then fused into a single global transformation (Brock et al., 2005).

For images containing rigid structures, *local rigidity regularization* is necessary to ensure rigid deformations of rigid structures while allowing nonlinear deformations of surrounding soft tissue. This is encountered, for instance, with the skull in head-neck (Little et al., 1997) or the ribs in lung registration (Baluwala et al., 2011). Also, local rigidity may be desired for the registration of tumors to allow a manual comparison by an expert (Tanner et al., 2000; Staring et al., 2007a,b). An implicit approach to address local rigidity is the spatially varying parameterization of the deformation model. For example, in Little et al. (1997) and Greene et al. (2009) the structures are individually registered with either rigid/affine or nonlinear deformations depending on their characteristics before being fused into a global deformation. To assist the fusion process, nonlinear deformations can be additionally constrained to vanish near the boundaries of rigid structures (Greene et al., 2009). Further extensions include fuzzy rigid regions that are parameterized by Gaussians centered around anchor points (Arsigny et al., 2005) and ensuring global invertibility of the fused deformation in log-Euclidean polyaffine approaches (Commowick et al., 2008; Arsigny et al., 2009). Locally rigid FFD registration is obtained with control point coupling within each rigid region in Tanner et al. (2000).

Explicit regularization methods include the use of spatially varying weight maps that locally switch between different types of transformations, (rigid, fluid, and soft tissue deformations) (Edwards et al., 1998), and the successive application of a smoothing filter that averages the displacements and converges to a constant displacement within each rigid region (Staring et al., 2007a). The latter approach has been combined with linear elasticity regularization in Baluwala et al. (2011).

To promote local rigidity, explicit variational loss terms can be further employed based on the Jacobian determinant $det\mathbf{J}$. A deformation is locally rigid if $det\mathbf{J}$ is orthogonal, i.e., $(det\mathbf{J})^T det\mathbf{J} = 1$. Consequently, local deviations of $det\mathbf{J}$ from orthogonality are be penalized in rigid regions in Loeckx et al. (2004), Ruan et al. (2006). Building upon this, the constraints proposed by Staring et al. (2007b), Modersitzki (2008) additionally enforce local affine-ness and orientation-preservation by penalizing deviations of the second-order derivatives $\partial^2\mathbf{u}$ from zero, as well as deviations of $det\mathbf{J}$ from unity. This combination of constraints shows better local rigidity preservation than their individual application. Haber et al. (2009) have proposed a further method that guarantees local rigidity by reformulating locally rigid registration as an unconstrained

Table 2
Problem specific regularization methods – Multistructure registration (■ = explicit, ■ = implicit, ■ = guidance, ■ = conventional, ■ = learning-based, abd. = abdominal, seg. = segmentation, reg. = registration).

registration problem		reference	type	approach	modality and anatomy	registration framework
multistructure registration	structure specific properties	(Forsberg et al., 2010)	explicit	size-adaptive Gaussian kernel	brain MR	conventional
		(Wei et al., 2022)	explicit	size-adaptive Gaussian kernel	brain MR	learning-based
		(Freiman et al., 2011)	explicit	anisotropic diffusion	abd. CT	conventional
		(Wang et al., 2023d)	explicit	Gaussian smoothing in folding regions	liver CT/brain MR	learning-based
		(Stefanescu et al., 2004)	explicit	varying smoothing weight	brain MR	conventional
		(Ye et al., 2023)	explicit	varying smoothing weight	cardiac MR/US	learning-based
		(Wei et al., 2022)	explicit	region-wise incompressibility	brain MR	learning-based
		(Kabus et al., 2005)	explicit	varying elasticity parameters	toy data	conventional
		(Risholm et al., 2010)	explicit	varying elasticity parameters	brain MR	conventional
		(Drakopoulos et al., 2014)	explicit	varying elasticity parameters	brain MR	conventional
		(Lester et al., 1999)	explicit	varying viscosity parameters	neck MR	conventional
		(Brock et al., 2005)	implicit	varying elasticity parameters	lung/abd. MR	conventional
		(Little et al., 1997)	implicit	region-wise then fuse	neck MR	conventional
		(Greene et al., 2009)	implicit	region-wise then fuse	prostate CT	conventional
		(Chen et al., 2021)	implicit	region-wise then fuse	cardiac MR	learning-based
		(Arsigny et al., 2005)	implicit	poly-rigid	hist. slices	conventional
		(Commowick et al., 2008)	implicit	poly-rigid/affine	brain MR/abd. CT	conventional
		(Edwards et al., 1998)	implicit	varying transformations	brain MR	conventional
		(Tanner et al., 2000)	implicit	locally rigid FFD	breast MR	conventional
		(Staring et al., 2007a)	explicit	successive smoothing in rigid regions	lung CT	conventional
		(Loeckx et al., 2004)	explicit	orthogonality constraint on $det\mathbf{J}$	full-body PET	conventional
		(Ruan et al., 2006)	explicit	orthogonality constraint on $det\mathbf{J}$	lung CT	conventional
		(Staring et al., 2007b)	explicit	affine and orthonormality constraints	lung CT	conventional
		(Modersitzki, 2008)	explicit	affine and orthonormality constraints	knee CT	conventional
		(Haber et al., 2009)	explicit	reformulation of local rigidity constraints	toy data	conventional
	multistructure topology preservation	(Hu et al., 2018c)	guidance	Dice in training loss	prostate MR/US	learning-based
		(Balakrishnan et al., 2019)	guidance	Dice in training loss	brain MR	learning-based
		(Mok and Chung, 2021c)	guidance	Dice in training loss	abd. CT/brain MR	learning-based
		(Lu et al., 2023)	guidance	Dice in training loss	cardiac MR	learning-based
		(Mahapatra et al., 2018)	guidance	joint reg. + seg., multitask CycleGAN	lung x-ray	learning-based
		(Khor et al., 2023)	guidance	joint reg. + seg., cross-task attention	brain/uterus MR	learning-based
		(Estienne et al., 2019)	guidance	joint reg. + seg., multi-decoder branches	brain MR	learning-based
		(Elmahdy et al., 2021)	guidance	joint reg. + seg., multi-decoder branches	prostate CT	learning-based
		(Xu and Niethammer, 2019)	guidance	joint reg. + seg., multi-network	brain/knee MR	learning-based
		(Chen et al., 2022)	guidance	joint reg. + seg., multi-network	cardiac MR	learning-based
		(Raveendran et al., 2024)	guidance	joint reg. + seg., multi-network	lung CT/abd. MR	learning-based
		(Großbröhmer, 2024)	guidance	learned segmentation encodings	abd. CT/MR	learning-based
		(Rühaak et al., 2017)	guidance	keypoint constraints	lung CT	conventional
		(Papenberg et al., 2009)	guidance	keypoint constraints	liver MR/CT	conventional
		(Kearney et al., 2014)	guidance	keypoint constraints	head/neck CT	conventional
		(Matkovic et al., 2024)	guidance	keypoint constraints	lung CT	learning-based
		(Heinrich et al., 2015)	guidance	keypoint graph	lung CT	conventional
		(Hansen and Heinrich, 2021)	guidance	keypoint graph	lung CT	learning-based
		(Heinrich and Hansen, 2022)	guidance	keypoint graph	abd./lung CT	learning-based
		(Wang et al., 2023a)	guidance	joint keypoint learning and matching	brain MR	learning-based
		(Wang et al., 2024)	guidance	joint keypoint learning and matching	brain MR	learning-based

problem. It parameterizes rigid deformations directly at pixel locations of rigid structures.

Despite extensive exploration in conventional registration frameworks, local rigidity is less commonly adapted to learning-based settings. A notable exception is the work of Chen et al. (2021), where a multichannel registration network predicts structure specific velocity fields that are fused together. Since no smoothing is applied during fusion, local discontinuities are preserved at the organ boundaries. Structure specific physical properties remains equally unexplored.

Multi-structure topology and shape preservation: Under natural body motion, the relative positions and shapes of the individual structures should remain consistent. Consequently, preserving the overall inter-structure topology and shapes is critical in multistructure registration. Segmentation maps are particularly useful for guiding registration tasks since they provide detailed location and shape information. By directly incorporating segmentation maps in the optimization process, robustness to variations in image intensity and complex deformations can be increased.

The state-of-the-art approach to incorporating segmentation maps for image registration uses overlap measures as guiding loss terms in the objective or training function. Typically, the Dice score is used, as is frequently found in learning-based registration, e.g., in Hu et al. (2018c,b), Balakrishnan et al. (2019), Mok and Chung (2021c), Lu et al. (2023). Since ground truth segmentations are required during training, this is called weak supervision. To alleviate this requirement, other works adopt multitask strategies to jointly learn the segmentation and registration from input images. This approach has been implemented across various network architectures, including CycleGANs (Mahapatra et al., 2018), cross-task attention mechanisms (Khor et al., 2023), encoder-decoder architectures with dual decoder branches (Estienne et al., 2019; Elmahdy et al., 2021) and paired networks that interact during training (Xu and Niethammer, 2019; Chen et al., 2022; Raveendran et al., 2024). Notably, Khor et al. (2023) propose a network that locally adapts the influence of segmentation guidance on the registration based on the segmentation overlap, enhancing registration performance.

Table 3
Problem specific regularization methods – organ specific registration (■ = explicit, ■ = implicit, ■ = conventional, ■ = learning-based, abd. = abdominal, Id. = identity).

registration problem		reference	type	approach	modality and anatomy	registration framework
organ specific registration	sliding motion	(Yin et al., 2010)	explicit	suppress smoothing near boundary	lung CT	conventional
		(Jud et al., 2017b)	explicit	suppress smoothing near boundary	lung CT	conventional
		(Heinrich et al., 2010)	explicit	L_p-norm	lung CT	conventional
		(Gong et al., 2020)	explicit	L_p-norm	lung CT/PET	conventional
		(Duan et al., 2023c)	explicit	L_p-norm, boundaries are learned	lung CT	learning-based
		(Luo et al., 2023)	explicit	L_p-norm	lung CT	learning-based
		(Ruan et al., 2008)	explicit	anisotropic diffusion	lung CT	conventional
		(Schmidt-Richberg et al., 2009)	explicit	anisotropic diffusion	lung CT	conventional
		(Pace et al., 2011)	explicit	anisotropic diffusion	lung CT	conventional
		(Pace et al., 2013)	explicit	anisotropic diffusion	lung CT	conventional
		(Tanner et al., 2013)	explicit	anisotropic diffusion	abd. MR	conventional
		(Delmon et al., 2011)	explicit	anisotropic diffusion	lung CT	conventional
		(Risser et al., 2013)	explicit	anisotropic diffusion	lung CT	conventional
		(Jud et al., 2016)	explicit	anisotropic diffusion	lung CT	conventional
		(Schmidt-Richberg et al., 2012)	explicit	anisotropic diffusion	lung CT	conventional
		(Risser et al., 2011)	implicit	region-wise in tangential direction	lung CT	conventional
		(Papież et al., 2014)	explicit	bilateral filter	lung CT	conventional
		(Papież et al., 2015)	explicit	adaptive Gaussian filter	liver CT	conventional
		(Papież et al., 2018)	explicit	adaptive Gaussian filter	lung CT/liver MR	conventional
		(Berendsen et al., 2014b)	implicit	region-wise then fuse, boundary constraint	lung CT	conventional
		(Derksen et al., 2015)	implicit	region-wise then fuse, boundary constraint	lung CT	conventional
		(Preston et al., 2016)	implicit	region-wise then fuse, label constraint	lung CT	conventional
		(Eiben et al., 2018)	implicit	region-wise then fuse, boundary constraint	lung CT	conventional
		(Ruan et al., 2009)	explicit	constraints on Helmholtz-Hodge components	lung CT	conventional
		(Ai et al., 2019)	explicit	constraints on Helmholtz-Hodge components	abd. CT	conventional
		(Sandkühler et al., 2018)	explicit	graph diffusion, zero cross-boundary weights	lung CT	conventional
		(Jud et al., 2018)	explicit	graph TV	lung CT	conventional
		(Andrade and Hurtado, 2021)	explicit	elasto-plasticity	lung CT	conventional
		(Ng and Ebrahimi, 2020)	explicit	penalize non-parallel motion	lung CT	learning-based
		(Lu et al., 2023)	explicit	suppress smoothing near boundaries	cardiac MR	learning-based
	cyclic motion	(Shen et al., 2005)	explicit	smoothness between last/first image	cardiac MR	conventional
		(Ledesma-Carbayo et al., 2005)	explicit	smoothness between last/first image	cardiac US	conventional
		(Metz et al., 2011)	explicit	smoothness between last/first image	lung/cardiac CT	conventional
		(Vandemeulebroucke et al., 2011)	explicit	smoothness between last/first image	lung CT	conventional
		(Ye et al., 2023)	explicit	smoothness between last/first image	cardiac US/MR	learning-based
		(Brehm et al., 2012)	explicit	penalize deformation cycle ≠ Id.	lung CT	conventional
		(Fechter and Baltas, 2019)	explicit	penalize deformation cycle ≠ Id.	lung CT	conventional
		(Bai and Brady, 2009)	explicit	cyclic B-Spline coefficients	lung PET	conventional
		(McEachen et al., 2000)	implicit	cyclic basis functions in FFD	cardiac MR	conventional
		(Wiputra et al., 2020)	implicit	cyclic basis functions in FFD	cardiac US	conventional

Recently, capsule networks (Sabour et al., 2017) have been leveraged within image registration to model part-whole relationships among anatomical structures (Yan et al., 2024). These networks capture detailed pose and shape information, making them well suited for incorporating relative relationships between structures and their components. Finally, Großbröhmer and Heinrich (2024) introduce a registration network that is based on learned segmentation encodings rather than image features, demonstrating high generalizability.

Beyond segmentation maps, corresponding keypoint distance can also serve as a guiding mechanism for registration. Keypoints can enhance registration robustness by providing reliable anchors across and within structures. Although this approach is less popular, it is found, for instance, in Rühaak et al. (2017), Papenberg et al. (2009), Kearney et al. (2014). Moreover, graphs can be constructed from keypoints to guide a sparse registration (Heinrich et al., 2015; Hansen and Heinrich, 2021; Heinrich and Hansen, 2022). From the sparse result, a dense deformation is then derived, for instance, with thin plate splines. Recently, Wang et al. (2023a, 2024) have introduced registration networks capable of jointly detecting and matching keypoints for registration guidance, and Matkovic et al. (2024) have proposed to incorporate keypoint guidance in a GAN architecture.

3.2.2. *Organ specific registration with special motion properties*

While multistructure registration often considers different organs at the same time, other scenarios focus on single organs only. For instance, intra-patient cardiac and lung registration is employed to analyze motion dynamics from spatio-temporal data, with applications in functional analysis or radiotherapy treatment planning (Keall et al., 2005a; Reinhardt et al., 2008; Choi et al., 2013). However, these organs exhibit unique deformation characteristics that are critical to consider during registration. Specifically, cardiac and respiratory motion is periodic and quasi-cyclic in nature and breathing induces sliding motion at organ boundaries (Fig. 5, bottom). An overview of the methods discussed in this section is shown in Table 3.

Sliding motion: At organ boundaries, motion in opposing directions leads to local discontinuities, such as the sliding of lungs, diaphragm, and liver against the pleural wall or between lung lobes along fissures. This cannot be modeled with standard regularization. Methods that address sliding motion combine smoothness and discontinuity regularization and either adapt to (a) boundary proximity, (b) deformation direction, or (c) use region-wise registration.

Explicit diffusion regularization can be adapted to allow discontinuities near sliding boundaries while maintaining smoothness elsewhere.

This is achieved by *suppressing smoothing* near boundaries (Yin et al., 2010; Jud et al., 2017b) or by switching from diffusion (L_2-norm) to TV (L_1-norm) regularization. This is called L_p-norm regularization ($1 < p < 2$) and encountered in conventional (Heinrich et al., 2010; Gong et al., 2020) and learning-based registration (Duan et al., 2023c; Luo et al., 2023).

Apart from boundary distance, the *deformation direction* can be considered: Sliding motion requires tangential smoothness along boundaries while exhibiting discontinuities in the normal direction. A common method to address this is to leverage anisotropic diffusion that decomposes smoothing into tangential and normal components: Isotropic smoothing is applied within organs and anisotropic smoothing that vanishes in the normal direction is applied near boundaries (Ruan et al., 2008; Schmidt-Richberg et al., 2009; Pace et al., 2011, 2013; Tanner et al., 2013; Delmon et al., 2011; Risser et al., 2013; Jud et al., 2016). Anisotropic smoothing is extended in Schmidt-Richberg et al. (2012) to locally adapt to the estimated amount of slippage. To this end, the deformation variations are compared at sampled points on both sides of the boundary. Another approach is to employ global smoothing in the normal direction while performing tangential smoothing independently at each side of the boundary (Risser et al., 2011). Anisotropic smoothing can furthermore be achieved with the bilateral filter proposed in PapieÅ¼ et al. (2014). This filter balances local discontinuities and smoothness by adapting to intensity differences, spatial smoothness, and local deformation field similarities. In Fu et al. (2018) the bilateral filter is applied in the tangential direction only, while isotropic normal smoothing is used. Adaptive Gaussian filters derived from super-voxel clusters of the image further enhance sliding boundary fidelity by reducing smoothing in areas of high intensity or deformation variance (Bartlomiej et al., 2015; Bartłomiej W. et al., 2018). Since supervoxel clusters capture local discontinuities, the filters can effectively transfer discontinuity information to the deformation.

Besides this, sliding motion can be addressed with *region-wise* registration, such as in (Risser et al., 2013; Berendsen et al., 2014b; Derksen et al., 2015; Preston et al., 2016; Eiben et al., 2018). First, smooth registration is performed independently for each side of a sliding boundary. Then, the resulting deformations are fused into a global deformation. To preserve discontinuities at boundaries, no smoothing is used during fusion. A major challenge with this approach is the presence of gaps and overlaps at the sliding boundaries. Solutions include penalizing misalignment of boundaries during the region-wise registration (Berendsen et al., 2014b; Derksen et al., 2015; Eiben et al., 2018) or constraining the deformed segmentation maps to a single label per voxel (Preston et al., 2016).

Further advancements in sliding motion regularization include component-wise regularization of the divergence-free, curl-free, and harmonic components of the deformation (which can be obtained with the Helmholtz decomposition) to preserve large shears along boundaries (Ruan et al., 2009; Ai et al., 2019). Graph-based methods extend diffusion regularization by assigning zero-weight edges across sliding boundaries (Sandkühler et al., 2018) or adapt TV regularization (Jud et al., 2018). Physics inspired regularization has been leveraged for sliding motion in Andrade and Hurtado (2021) by combining linear elastic and van Mises plasticity models in the regularization to allow high shear deformations along sliding boundaries. Region-wise thin-plate spline and B-spline registration have been proposed in Xie et al. (2011), Hua et al. (2017).

Although extensively studied in conventional registration, sliding motion regularization has seen limited adoption in learning-based registration frameworks. Explicit sliding motion regularization has been proposed for network training, including penalization of non-parallel motion of neighboring voxels (Ng and Ebrahimi, 2020), smoothing suppression at sliding boundaries with a binary mask (Lu et al., 2023) and L_p-norm regularization (Duan et al., 2023c). Additionally, multitask learning is leveraged to learn boundary locations jointly with the registration in Duan et al. (2023c).

Cyclic motion: Registration of 4D (3D + t) image data often involves capturing a patient's cardiac or respiratory cycles, for instance, in the context of cardiac function analysis, (Pan et al., 2003), radiation therapy (Keall et al., 2005b) and motion correction (Spieker et al., 2024). For such data, incorporating the cyclic nature of the deformation in the registration is particularly important. Periodicity can be explicitly accounted for by ensuring that the last image in a sequence maps back to the first image seamlessly, as found in conventional (Shen et al., 2005; Ledesma-Carbayo et al., 2005; Metz et al., 2011; Vandemeulebroucke et al., 2011) and learning-based (Ye et al., 2023) registration. Alternatively, deviations from the full-cycle deformation to the identity deformation can be penalized (Brehm et al., 2012; Fechter and Baltas, 2019).

Implicit cyclic extensions to FFD registration use periodic B-spline coefficients (Bai and Brady, 2009) and cyclic basis functions such as harmonic sinusoid or Fourier functions (McEachen et al., 2000; Wiputra et al., 2020). It is observed that, in general, despite the prevalence of 3D cardiac and lung image registration studies, relatively few are concerned with cyclic regularization of 3D + t data. Cyclic regularization in the context of learning-based registration remains to be explored.

3.2.3. Registration of images with topological change

A common assumption in image registration is that the underlying topology of the image remains unchanged, implying that every location in M corresponds to a location in F. However, there are scenarios where this assumption is not true, particularly in clinical settings where topology changes can arise for various reasons. Examples include changing tissue due to lesion development (Niethammer et al., 2011; François et al., 2022), missing regions after surgical resection (Risholm et al., 2009; Nithiananthan et al., 2012; Chen et al., 2015; Wodzinski et al., 2021), variable gastrointestinal contents (Suh and Wyatt, 2011), and removal of medical devices (Berendsen et al., 2013). In such cases, including prior knowledge about the clinical context in the registration is valuable, particularly when combined with spatial information about topologically changing regions. An overview of the methods discussed in this section is shown in Tab. 4.

Growing and shrinking regions: If an area with missing correspondences is partially present in M and F, this implies region growth or shrinkage. Typically this involves smooth tissue change due to the development of pathologies. One approach that addresses such topology changes is cost function masking that restricts the optimization to topologically consistent regions (Brett et al., 2001). This ensures that changing regions do not bias the registration.

Alternatively, local topology changes are accounted for through adaptations of the metamorphosis framework, which disentangles deformations from appearance changes in the loss function (Trouvé and Younes, 2005; Younes, 2010). For instance, geometric metamorphosis (Niethammer et al., 2011) models topology changes with a geometric model decoupled from the deformation of the surrounding tissue. This isolation enables the quantification of topology change which is valuable for downstream applications such as automatic lesion growth analysis. In François et al. (2022), the framework is refined to limit geometric changes to predefined regions.

Metamorphic registration has also been adapted to learning-based registration. The metamorphic autoencoder of Bône et al. (2020) decouples low-dimensional representations of shape and appearance changes in latent space, and metamorphic ResNet architectures are found in Maillard et al. (2022), Joshi and Hong (2023a). Although these methods require prior segmentation maps of topologically changing regions, the metamorphic registration network by Wang et al. (2023c) eliminates this dependency by jointly learning the location of appearance changing regions. Further approaches combine registration with predicting a quasi-normal (pathology-free) image, enabling registration between pathological and healthy images (Han et al., 2020), and explicit regularization that ensures that the volume change of lesions matches the one of surrounding tissue (Dong et al., 2023).

Table 4
Problem specific regularization methods – Registration of images with topological changes (■ = explicit, ■ = implicit, ■ = conventional, ■ = learning-based, abd. = abdominal).

registration problem		reference	type	approach	modality and anatomy	registration framework
topology changes	growing/shrinking regions	(Brett et al., 2001)	explicit	cost function masking	brain MR	conventional
		(Niethammer et al., 2011)	implicit	geometric metamorphosis	brain MR	conventional
		(François et al., 2022)	explicit	region-limited metamorphosis	brain MR	conventional
		(Wang et al., 2023c)	explicit	region-limited metamorphosis	brain MR	learning-based
		(Bône et al., 2020)	implicit	metamorphic autoencoder	brain MR	learning-based
		(Maillard et al., 2022)	implicit	ResNet-based metamorphosis	brain MR	learning-based
		(Joshi and Hong, 2023a)	implicit	ResNet-based metamorphosis	brain MR/liver CT	learning-based
		(Dong et al., 2023)	explicit	constrain lesion volume change	brain MR/abd. CT	learning-based
	missing regions	(Berendsen et al., 2014a)	explicit	minimize volume	cervical MR	conventional
		(Chen et al., 2015)	explicit	minimize volume	brain MR	conventional
		(Wodzinski et al., 2021)	explicit	minimize volume	breast MR	learning-based
		(Risholm et al., 2009)	explicit	diffusion sink	brain MR	conventional
		(Suh and Wyatt, 2011)	implicit	auxiliary deformation dimension	colorectal CT	conventional
		(Nithiananthan et al., 2012)	implicit	auxiliary deformation dimension	head CT	conventional
		(Nielsen et al., 2019a)	implicit	expand voids from pre-defined points	brain MR	conventional
		(Czolbe et al., 2021)	explicit	cost function masking in training	brain MR	learning-based
		(Mok and Chung, 2022)	explicit	IC loss-based cost function masking	brain MR	learning-based
		(Wodzinski et al., 2023)	explicit	IC loss-based cost function masking	brain MR	learning-based
		(Feng et al., 2024)	explicit	IC loss-based corrected attention layers	brain MR	learning-based

Missing regions: In contrast to growing regions, missing regions are entirely absent in one of the two images. Such a scenario is found, for instance, in the registration of pre-to-post resection images. To address this, explicit regularization can be employed to minimize the volume of regions without correspondence in the other image (Berendsen et al., 2014a; Chen et al., 2015; Wodzinski and Skalski, 2018; Wodzinski et al., 2021). Another option is to use a diffusion sink that restricts diffusion regularization such that image forces originating within a resected region diffuse outward to surrounding areas but not in the reverse direction (Risholm et al., 2009).

Implicit regularization methods that leverage the parameterization of the transformation model include modeling tissue removal in an auxiliary deformation dimension (Suh and Wyatt, 2011; Nithiananthan et al., 2012) or by expanding voids from selected image locations (Nielsen et al., 2019). To alleviate the need for prior segmentation maps, joint registration and segmentation of missing regions has been further proposed for conventional (Periaswamy and Farid, 2006; Chitphakdithai and Duncan, 2010; Chen et al., 2015) and learning-based registration with conditional autoencoders (Czolbe et al., 2021) and convolutional neural networks (CNNs) (Mok and Chung, 2022; Wodzinski et al., 2023; Liu and Gu, 2023). Here, cost function masking is applied to suppress the influence of missing regions on the registration.

An elegant recently proposed approach automatically identifies missing regions with model based regularization within the training of registration networks (Mok and Chung, 2022; Wodzinski et al., 2023): Local areas with a high inverse-consistency regularization loss (Section 3.1.3) are interpreted as missing in the other image. This information is then used for masking or weighting the training loss. Another weighting-based method is used in the bi-directional registration network by Feng et al. (2024) where a weight map guides the attention layers to focus on pathological and missing regions.

3.2.4. Discussion

Problem specific regularization extends beyond the global, general-purpose constraints of model based approaches by integrating data knowledge and adapting to local deformation characteristics. The spatial adaptivity enables more realistic modeling of complex deformations which global regularization methods fail to capture. The majority of the problem specific methods extend model based regularization methods presented in Section 3.1 to spatial adaptivity, either by location dependent regularization weight maps, as seen in sliding motion regularization, or location dependent formulation of the regularization itself, for instance, to accomplish local rigidity.

Despite their clear advantages, problem specific regularization methods face challenges that should be considered for successful application. A major challenge is that many of the presented methods rely on accurate prior segmentation maps or boundary definitions, for instance, Risser et al. (2013), Schmidt-Richberg et al. (2012). While manual annotations by clinicians provide high precision, they are costly to obtain. This is particularly true for methods embedded within learning-based registration frameworks, where segmentation maps of the full training dataset are often required for training. To mitigate this, segmentations can be inferred directly from images or estimated deformations, or multitask learning can be employed to jointly learn the registration and the spatial information, such as in Czolbe et al. (2021), Wang et al. (2023c), Duan et al. (2023c). Moreover, the rapid advancements of open-source, pre-trained segmentation networks like TotalSegmentator (Wasserthal et al., 2023) offer a convenient solution for automatic segmentations that can be used in registration frameworks without notable computation overhead. However, such segmentations are probably not as precise as manual ones. Consequently, to reduce the dependency of registration results on annotation quality, regularization methods need to be adapted to noisy segmentations, as in Gong et al. (2020), Raveendran et al. (2024).

Apart from that, problem specific methods are tailored to address specific anatomical or pathological characteristics. On the one hand, careful parameter tuning might be required, for instance for local physical parameters in Andrade and Hurtado (2021), hyperparameters that balance geometric change and deformations in (Bône et al., 2020), or hyperparameters of Gaussian filters in (PapieÅ¼ et al., 2014). On the other hand, different methods have different requirements about the specific scenario. For example, when addressing topology changes, some methods can only register healthy to pathological images, for instance, François et al. (2021), while others can only register in the other direction, e.g., Maillard et al. (2022), Han et al. (2020). Consequently, their generalizability to new applications and data that slightly differ from the validation scenarios is limited. In particular, the high dependency on parameter tuning complicates registration network training, making their clinical application challenging.

Overall, a gap in regularization method transfer from conventional to learning-based registration is observed. For multistructure registration, local physical properties and rigidity have seen limited integration into learning-based registration. In contrast, segmentation guidance can be considered state-of-the-art in learning-based registration. Sliding motion, though well-studied in conventional registration, also remains to be explored more with registration networks. In particular, integrating local physical properties and rigidity could drive the capabilities of registration networks forward since many applications face rigid structures or varying material properties.

In summary, the capability of problem specific regularization to address local deformation characteristics and real-world clinical scenarios makes it indispensable for targeted applications. However, methods heavily rely on design choices and hyperparameter tuning. This highlights the need for more flexible regularization frameworks capable of automatically identifying deformation properties from the data itself, which is addressed with the learned regularization methods in the following section.

3.3. Learned regularization

This section presents and discusses the rapidly growing field of learned regularization, organized by what is learned from training data. While problem specific regularization incorporates data knowledge and adapts to local deformation characteristics, it still requires careful user design and parameter tuning, which can limit scalability and adaptability. In contrast, *learned* regularization leverages data-driven techniques to infer local properties directly from training data. For this, the regularization component of a registration framework is parameterized with a machine or deep learning model (see, for instance, Fig. 7). We identify three subcategories of learned regularization: Methods that learn (i) local smoothness properties (Section 3.3.1), (ii) feasible deformation spaces (Section 3.3.2), and (iii) test time adaptive regularization (Section 3.3.3). An overview of learned methods is given in Tab. 5.

3.3.1. Learned local smoothing and discontinuities

Spatially varying smoothing, which automatically adapts to local image properties, can be effectively learned using deep neural networks. For instance, Niethammer et al. (2019) have proposed a shallow CNN within a conventional diffeomorphic LDDMM framework (see Section 3.1.4). The CNN takes a momentum vector field and an image as inputs. It predicts a smoothed vector field by learning the weights of a spatially adaptive multi-Gaussian smoothing kernel. To ensure that the regularized output remains diffeomorphic and transfers edge information from the image to the deformation, the learned weights are additionally prevented from degenerating through total variation (TV) meta-regularization. By bounding the variance of the weights, a desired smoothing level can be further specified. Optimization is performed in two stages: First, only the momenta are optimized while the Gaussian weights are carefully chosen, then the CNN parameters and the initial momentum vector fields are jointly optimized. An extension of this approach to spatio-temporal velocity fields has been proposed in Shen et al. (2019b). Here, two separate CNNs predict the initial momentum vector field and the smoothing weights, respectively.

A more generalized approach is presented in Al Safadi and Song (2021), where the regularization is parameterized as a trainable convolutional layer applied to the predicted deformation of a registration network. This method aims to minimize folding and increase anatomical plausibility. Building upon the Reproducing Kernel Hilbert Space (RKHS) theory, the authors demonstrated that constraining the convolutional filters to be positive, semi-definite, and radially symmetric approximates RKHS regularization. These constraints are explicitly enforced in the meta-regularization of the regularization layers. By imposing these constraints on the learned filters, they offer learned spatially adaptive smoothing filters that are highly generalizable and can adapt well to large deformations.

While the methods presented above focus on locally adapting the smoothing strength, local discontinuities are learned in Jia et al. (2022), Lai et al. (2023). Using a variable splitting scheme and an auxiliary splitting variable, the registration problem of Eq. 1 is divided into two simpler subproblems: a similarity and a regularization component. These subproblems are individually parameterized by a neural network, where a ResNet-based denoising network is employed for the regularization part. Optimization is performed by alternating parameter updates of the two networks or joint training. Conveniently, regularization hyperparameters such as α and additional weights resulting from the variable splitting scheme can be absorbed in the denoising network, alleviating manual tuning. The regularization network effectively learns local TV regularization that avoids over-smoothing and allows for local discontinuities (Jia et al., 2022) or focuses on modeling sliding motion (Lai et al., 2023).

3.3.2. Learned deformation spaces

Due to the shared characteristics of human anatomy, anatomical structures exhibit similar deformation patterns across different subjects. Thus, deformations can be assumed to reside within a lower-dimensional subspace. This subspace of feasible deformations can be learned from training data with machine or deep learning models. Once trained, the models offer a compact and efficient deformation space representation with generative capabilities, i.e., they can generate novel deformation instances of the learned space.

The overall process of learning feasible deformation spaces is shown in Fig. 6. Typically, first, a set of ground truth deformations is obtained that adequately spans the feasible deformation space. This training dataset is then used to train the deformation space model. Finally, the trained model is embedded within a registration framework where it parameterizes the transformation. Thus, the registration is implicitly regularized to produce deformations that remain within the learned subspace. This method inherently offers spatially adaptive regularization.

We identify two model types that dominate the literature: Learning (i) linear subspaces with principal component analysis (PCA) and (ii) nonlinear manifolds with deep neural networks.

Principal Component Analysis (PCA): PCA is a linear dimensionality reduction technique that identifies dominant modes of variation in a dataset. By projecting data onto the learned subspace, PCA enables reconstruction and data generation through linear combinations of the principal eigenvectors. When applied to deformation datasets, PCA offers statistical deformation models that capture local deformation variations within the training data and (ideally) represent the space of feasible deformations.

Embedding a trained PCA model within registration greatly reduces the dimensionality of the registration since optimization can be performed with respect to the principal component coefficients instead of the deformation parameters. This approach has been employed across various registration techniques, including viscous fluid (Wouters et al., 2006) and standard gradient-based (Hu et al., 2008) registration. In the context of diffeomorphic registration, PCA models have been proposed to learn the space of feasible initial momenta in the LDDMM framework (Qiu et al., 2012) and local velocity fields in the log-Euclidean framework (Zeng et al., 2018). Additionally, PCA has been applied to control points of FFD B-spline deformations in Loeckx et al. (2003). This further reduces registration complexity.

A challenge with global PCA models is their limited flexibility. To address this, extensions have been developed that enhance representation capabilities. Dual PCA models, for instance, capture complementary deformation properties based on the Jacobian determinants and displacement vectors. Within registration, they ensure that deformations lie in the intersection of both subspaces (Xue et al., 2006). A similar approach has been proposed to model tumor-induced deformation and intra-population variations in the context of tumor-to-healthy interpatient registration (Mohamed et al., 2006). Further developments include localized PCA models that represent local patches across the image domain (Tang et al., 2018), finding plausible initial solutions with PCA models before registration (Kim et al., 2008; Tanner et al., 2009), and learning a PCA model from a combination of images and segmentation maps (Onofrey et al., 2015b).

Table 5
Learned regularization methods (■ = explicit, ■ = implicit, ■ = guidance, ■ = conventional, ■ = learning-based, abd. = abdominal, phys. params. = physical parameters).

learns	reference	type	regularization model	approach	modality and anatomy	registration framework
local smo. /disc.	(Niethammer et al., 2019)	explicit	CNN	local multi-Gaussian weights	brain MR	conventional
	(Shen et al., 2019b)	explicit	two CNNs	local multi-Gaussian weights	knee MR/lung CT	conventional
	(Al Safadi and Song, 2021)	explicit	convolution layer	RKHS convolution filter	cardiac US/lung x-ray	learning-based
	(Jia et al., 2022)	explicit	denoising ResNet	variable splitting	cardiac MR	learning-based
	(Lai et al., 2023)	explicit	denoising ResNet	variable splitting	brain MR/lung CT	learning-based
feasible deformation space	(Wouters et al., 2006)	implicit	PCA	opt. w.r.t. PCA coeffs.	brain MR	conventional
	(Hu et al., 2008)	implicit	PCA	opt. w.r.t. PCA coeffs.	prostate US	conventional
	(Qiu et al., 2012)	implicit	PCA	opt. w.r.t. PCA coeffs.	brain MR	conventional
	(Zeng et al., 2018)	implicit	PCA	opt. w.r.t. PCA coeffs.	brain MR	conventional
	(Loeckx et al., 2003)	implicit	PCA	PCA on FFD control points	lung CT	conventional
	(Kim et al., 2008)	guidance	PCA	PCA for initialization	brain MR	conventional
	(Tanner et al., 2009)	guidance	PCA	PCA for initialization	breast MR/x-ray	conventional
	(Cui et al., 2017)	explicit	PCA	constrained PCA coeffs.	lung SPECT	conventional
	(Albrecht et al., 2008)	explicit	PCA	constrained PCA coeffs.	upper leg x-ray	conventional
	(Berendsen et al., 2013)	explicit	PCA	constrained PCA coeffs.	cervical MR	conventional
	(Gu et al., 2021)	explicit	PCA	constrained PCA coeffs.	brain MR	learning-based
	(Hu et al., 2015)	explicit	PCA	4D motion model	rectal US	conventional
	(Jud et al., 2017a)	implicit	reproducing kernel	4D motion model	lung CT	conventional
	(Onofrey et al., 2015b)	implicit	PCA	4D FFD model	prostate	conventional
	(Xue et al., 2006)	explicit	two PCAs	$det\mathbf{J} + \mathbf{u}$ PCA	brain MR	conventional
	(Mohamed et al., 2006)	explicit	two PCAs	healthy+pathological PCA	brain MR	conventional
	(Tang et al., 2018)	implicit	local PCAs	patch-based PCAs	brain MR	conventional
	(Gao et al., 2021)	implicit	autoencoder	learned PCA coeffs.	upper leg CT	conventional
	(Hu et al., 2018a)	explicit	GAN	FEM-based adversarial loss	prostate MR/US	learning-based
	(Bhalodia et al., 2019)	explicit	autoencoder	reconstruction loss	brain MR	learning-based
	(Mansilla et al., 2020)	explicit	autoencoder	reconstruction loss	lung x-ray	learning-based
	(Sang and Ruan, 2020)	explicit	autoencoder	reconstruction loss	cardiac MR	learning-based
	(Qin et al., 2020)	explicit	autoencoder	reconstruction loss	cardiac MR	learning-based
	(Sang and Ruan, 2021)	explicit	autoencoder	reconstruction loss	lung CBCT	learning-based
	(Sang et al., 2022)	explicit	autoencoder	reconstruction loss	cardiac CTA/MR	learning-based
	(Sang et al., 2020)	implicit	decoder-only	opt. w.r.t latent vector	cardiac MR/lung CT	conventional
	(Qin et al., 2023)	implicit	decoder-only	opt. w.r.t latent vector	cardiac MR	conventional
test time regularization	(Mok and Chung, 2021a)	explicit	CIN layers	learn effect of α (diffusion)	brain MR	learning-based
	(Hoopes et al., 2021)	explicit	hypernet	learn effect of α (diffusion)	brain MR	learning-based
	(Wang et al., 2023d)	explicit	CIN layers	learn effect of α (diffusion)	brain MR	learning-based
	(Chen et al., 2023)	explicit	CIN/hypernet	learn effect of α (diffusion)	brain MR	learning-based
	(Zhu et al., 2024)	explicit	CIN layers	learn effect of α (diffusion)	brain MR/lung CT	learning-based
	(Shuaibu et al., 2024)	explicit	MLP	learn optimal α(diffusion)	brain MR	learning-based
	(Reithmeir et al., 2024a)	explicit	hypernet	learn effect of phys. params.	lung CT/cardiac MR	learning-based
	(Reithmeir et al., 2024b)	explicit	hypernet	learn effect of phys. params.	lung CT	learning-based
	(Xu et al., 2022)	explicit	mean-teacher net	dynamic α during training	abd. MR/CT	learning-based

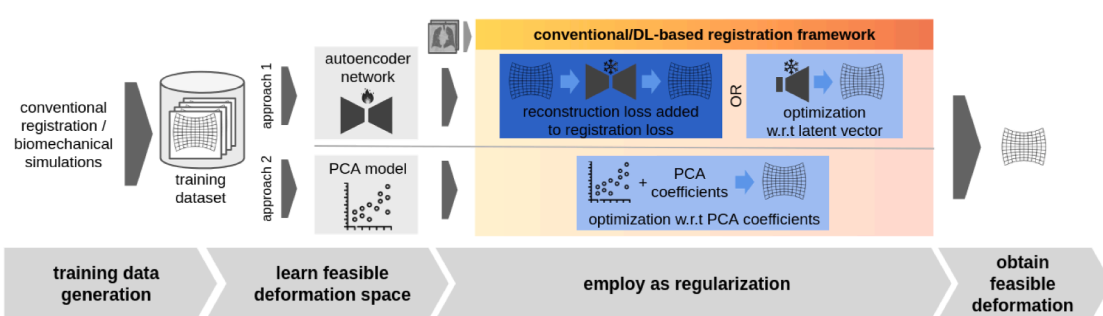

Fig. 6. Learned Regularization – Learned deformation spaces: Low-dimensional deformation spaces representing the set of feasible deformations can be learned from a training dataset. Two approaches of learned deformation spaces are found in the literature: (i) PCA models and (ii) autoencoder networks. Once trained, the regularization model is embedded within the registration framework, either as explicit (■) or implicit (■) regularization.

Moreover, learned PCA models can be leveraged within the regularization loss term of the registration. They can avoid infeasible deformations through soft constraints, for example, in a probabilistic formulation (Albrecht et al., 2008) or by penalizing deviations from the mean of the distribution (Berendsen et al., 2013). In Cui et al. (2017), Gu et al. (2021), deformation eigenmodes are constrained to lie within a certain value range for the generation of novel deformations from the PCA model, improving flexibility without sacrificing representational fidelity Moreover, a deep learning approach using an autoencoder network has been proposed to learn optimal PCA coefficients for a trained PCA model during registration (Gao et al., 2021).

Most of the methods above focus on capturing intra-population shape variations for application in inter-patient registration and atlas building. In contrast, intra-patient registration is often used as a tool *for* the generation of 4D motion models of the lung (He et al., 2010; King et al., 2012; Han et al., 2017) or liver (Preiswerk et al., 2014). Less work is found that, in turn, applies PCA for regularization purposes *within* registration. Exceptions include PCA models trained on biomechanical FEM simulations (Hu et al., 2015) and FFD-based PCA models trained on pre-to-intra-operative images (Onofrey et al., 2015a). The subject-specific statistical motion model in (Jud et al., 2017a) is learned from labeled inhale-exhale lung images and successfully transfers sliding motion properties from the training data to unseen, unlabeled images.

Deep neural networks: In contrast to linear PCA models, deep neural networks can learn nonlinear manifolds from training data. Different model architectures and training strategies have been explored, and we identify three approaches: Employing (i) generative adversarial networks (GANs) that distinguish between ground truth and estimated deformations, (ii) autoencoder networks trained to reconstruct ground truth deformations, and (iii) decoder-only architectures that generate deformations from low-dimensional latent representations.

GANs employ generator-discriminator frameworks where the generators act as registration networks. The discriminators are trained to distinguish between estimated and ground truth deformations, which drives the generators to produce results that closely resemble the ground truth data. GANs can be employed to produce biomechanically plausible deformations that align closely with, for instance, biomechanical FEM simulations Hu et al. (2018a).

Another approach involves *autoencoder networks* trained to reconstruct input deformations and, thereby, learning a low-dimensional deformation manifold encoded in the latent space. Trained autoencoders can serve as regularization during registration by penalizing deformations that deviate from the learned manifold. Typically, this is achieved by autoencoding the estimated deformation and adding its reconstruction loss to the registration optimization objective function. Regularizing autoencoders can be jointly trained with a registration network Bhalodia et al. (2019) or their training can be decoupled from registration network training, as in Sang and Ruan (2020, 2021), Sang et al. (2022). In this case, the autoencoders are trained on separate training datasets and embedded with frozen trained weights in the training of registration networks. Variations of this approach include learning to reconstruct deformation gradients instead of deformations themselves (Qin et al., 2020) and denoise noisy segmentations (Mansilla et al., 2020). Typically, training data for the autoencoder is generated a priori with conventional registration algorithms (Sang and Ruan, 2020, 2021; Sang et al., 2022), or biomechanical FEM simulations (Qin et al., 2020).

A third approach uses only the *decoder component* of trained encoder-decoder architectures. When embedded into a registration framework, optimization is performed directly in the low-dimensional latent space rather than the high-dimensional deformation space. Thus, the registration aims at finding the optimal latent vector that encodes the deformation between M and F. Sang et al. (2020) have proposed to use alternating backpropagation to jointly optimize the decoder parameters and latent vector. Similarly, Qin et al. (2023) have employed a temporal variational autoencoder that was trained on 4D FEM simulated deformation sequences. In both methods, the trained network's decoder is integrated into a conventional registration framework, enabling efficient and accurate regularization of deformation properties.

3.3.3. Learned test-time regularization

A core regularization component in the registration objective function (Fig. 1) is the regularization weight α. It balances the regularization constraints and the similarity loss, and its value determines the strength of the applied regularization. Typically, α is manually tuned as a hyperparameter. However, this is a time-intensive and cumbersome process, particularly for learning-based registration models where separate training is required for each candidate value. Moreover, a single value applied uniformly across all image pairs is unlikely to yield optimal results due to the variability in deformation properties across different subjects. To overcome these challenges, advanced deep learning techniques are used within registration networks to learn regularization that can be dynamically adapted at test time.

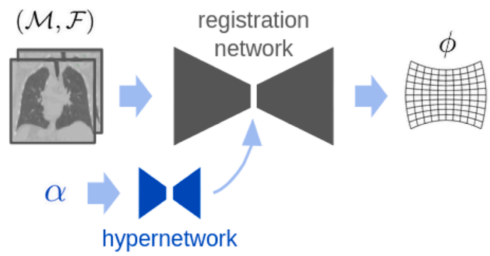

Fig. 7. Learned regularization – Test time regularization: A hypernetwork can allow the user to adapt the regularization weight at test time. During training, the weights are randomly sampled.

A popular approach is to learn the effect of the regularization weight on deformation fields and, thus, on registration network parameters. During training, α values are randomly sampled to learn a wide range of regularization effects. At test time, the user specifies a desired value, and the registration network estimates a regularized deformation accordingly. To achieve this, conditional neural networks can be used that employ conditional instance normalization (CIN) layers that normalize and shift feature representations based on the specified α (Mok and Chung, 2021a). Similarly, the HyperMorph framework (Hoopes et al., 2021) leverages a hypernetwork architecture where a secondary network predicts the parameters of the primary registration network, conditioned on α (see Fig. 7). Both methods are trained end-to-end and use a global α for balancing a diffusion-based smoothing term.

Recent advances have extended these methods for spatially adaptive regularization. Wang et al. (2023e) enhance the CIN-based approach by introducing a regularization weight matrix for tissue-specific smoothing. Chen et al. (2023) employ a dual decoder registration network that learns the weight matrix, which forms the hypernetwork input alongside the deformation. Traditional single-level CIN layers can be extended to multiple levels with a conditional multilevel architecture combining CIN layers, dynamic convolutional layers, and attention layers Zhu et al. (2024). To extend test-time regularization to physics-inspired methods, Reithmeir et al. (2024b) have proposed a hypernetwork that learns the influence of the physical parameters λ, μ on the deformation for linear elastic regularization. This approach has been extended to spatially-adaptive, tissue-specific parameters in Reithmeir et al. (2024a).

Apart from offering the user to adapt the regularization at test time, the above methods offer a second advantage: The optimal regularization weight value can be identified at inference time, not only for a test dataset but also for each registration individually. This can be achieved, for instance, with a grid search over the parameter space (Hoopes et al., 2021; Reithmeir et al., 2024a). A learned approach was instead proposed in Shuaibu and Simpson (2024). Here, a multilayer perception is trained to predict the Dice score and amount of folding from input images and a specified α, enabling a learning-based identification of optimal α values at test time.

Beyond this, automatic adaptation of α during training has been explored to optimize the trade-off between smoothness and registration accuracy during the training process. Xu et al. (2022) have introduced a teacher-student architecture where the teacher model updates its weights based on the performance of the student model across consecutive iterations. With Monte Carlo dropout, the teacher model estimates deformation and intensity uncertainty, which is then used to dynamically adjust α to each individual image pair and training step. Stronger regularization is applied to more challenging or uncertain image pairs.

3.3.4. Discussion

Learned regularization has emerged as a promising approach in medical image registration. Leveraging data-driven techniques to derive local deformation properties from training data offers distinctive advantages over model based and problem specific regularization. Compared to problem specific methods, fewer explicit modeling and manual tuning towards individual registration instances is required. Also, a major strength of learned regularization lies in its flexibility. For instance, learned smoothness can automatically find the optimal level of local regularization based on the image information, and over-smoothing can be effectively mitigated (Jia et al., 2022). This automatic adaptability to data is particularly beneficial in scenarios where anatomical structures exhibit highly variable or complex deformation characteristics.

However, learned regularization also faces some challenges. In the context of learned deformation spaces, methods require large, high-quality training datasets with accurate ground truth deformations. If the training dataset is smaller than the degrees of freedom of the deformation, PCA models can be overly restrictive and cannot represent the deformation space well (Cui et al., 2017). Moreover, since ground truth deformations are inexistent for medical image registration, auxiliary ground truth deformations are commonly generated, for instance, with elastic FEM simulations (Hu et al., 2008, 2018a; Qin et al., 2020, 2023) or conventional registration methods (Tang et al., 2018; Sang and Ruan, 2021). Both approaches have inherent limitations. Conventional registration-generated training data depend on the size and quality of available training images. Learned deformation spaces can only capture deformation properties modeled in the training data, thus requiring adequate design choices during the registration that generates ground truth deformations. For instance, if a global diffusion regularization is used here, the learned deformation spaces can model global smoothness but fail to capture, for instance, local discontinuities. In contrast, FEM simulations can generate quasi-unlimited training data but require careful simulation design and predefined physical parameters, which may be ambiguous.

Another challenge for learned deformation spaces is their limited generalizability, particularly when encountering previously unseen anatomical variations or pathological changes. Recent advancements address this limitation by learning modality-agnostic deformation spaces from segmentation maps rather than images (Hu et al., 2018a; Mansilla et al., 2020; Qin et al., 2023). Additionally, cross-modality transfer has shown promise, where deformation spaces are learned from "easier" modalities, e.g., FBCT or CTA, and successfully transferred to more "complex" modalities, e.g., CBCT or MRI (Sang and Ruan, 2021; Sang et al., 2022). Interestingly, regularizing PCA models have been widely adopted for representing population-level shape variations in inter-patient registration and atlas building, but their application in intra-patient registration, where they could represent 4D time-dependent motion patterns, remains underexplored.

The innovative advancements of test-time regularization, as introduced in Hoopes et al. (2021), Mok and Chung (2021a), not only streamline the training process for learning-based registration but also enable scenario- and instance-specific regularization. This aligns well with the inherent variability and subject-specific nature of human body deformations. The tailored regularization during inference bridges the gap between the versatility of instance-specific regularization found in conventional registration and the rapid inference capabilities of learning-based registration. However, training time and model complexity are increased over standard frameworks due to the network architectures and random sampling during training.

Despite its advantages, learned regularization faces interpretability challenges. Neural networks inherently function as black-box models, which complicates the task of understanding and verifying the regularization applied during registration. To better explore learned regularization effects, neural network-based regularization methods can be embedded within conventional registration frameworks where no additional interpretability difficulties are introduced and where it is easier to isolate the regularization effects. This is already found for some of the presented methods, for instance, in Niethammer et al. (2019), Qin et al. (2023). Also, learned regularization still relies on manually designed components. For example, many frameworks predict weight maps for predefined model based regularization terms (Mok and Chung, 2021a; Hoopes et al., 2021; Chen et al., 2023; Reithmeir et al., 2024a) or local smoothing filters with fixed isotropic shapes (Niethammer et al., 2019). Overall, learned regularization often requires significant computational resources and large training data (possibly in addition to registration training data). Careful model design and hyperparameter selection remain essential to prevent overfitting and ensure stable training.

In conclusion, learned regularization is an emerging and highly promising category of regularization methods in medical image registration. While some methods, to some extent, use model based or problem specific regularization, these techniques offer a powerful data-driven approach for capturing complex deformation properties and providing high adaptability of the regularization at inference time. As the generalizability, robustness, and interpretability of such methods are addressed, learned regularization has the potential to become fundamental to modern medical image registration frameworks.

4. Open challenges and future perspectives

Regularization is a key component of conventional and learning-based image registration. Despite significant advancements in the field, open challenges persist. This section discusses the key limitations of the presented regularization methods and outlines promising directions for future research.

Gaps in method transfer from conventional to learning-based registration: While many regularization methods have been successfully transferred from conventional to learning-based registration, noticeable gaps remain. Most model based regularization methods are widely adopted in learning-based registration. However, physics-inspired regularization has seen limited exploration in deep learning contexts. Similarly, problem specific regularization methods that deal with locally rigid, cyclic, and sliding motion - once a major focus in conventional registration - are underrepresented in learning-based approaches.

Addressing these gaps could substantially enhance the physical plausibility of learning-based registration models. The growing research area of physics-informed deep learning presents a valuable opportunity to revisit and expand upon physics-inspired regularization, as demonstrated, for instance, by Arratia LÃ³pez et al. (2023), Min et al. (2023, 2024). Moreover, pre-trained segmentation networks, such as Totalsegmentator (Wasserthal et al., 2023), could facilitate the transfer of tissue-specific regularization techniques into learning-based frameworks, potentially leading to more anatomically meaningful results.

Overreliance on global smoothness regularization: Global L_2-norm smoothing is featured in *14 out of 21* methods from the Learn2Reg challenge 2022 (Hering et al., 2023), as well as in most state-of-the-art learning-based registration frameworks such as VoxelMorph (Balakrishnan et al., 2019) or LapIRN (Mok and Chung, 2020). Moreover, the primary focus of many regularization strategies lies in achieving diffeomorphic registrations and minimizing folding. This widespread reliance on global smoothness and diffeomorphic regularization poses a significant limitation in modern registration methods. It is not only overly restrictive and may fail to capture anatomically plausible deformations, but also might not be suitable in many real-world clinical applications where local discontinuities and pathology-induced topology changes occur. Consequently, modern registration frameworks should shift their focus toward flexible, problem specific regularization strategies that can accommodate real-world scenarios and that can handle missing correspondences.

Limited anatomical diversity in the evaluation of problem specific regularization: To effectively assess problem specific regularization in medical image registration, the evaluation must consider anatomically appropriate anatomies and scenarios. The literature reveals a limited range of anatomical structures for evaluation. It is dominated by the *brain*, which is the most commonly studied anatomy for regularization strategies involving structure specific smoothness, physical properties, multistructure topological consistency, and topological changes. The *lungs* are the second most studied anatomy, particularly for addressing sliding motion and local rigidity. Less explored are cardiac data to evaluate cyclic motion and liver data in the context of sliding motion regularization. Moreover, brain and cardiac data dominate learned regularization.

Exceptions include single studies that use private data for evaluation. These special cases involve prostate images in the context of learned deformation spaces (Hu et al., 2015, 2018a), images of the colon and cervix in the context of topology changes (Suh and Wyatt, 2011; Berendsen et al., 2014a), and knee images for various scenarios (Shen et al., 2019a,b; Xu and Niethammer, 2019; Greer et al., 2021). In the context of multistructure registration, exceptions include abdominal, head and neck, and prostate images, e.g., in Freiman et al. (2011), Greene et al. (2009), Hu et al. (2018c), Großbröhmer and Heinrich (2024). However, such data are not used for benchmarking of different methods.

This observed narrow anatomical diversity may result from the **limited availability of diverse, open-access data**. More diverse data that include pathological, longitudinal, and pre-to-post resection images are needed to increase the meaningfulness of method evaluation. Of particular value would be large multiorgan abdominal data, as they align well with many problem specific regularization categories. These include varying organ specific properties, multiorgan topology preservation, local rigidity of bones, sliding motion, and changing topologies within the gastrointestinal tract. The open availability of such data would not only improve the transferability of regularization methods to clinical practice but also facilitate more robust and comparative evaluation across different approaches. Overall, more diverse evaluation scenarios will be critical in driving the field forward.

Simplified evaluation of regularization properties: Evaluating the effectiveness of regularization in image registration remains challenging due to the lack of ground truth deformations. Commonly used measures, such as the fraction of negative Jacobian determinants, assess smoothness and related properties such as inverse-consistency, diffeomorphism, and invertibility. However, these measures alone fail to capture the physical realism of deformations. For instance, sliding motion can increase folding, which leads to higher fractions of negative Jacobian determinants despite being anatomically realistic (Heinrich et al., 2010). In the case that registration involves multistructure segmentations, overlap measures such as the Dice score or Hausdorff distance are often employed – even though it is well-known that they do not necessarily reflect the registration accuracy (Rohlfing, 2012). Moreover, recent work by Liu et al. (2024) demonstrates that the commonly used finite difference approximation of the Jacobian determinant fails to capture all foldings in practice, and therefore does not reliably indicate whether a deformation is truly diffeomorphic. The authors propose to measure the non-diffeomorphic volume instead, which more accurately quantifies the extent of deformation irregularities.

More targeted measures have been proposed for specific scenarios. For instance, sliding motion has been evaluated with the maximum shear, calculated via eigenvalue decomposition of the shear tensor (PapieÅ¼ et al., 2014; Goksel et al., 2016) or the angle between the normal direction and variation in normal motion (Schmidt-Richberg et al., 2012). In the context of learned deformation spaces, the reconstruction error provides a measure of deformation plausibility. Yet, such targeted metrics are rarely employed in evaluating registration frameworks that incorporate problem specific or learned regularization. Overall, there is a strong need to develop more sophisticated measures to assess complex and local deformation properties, for instance, for evaluating local rigidity and topological changes.

Translation of problem specific regularization to clinical practice is hindered: Despite the variety of regularization methods developed for specific registration tasks, their translation to clinical practice faces several challenges. In addition to the frequent reliance on global smoothness regularization, as discussed above, simplified conditions in problem specific regularization cause difficulties and require careful consideration. Examples include the assumption of linear sliding boundaries, as in Schmidt-Richberg et al. (2012), Delmon et al. (2011), and single rigid regions, as in Lester et al. (1999). Such assumptions limit their applicability to more complex real-world scenarios.

Additionally, the inherently **subject- and instance-specific** nature of registration problems poses a significant hurdle for generalizing problem specific regularization techniques across different patients. For instance, cyclic constraints are not suitable for patients with arrhythmia (Wiputra et al., 2020), and physical properties such as tissue elasticity can vary due to individual factors such as age (Cocciolone et al., 2018). These challenges highlight the importance of robust and generalizable regularization methods that can adapt to individual registration problems and they show that the successful application of problem specific regularization remains in the hands of the user.

Suitable regularization for a given registration problem depends on many factors: The taxonomy proposed in this work may serve as a practical starting point to systematically narrow down the search space based on the nature of the data. Additional guiding principles (Fig. 8) can assist developers in selecting a suitable method by considering the application and algorithmic context and available resources:

- *Application setting:* The overall setting in which the algorithm is applied needs to be considered. For example, intra-patient registration typically benefits from anatomically plausible or diffeomorphic transformations, especially in serial imaging where small deformations are present. In contrast, inter-patient or longitudinal registration may require more flexibility due to larger or non-biological deformations.
- *Downstream task:* It should be considered how the registration result is used in practice. For instance, if the registration is employed as an integral part of an automated lesion analysis pipeline, allowing topology changes may be useful. In contrast, for manual comparison by a clinician, preserving lesion volume and shape may be preferred.
- *Anatomical and regional focus:* Sometimes it may not be necessary to take the whole image into account and the focus can be on the accurate registration of individual anatomical structures or image regions. In this case, spatially adaptive regularization that specifically targets the properties of the image parts in focus can be considered. For example, if the registration of bone structures is in focus, regularization that can precisely ensure rigidity should be chosen.
- *Data availability:* When deciding whether to use learned regularization, the availability of training data is crucial - not only in terms of quantity but also representativeness. For instance, when the available training data consists of longitudinal exhale-only lung images, it might not be useful to select a regularization method that models sliding motion. Moreover, the availability of public datasets and statistical motion models can influence method selection.
- *Availability of auxiliary information:* In most cases, spatially adaptive regularization is preferred over global regularization. Thus, it should always be considered whether manually annotated or automatically generated segmentation maps can be obtained. These maps can be used to inform spatially varying regularization terms, for example by adapting smoothness constraints at organ boundaries or enforcing structure-specific deformation properties.
- *Computational constraints:* Naturally, computational aspects constrain the method choice. In particular, the constraints of the final device on which the downstream task is performed, as well as the application constraints, are crucial. For instance, in time critical settings and real-time applications, efficient methods like low order constraints or implicit regularization may be preferable to complex methods such as PDE-based models.

These factors should be carefully considered for each registration task. We regard the design of the regularization strategy as a core component of algorithm development, equally important as choosing the image similarity measure or hyperparameter tuning in learning-based methods. Overall, we encourage the community to consider less commonly applied alternatives when they better align with the specific

application			resources				algorithm
application setting	downstream task	structural focus	auxiliary information	training data	open source resources	runtime / development resources	deformation model
intra-patient serial longitudinal inter-patient lesion presence	quantitative analysis manual comparison by clinician	whole image individual structure localized region	segmentation maps landmarks	reflecting the desired deformation properties big enough	similar datasets for training statistical motion models	real-time registration development constraints runtime / downstream device constraints	implicit deformation properties

Fig. 8. Many factors can influence the choice of the regularization method. They should be assessed carefully for every registration problem. Identification of a suitable method should be considered as an integral part of registration algorithm development.

requirements of a registration problem, rather than defaulting to standard choices like the $\mathcal{L}_2$ norm.

This manuscript is intended as a starting point for guiding the regularization method selection. For more detailed and practical guidance, an in-depth evaluation that systematically compares regularization methods across datasets and tasks, as well as sets them in the context of the aspects discussed above, would be highly valuable for the community. Such an evaluation is beyond the scope of this review and we identify it as a key direction for future work in the field.

Given the rapid advancements of deep learning research, we anticipate further developments in methods that can precisely and automatically tailor regularization to individual image pairs and leverage advanced deep learning architectures to capture feasible and local deformation properties more effectively. Recent innovations, such as the conditional regularization approaches proposed by Hoopes et al. (2021), Mok and Chung (2021a), have introduced a paradigm shift in learning-based registration towards adapting the regularization to user requirements at test time while offering high registration speed. Overall, user interaction for adaptive regularization at test time could gain importance in the future.

Another promising direction involves exploiting advanced deep learning architectures for regularization purposes, as done with physics-informed networks (PINNs) and Lipschitz-continuous ResNet blocks to solve biomechanics-inspired and diffeomorphic PDEs (Joshi and Hong, 2022; Arratia LÃ³pez et al., 2023; Min et al., 2023), or with attention mechanisms to provide targeted control over local regions during registration (Feng et al., 2024). Beyond this, fully automated adaptation of regularization to given registration instances represents a compelling direction for future research. An already versatile smoothness regularization is offered by the GradICON regularization (Tian et al., 2023) which has demonstrated robust smoothness across diverse datasets without requiring customized regularization strategies. It is successfully leveraged in the recently introduced UniGradICON framework (Tian et al., 2024), presented as the first foundation model for image registration. Further advanced approaches, such as Auto-ML frameworks (Fan et al., 2023) for automatic regularization learning or data-driven general purpose regularization, remain to be explored.

5. Conclusion

Regularization is a fundamental building block of image registration. It ensures that derived deformations align with physical and anatomical plausibility. This review systematically classified the wide range of proposed regularization methods in the literature. Three main categories were identified: (i) *model based regularization* that uses prior assumptions, (ii) *problem specific regularization* that incorporates prior data knowledge, and (iii) *learned regularization* that derives deformation properties from training data. Each category addresses distinct challenges in registration while contributing to the ongoing advancements of medical image registration.

Model based regularization remains the foundation of both conventional and learning-based registration algorithms. Techniques such as L_2-norm smoothness and diffeomorphic registration offer robust and interpretable frameworks, which have been effectively integrated into registration networks, for instance, through differentiable regularization layers and explicit training loss terms. However, while their handcrafted nature facilitates interpretability, the global assumptions often limit their ability to model complex and heterogeneous deformations seen in clinical data.

Problem specific regularization addresses these limitations by leveraging spatial and contextual knowledge to enable more realistic deformation modeling. By locally adapting the deformation properties, these methods are suitable for challenging scenarios, including sliding motion, topological changes, and organ specific deformation properties. Despite their potential, their dependency on high quality spatial information and their design toward specific registration problems can restrict their scalability and generalizability, particularly in learning-based registration. While many problem specific regularization methods have already been successfully adapted to learning-based frameworks, some remain to be transferred.

Learned regularization leverages data-driven techniques to learn deformation properties from a training dataset, enabling more flexible solutions. The parameterization of the regularization as neural networks opens new opportunities, such as learning low-dimensional feasible deformation spaces and exploiting the inherent properties of advanced architectures for regularization purposes. A key innovation is test time regularization within learning-based registration frameworks, which offers adaptation to subject- and instance-specific deformation properties of human body motion. An open challenge is posed by the limited interpretability and need for additional training datasets compared to model based and problem specific methods.

Looking ahead, hybrid regularization methods that combine the interpretability and robustness of model based methods with the adaptability of learned techniques are particularly promising. Additionally, fully automated regularization adaptation and general purpose methods may gain importance in the future. We want to emphasize the strong need for (i) more diverse open-access registration datasets that represent a broader spectrum of anatomical and pathological conditions, and (ii) improved evaluation measures that assess local deformation properties, which are equally critical for driving the field forward. By addressing the presented research gaps, regularization can play an even greater role in improving the accuracy, reliability, and applicability of image registration in clinical practice.

This review has highlighted the importance of regularization, which persists today in the era of learning-based image registration, and demonstrated that it is a rapidly evolving research field – alongside the development of novel modern registration algorithms. Advancements in regularization methods for image registration could also impact connected research fields, including motion correction, segmentation, and medical image reconstruction. We hope that this review inspires the research community to reconsider regularization strategies in current state-of-the-art registration methods and to explore open challenges and novel developments to further advance the field of image registration methods.

CRediT authorship contribution statement

Anna Reithmeir: Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization; **Veronika Spieker:** Writing – review & editing, Visualization, Methodology, Conceptualization; **Vasiliki Sideri-Lampretsa:** Writing – review & editing; **Daniel Rueckert:** Writing – review & editing; **Julia A. Schnabel:** Writing - review & editing, Supervision, Funding acquisition, Conceptualization; **Veronika A. Zimmer:** Writing - review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Aggrawal, H.O., Andersen, M.S., Modersitzki, J., 2020. An image registration framework for discontinuous mappings along cracks. In: Biomedical Image Registration: 9th International Workshop, WBIR 2020, Portorož, Slovenia, December 1–2, 2020, Proceedings 9. Springer, pp. 163–173.
Ai, D., Liu, D., Wang, Y., fu, T., Huang, Y., Jiang, Y., Song, H., Wang, Y., Liang, P., Yang, J., 2019. Nonrigid registration for tracking incompressible soft tissues with sliding motion. Med. Phys. 46.
Al Safadi, E., Song, X., 2021. Learning-based image registration with meta-regularization. In: Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition, pp. 10928–10937.
Albrecht, T., Luthi, M., Vetter, T., 2008. A statistical deformation prior for non-rigid image and shape registration. In: 2008Del InsThinspace IEEE Conference on Computer Vision and Pattern Recognition, pp. 1–8.
Alvarez, P., Cotin, S., 2024. Deformable image registration with stochastically regularized biomechanical equilibrium. In: 2024Del InsThinspace IEEE International Symposium on Biomedical Imaging (ISBI), pp. 1–5.
Andrade, C.I., Hurtado, D.E., 2021. Inelastic deformable image registration (i-DIR): capturing sliding motion through automatic detection of discontinuities. Mathematics 9 (1).
Arratia LÃ³pez, P., Mella, H., Uribe, S., Hurtado, D.E., Sahli Costabal, F., 2023. WarpPINN: cine-MR image registration with physics-informed neural networks. Med. Image Anal. 89, 102925.
Arsigny, V., Commowick, O., Ayache, N., Pennec, X., 2009. A fast and log-euclidean polyaffine framework for locally linear registration. J. Math. Imaging Vis. 33, 222–238.
Arsigny, V., Commowick, O., Pennec, X., Ayache, N., 2006. A log-euclidean framework for statistics on diffeomorphisms. In: Medical Image Computing and Computer-Assisted Intervention (MICCAI). Springer, pp. 924–931.
Arsigny, V., Pennec, X., Ayache, N., 2005. Polyrigid and polyaffine transformations: a novel geometrical tool to deal with non-rigid deformations–application to the registration of histological slices. Med. Image Anal. 9 (6), 507–523.
Ashburner, J., Friston, K.J., 2011. Diffeomorphic registration using geodesic shooting and gauss-newton optimisation. Neuroimage 55, 954–967.
Avants, B.B., Epstein, C.L., Grossman, M., Gee, J.C., 2008. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. Med. Image Anal. 12.
Bai, W., Brady, S.M., 2009. Spatio-temporal image registration for respiratory motion correction in PET imaging. In: 2009Del InsThinspace IEEE International Symposium on Biomedical Imaging: From Nano to Macro, pp. 426–429.
Baid, U., Ghodasara, S., Mohan, S., Bilello, M., Calabrese, E., Colak, E., Farahani, K., Kalpathy-Cramer, J., Kitamura, F.C., Pati, S., et al., 2021. The rsna-asnr-miccai brats 2021 benchmark on brain tumor segmentation and radiogenomic classification. arXiv:2107.02314
Balakrishnan, G., Zhao, A., Sabuncu, M.R., Guttag, J., Dalca, A.V., 2019. Voxelmorph: a learning framework for deformable medical image registration. IEEE Trans. Med. Imaging 38 (8), 1788–1800.
Baluwala, H.Y., Saddi, K.A., Schnabel, J.A., 2011. Elastic registration of chest CT images with log un-biased deformations and rigidity constraint. In: Proceedings - International Symposium on Biomedical Imaging (ISBI), pp. 1235–1238.
Bartlomiej, P., Franklin, J., Heinrich, M.P., Gleeson, F.V., Schnabel, J.A., 2015. Liver motion estimation via locally adaptive over-segmentation regularization. In: Navab, N., Hornegger, J., Wells, W.M., Frangi, A.F. (Eds.), Medical Image Computing and Computer-Assisted Intervention – MICCAI 2015. Springer International Publishing, Cham, pp. 427–434.
Bartłomiej W., P., Franklin, J.M., Heinrich, M.P., Gleeson, F.V., Brady, M., Schnabel, J.A., 2018. Gifted demons: deformable image registration with local structure-preserving regularization using supervoxels for liver applications. J. Med. Imaging 5 (2), 024001.
Beg, M.F., Khan, A., 2007. Symmetric data attachment terms for large deformation image registration. IEEE Trans. Med. Imaging 26, 1179–1189.
Beg, M.F., Miller, M.I., TrouvÃ©, A., Younes, L., 2005. Computing large deformation metric mappings via geodesic flows of diffeomorphisms. Int. J. Comput. Vis. 61.
Berendsen, F.F., Kotte, A.N.T.J., de Leeuw, A. A.C., JÃ¼rgenliemk-Schulz, I.M., Viergever, M.A., Pluim, J.P.W., 2014a. Registration of structurally dissimilar images in MRI-based brachytherapy. Phys. Med. Biol. 59 (15), 4033.
Berendsen, F.F., Kotte, A. N.T.J., Viergever, M.A., Pluim, J. P.W., 2014b. Registration of organs with sliding interfaces and changing topologies. In: Ourselin, S., Styner, M.A. (Eds.), Medical Imaging 2014: Image Processing. International Society for Optics and Photonics. SPIE, p. 90340E.
Berendsen, F.F., van der Heide, U.A., Langerak, T.R., Kotte, A. N.T.J., Pluim, J. P.W., 2013. Free-form image registration regularized by a statistical shape model: application to organ segmentation in cervical MR. Comput. Vision Image Understanding 117 (9), 1119–1127.
Bernard, O., Lalande, A., Zotti, C., Cervenansky, F., Yang, X., Heng, P.-A., Cetin, I., Lekadir, K., Camara, O., Ballester, M. A.G., et al., 2018. Deep learning techniques for automatic MRI cardiac multi-structures segmentation and diagnosis: is the problem solved? IEEE Trans. Med. Imaging 37 (11), 2514–2525.
Bhalodia, R., Elhabian, S.Y., Kavan, L., Whitaker, R.T., 2019. A cooperative autoencoder for population-based regularization of CNN image registration. In: Shen, D., Liu, T., Peters, T.M., Staib, L.H., Essert, C., Zhou, S., Yap, P.-T., Khan, A. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2019. Springer International Publishing, Cham, pp. 391–400.
Bierbrier, J., Gueziri, H.-E., Collins, D.L., 2022. Estimating medical image registration error and confidence: a taxonomy and scoping review. Med. Image Anal. 81, 102531.
Bistoquet, A., Oshinski, J., Å krinjar, O., 2008. Myocardial deformation recovery from cine MRI using a nearly incompressible biventricular model. Med. Image Anal. 12 (1), 69–85.
Bône, A., Vernhet, P., Colliot, O., Durrleman, S., 2020. Learning joint shape and appearance representations with metamorphic auto-encoders. In: Medical Image Computing and Computer Assisted Intervention – MICCAI 2020. Springer International Publishing, Cham, pp. 202–211.
Bookstein, F.L., 1989. Principal warps: thin-plate splines and the decomposition of deformations. IEEE Trans. Pattern Anal. Mach. Intell. 11, 567–585.
Brehm, M., Paysan, P., Oelhafen, M., Kunz, P., Kachelrieß, M., 2012. Self-adapting cyclic registration for motion-compensated cone-beam CT in image-guided radiation therapy. Med. Phys. 39 (12), 7603–7618.
Brett, M., Leff, A.P., Rorden, C., Ashburner, J., 2001. Spatial normalization of brain images with focal lesions using cost function masking. Neuroimage 14 (2), 486–500.
Brock, K.K., Sharpe, M.B., Dawson, L.A., Kim, S.M., Jaffray, D.A., 2005. Accuracy of finite element model-based multi-organ deformable image registration. Med. Phys. 32 (6Part1), 1647–1659.
Broit, C., 1981. Optimal registration of deformed images.
Burger, M., Modersitzki, J., Ruthotto, L., 2013. A hyperelastic regularization energy for image registration. SIAM J. Sci. Comput. 35 (1), B132–B148.
Chen, J., Liu, Y., He, Y., Du, Y., 2023. Spatially-varying regularization with conditional transformer for unsupervised image registration. arXiv preprint arXiv:2303.06168 .
Chen, J., Liu, Y., Wei, S., Bian, Z., Subramanian, S., Carass, A., Prince, J.L., Du, Y., 2024. A survey on deep learning in medical image registration: new technologies, uncertainty, evaluation metrics, and beyond. Med. Image Anal. , 103385.
Chen, K., Derksen, A., Heldmann, S., Hallmann, M., Berkels, B., 2015. Deformable image registration with automatic non-correspondence detection. In: Aujol, J.-F., Nikolova, M., Papadakis, N. (Eds.), Scale Space and Variational Methods in Computer Vision. Springer International Publishing, Cham, pp. 360–371.
Chen, X., Xia, Y., Ravikumar, N., Frangi, A.F., 2021. A deep discontinuity-preserving image registration network. In: Medical Image Computing and Computer Assisted Intervention–MICCAI 2021: 24th International Conference, Strasbourg, France, September 27–October 1, 2021, Proceedings, Part IV 24. Springer, pp. 46–55.
Chen, X., Xia, Y., Ravikumar, N., Frangi, A.F., 2022. Joint segmentation and discontinuity-preserving deformable registration: Application to cardiac cine-mr images. arXiv preprint arXiv:2211.13828 .
Chitphakdithai, N., Duncan, J.S., 2010. Non-rigid registration with missing correspondences in preoperative and postresection brain images. In: Jiang, T., Navab, N., Pluim, J. P.W., Viergever, M.A. (Eds.), Medical Image Computing and Computer-Assisted Intervention – MICCAI 2010. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 367–374.

Choi, S., Hoffman, E.A., Wenzel, S.E., Tawhai, M.H., Yin, Y., Castro, M., Lin, C.-L., 2013. Registration-based assessment of regional lung function via volumetric CT images of normal subjects vs. severe asthmatics. J. Appl. Physiol. 115 (5), 730–742.

Christensen, G.E., 1994. Deformable shape models for anatomy. Washington University in St. Louis.

Christensen, G.E., Johnson, H.J., 2001. Consistent image registration. IEEE Trans. Med. Imaging 20.

Christensen, G.E., Rabbitt, R.D., Miller, M.I., 1996. Deformable templates using large deformation kinematics. IEEE Trans. Image Process. 5, 1435–1447.

Chumchob, N., 2013. Vectorial total variation-based regularization for variational image registration. IEEE Trans. Image Process. 22 (11), 4551–4559.

Chun, S.Y., Fessler, J.A., 2008. Regularized methods for topology-preserving smooth nonrigid image registration using b-spline basis. In: 2008 5Th IEEE International Symposium on Biomedical Imaging: From Nano to Macro, pp. 1099–1102.

Cocciolone, A.J., Hawes, J.Z., Staiculescu, M.C., Johnson, E.O., Murshed, M., Wagenseil, J.E., 2018. Elastin, arterial mechanics, and cardiovascular disease. Am. J. Physiol.-Heart Circul. Physiol. 315 (2), H189–H205.

Commowick, O., Arsigny, V., Isambert, A., Costa, J., Dhermain, F., Bidault, F., Bondiau, P.-Y., Ayache, N., Malandain, G., 2008. An efficient locally affine framework for the smooth registration of anatomical structures. Med. Image Anal. 12 (4), 427–441.

Cui, Z., Mahmoodi, S., Conway, J., Guy, M., Lewis, E., Havelock, T., Bennett, M., 2017. A novel non-rigid registration method based on nonparametric statistical deformation model for medical image analysis. In: 2017Del InsThinspace IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), pp. 1–3.

Czolbe, P.S., Feragen, A., Krause, O., 2021. Spot the difference: detection of topological changes via geometric alignment. In: Ranzato, M., Beygelzimer, A., Dauphin, Y., Liang, P.S., Vaughan, J.W. (Eds.), Advances in Neural Information Processing Systems. Curran Associates, Inc., pp. 14383–14395.

Dalca, A.V., Balakrishnan, G., Guttag, J., Sabuncu, M.R., 2019. Unsupervised learning of probabilistic diffeomorphic registration for images and surfaces. Med. Image Anal. 57.

de Vos, B.D., Berendsen, F.F., Viergever, M.A., Sokooti, H., Staring, M., IÅ¡gum, I., 2019. A deep learning framework for unsupervised affine and deformable image registration. Med. Image Anal. 52, 128–143.

Delmon, V., Rit, S., Pinho, R., Sarrut, D., Delmon, V., 2011. Direction dependent b-splines decomposition for the registration of sliding objects. In: Proceedings of the Fourth International Workshop on Pulmonary Image Analysis, pp. 45–55.

Derksen, A., Heldmann, S., Polzin, T., Berkels, B., 2015. Image registration with sliding motion constraints for 4d CT motion correction. In: Handels, H., Deserno, T.M., Meinzer, H.-P., Tolxdorff, T. (Eds.), Bildverarbeitung Für Die Medizin 2015. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 335–340.

Dong, Q., Du, H., Song, Y., Xu, Y., Liao, J., 2023. Preserving tumor volumes for unsupervised medical image registration. In: Proceedings of the IEEE/CVF International Conference on Computer Vision, pp. 21208–21218.

Drakopoulos, F., Foteinos, P., Liu, Y., Chrisochoides, N.P., 2014. Toward a real time multi-tissue adaptive physics-based non-rigid registration framework for brain tumor resection. Front. Neuroinform. 8.

Duan, B., Zhong, M., Yan, Y., 2023a. Towards saner deep image registration. In: Proceedings of the IEEE/CVF International Conference on Computer Vision (ICCV), pp. 12459–12468.

Duan, J., Jia, X., Bartlett, J., Lu, W., Qiu, Z., 2023b. Arbitrary order total variation for deformable image registration. Pattern Recognit. 137, 109318.

Duan, L., Cao, Y., Wang, Z., Liu, D., Fu, T., Yuan, G., Zheng, J., 2023c. Boundary-aware registration network for 4d-CT lung image with sliding motion. Biomed. Signal Process. Control 86, 105333.

Dupuis, P., Grenander, U., Miller, M.I., 1998. Variational problems on flows of diffeomorphisms for image matching. Q. Appl. Math. 56.

Edwards, P.J., Hill, D. L.G., Little, J.A., Hawkes, D.J., 1998. A three-component deformation model for image-guided surgery. Med. Image Anal. 2 (4), 355–367.

Eiben, B., Tran, E.H., Menten, M.J., Oelfke, U., Hawkes, D.J., McClelland, J.R., 2018. Statistical motion mask and sliding registration. In: Klein, S., Staring, M., Durrleman, S., Sommer, S. (Eds.), Biomedical Image Registration. Springer International Publishing, Cham, pp. 13–23.

Elmahdy, M.S., Beljaards, L., Yousefi, S., Sokooti, H., Verbeek, F., Van Der Heide, U.A., Staring, M., 2021. Joint registration and segmentation via multi-task learning for adaptive radiotherapy of prostate cancer. IEEE Access 9, 95551–95568.

Estienne, T., Vakalopoulou, M., Battistella, E., Henry, T., Lerousseau, M., Leroy, A., Paragios, N., Deutsch, E., 2021. Mics : Multi-steps, inverse consistency and symmetric deep learning registration network. arXiv:2111.12123.

Estienne, T., Vakalopoulou, M., Christodoulidis, S., Battistela, E., Lerousseau, M., Carre, A., Klausner, G., Sun, R., Robert, C., Mougiakakou, S., Paragios, N., Deutsch, E., 2019. U-ReSNet: ultimate coupling of registration and segmentation with deep nets. In: Shen, D., Liu, T., Peters, T.M., Staib, L.H., Essert, C., Zhou, S., Yap, P.-T., Khan, A. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2019. Springer International Publishing, Cham, pp. 310–319.

Fan, X., Li, Z., Li, Z., Wang, X., Liu, R., Luo, Z., Huang, H., 2023. Automated learning for deformable medical image registration by jointly optimizing network architectures and objective functions. IEEE Trans. Image Process. 32, 4880–4892.

Fechter, T., Baltas, D., 2019. One-shot learning for deformable medical image registration and periodic motion tracking. IEEE Trans. Med. Imaging 39, 2506–2517.

Feng, Y., Zheng, Y., Huang, D., Wei, J., Liu, T., Wang, Y., Liu, Y., 2024. Stepwise corrected attention registration network for preoperative and follow-up magnetic resonance imaging of glioma patients. Bioengineering 11 (9).

Ferrante, E., Paragios, N., 2017. Slice-to-volume medical image registration: a survey. Med. Image Anal. 39, 101–123.

Fidon, L., Ebner, M., Garcia-Peraza-Herrera, L.C., Modat, M., Ourselin, S., Vercauteren, T., 2019. Incompressible image registration using divergence-conforming b-splines. In: Shen, D., Liu, T., Peters, T.M., Staib, L.H., Essert, C., Zhou, S., Yap, P.-T., Khan, A. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2019. Springer International Publishing, Cham, pp. 438–446.

Fischer, B., Modersitzki, J., 2004. A unified approach to fast image registration and a new curvature based registration technique. Linear Algebra Appl. 380, 107–124.

Forsberg, D., Andersson, M., Knutsson, H., 2010. Adaptive anisotropic regularization of deformation fields for non-rigid registration using the morphon framework. In: 2010Del InsThinspace IEEE International Conference on Acoustics, Speech and Signal Processing, pp. 473–476.

François, A., Gori, P., Glaunès, J., 2021. Metamorphic image registration using aÂ semi-lagrangian scheme. In: Nielsen, F., Barbaresco, F. (Eds.), Geometric Science of Information. Springer International Publishing, Cham, pp. 781–788.

François, A., Maillard, M., Oppenheim, C., Pallud, J., Bloch, I., Gori, P., Glaunès, J., 2022. Weighted metamorphosis forÂ registration ofÂ images withÂ different topologies. In: Hering, A., Schnabel, J., Zhang, M., Ferrante, E., Heinrich, M., Rueckert, D. (Eds.), Biomedical Image Registration. Springer International Publishing, Cham, pp. 8 –17.

Freiman, M., Voss, S.D., Warfield, S.K., 2011. Demons registration with local affine adaptive regularization: application to registration of abdominal structures. In: 2011Del InsThinspace IEEE International Symposium on Biomedical Imaging: From Nano to Macro, pp. 1219–1222.

Fu, Y., Lei, Y., Wang, T., Curran, W.J., Liu, T., Yang, X., 2020. Deep learning in medical image registration: a review. Phys. Med. Biol. 65 (20).

Fu, Y., Liu, S., Li, H.H., Li, H., Yang, D., 2018. An adaptive motion regularization technique to support sliding motion in deformable image registration. Med. Phys. 45 (2), 735–747.

Gao, X., Tao, R., Zheng, G., 2022. Bidmir: bi-directional medical image registration with symmetric attention and cyclic consistency regularization. In: 2022Del InsThinspace IEEE 19Th International Symposium on Biomedical Imaging (ISBI), pp. 1–5.

Gao, X., Van Houtte, J., Chen, Z., Zheng, G., 2021. DeepASDM: a deep learning framework for affine and deformable image registration incorporating a statistical deformation model. In: 2021Del InsThinspace IEEE EMBS International Conference on Biomedical and Health Informatics (BHI), pp. 1–4.

Goksel, O., Vishnevsky, V., Carrillo, A.G., Tanner, C., 2016. Imaging of sliding visceral interfaces during breathing. In: 2016Del InsThinspace IEEE 13Th International Symposium on Biomedical Imaging (ISBI), pp. 298–301.

Gong, L., Duan, L., Dai, Y., He, Q., Zuo, S., Fu, T., Yang, X., Zheng, J., 2020. Locally adaptive total p-variation regularization for non-rigid image registration with sliding motion. IEEE Trans. Biomed. Eng. 67, 2560–2571.

Greene, W.H., Chelikani, S., Purushothaman, K., Knisely, J., Chen, Z., Papademetris, X., Staib, L.H., Duncan, J.S., 2009. Constrained non-rigid registration for use in image-guided adaptive radiotherapy. Med. Image Anal. 13 (5), 809–817.

Greer, H., Kwitt, R., Vialard, F.-X., Niethammer, M., 2021. Icon: learning regular maps through inverse consistency. In: 2021Del InsThinspace IEEE/CVF International Conference on Computer Vision (ICCV), pp. 3376–3385.

Greer, H., Tian, L., Vialard, F.-X., Kwitt, R., Bouix, S., San Jose Estepar, R., Rushmore, R., Niethammer, M., 2023. Inverse consistency byÂ construction forÂ multistep deep registration. In: Greenspan, H., Madabhushi, A., Mousavi, P., Salcudean, S., Duncan, J., Syeda-Mahmood, T., Taylor, R. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2023. Springer Nature Switzerland, Cham, pp. 688 –698.

Großbröhmer, C., Heinrich, M.P., 2024. Generalised 3d medical image registration withÂ learned shape encodings. In: Waiter, G., Lambrou, T., Leontidis, G., Oren, N., Morris, T., Gordon, S. (Eds.), Medical Image Understanding and Analysis. Springer Nature Switzerland, Cham, pp. 268–280.

Gu, D., Cao, X., Liu, G., Shen, D., Xue, Z., 2021. Multiresolution registration network (MRN) hierarchy with prior knowledge learning. In: Lian, C., Cao, X., Rekik, I., Xu, X., Yan, P. (Eds.), Machine Learning in Medical Imaging. Springer International Publishing, Cham, pp. 61–69.

Haak, A.J., Tan, Q., Tschumperlin, D.J., 2018. Matrix biomechanics and dynamics in pulmonary fibrosis. Matrix Biol. 73, 64–76.

Haber, E., Heldmann, S., Modersitzki, J., 2009. A framework for image-based constrained registration with an application to local rigidity. Linear Algebra Appl. 431 (459), 70.

Haber, E., Modersitzki, J., 2004. Numerical methods for volume preserving image registration. Inverse Probl. 20 (5), 1621.

Haber, E., Modersitzki, J., 2007. Image registration with guaranteed displacement regularity. Int. J. Comput. Vis. 71 (3), 361–372.

Han, L., Dong, H., McClelland, J.R., Han, L., Hawkes, D.J., Barratt, D.C., 2017. A hybrid patient-specific biomechanical model based image registration method for the motion estimation of lungs. Med. Image Anal. 39, 87–100.

Han, X., Shen, Z., Xu, Z., Bakas, S., Akbari, H., Bilello, M., Davatzikos, C., Niethammer, M., 2020. A deep network for joint registration and reconstruction of images with pathologies. Mach. Learn. Med. Imaging. MLMI 12436, 342–352.

Hansen, L., Heinrich, M.P., 2021. Graphregnet: deep graph regularisation networks on sparse keypoints for dense registration of 3d lung CTs. IEEE Trans. Med. Imaging 40 (9), 2246–2257.

van Harten, L.D., Stoker, J., IÅ¡gum, I., 2024. Robust deformable image registration using cycle-consistent implicit representations. IEEE Trans. Med. Imaging 43 (2), 784–793.

Haskins, G., Kruger, U., Yan, P., 2020. Deep learning in medical image registration: a survey. Mach. Vis. Appl. 31 (1), 8.

He, T., Xue, Z., Xie, W., Wong, S. T.C., 2010. Online 4-d CT estimation for patient-specific respiratory motion based on real-time breathing signals. In: Jiang, T., Navab, N., Pluim, J. P.W., Viergever, M.A. (Eds.), Medical Image Computing and Computer-Assisted Intervention – MICCAI 2010. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 392–399.
Heinrich, M.P., Handels, H., Simpson, I. J.A., 2015. Estimating large lung motion in COPD patients by symmetric regularised correspondence fields. In: Navab, N., Hornegger, J., Wells, W.M., Frangi, A. (Eds.), Medical Image Computing and Computer-Assisted Intervention – MICCAI 2015. Springer International Publishing, Cham, pp. 338–345.
Heinrich, M.P., Hansen, L., 2022. Voxelmorph + + going beyond the cranial vault with keypoint supervision and multi-channel instance optimisation. In: International Workshop on Biomedical Image Registration. Springer, pp. 85–95.
Heinrich, M.P., Jenkinson, M., Brady, M., Schnabel, J., 2010. Discontinuity preserving regularisation for variational optical-flow registration using the modified lp norm. Med. Image Anal. Clin.: Grand Chall. , 185–194.
Hering, A., van Ginneken, B., Heldmann, S., 2019. MlVIRNET: multilevel variational image registration network. In: Shen, D., Liu, T., Peters, T.M., Staib, L.H., Essert, C., Zhou, S., Yap, P.-T., Khan, A. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2019. Springer International Publishing, Cham, pp. 257 –265.
Hering, A., Hansen, L., Mok, T. C.W., Chung, A. C.S., Siebert, H., HÃ¤ger, S., Lange, A., Kuckertz, S., Heldmann, S., Shao, W., Vesal, S., Rusu, M., Sonn, G., Estienne, T., Vakalopoulou, M., Han, L., Huang, Y., Yap, P.-T., Brudfors, M., Balbastre, Y., Joutard, S., Modat, M., Lifshitz, G., Raviv, D., Lv, J., Li, Q., Jaouen, V., Visvikis, D., Fourcade, C., Rubeaux, M., Pan, W., Xu, Z., Jian, B., De Benetti, F., Wodzinski, M., Gunnarsson, N., SjÃ¶lund, J., Grzech, D., Qiu, H., Li, Z., Thorley, A., Duan, J., Großbröhmer, C., Hoopes, A., Reinertsen, I., Xiao, Y., Landman, B., Huo, Y., Murphy, K., Lessmann, N., van Ginneken, B., Dalca, A.V., Heinrich, M.P., 2023. Learn2reg: comprehensive multi-task medical image registration challenge, dataset and evaluation in the era of deep learning. IEEE Trans. Med. Imaging 42 (3), 697–712.
Hinkle, J., Fletcher, P.T., Wang, B., Salter, B., Joshi, S., 2009. 4D MAP image reconstruction incorporating organ motion. In: Prince, J.L., Pham, D.L., Myers, K.J. (Eds.), Information Processing in Medical Imaging. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 676–687.
Honkamaa, J., Marttinen, P., 2024. Sitreg: Multi-resolution architecture for symmetric, inverse consistent, and topology preserving image registration. arXiv preprint arXiv:2303.10211
Hoopes, A., Hoffmann, M., Fischl, B., Guttag, J., Dalca, A.V., 2021. Hypermorph: amortized hyperparameter learning for image registration. In: Information Processing in Medical Imaging (IPMI). Vol. 12729, p. 3–17.
Horn, B. K.P., Schunck, B.G., 1981. Determining optical flow. Artif. Intell. 17 (1–3), 185–203.
Hu, Y., Gibson, E., Ahmed, H.U., Moore, C.M., Emberton, M., Barratt, D.C., 2015. Population-based prediction of subject-specific prostate deformation for MR-to-ultrasound image registration. Med. Image Anal. 26 (1), 332–344.
Hu, Y., Gibson, E., Ghavami, N., Bonmati, E., Moore, C.M., Emberton, M., Vercauteren, T., Noble, J.A., Barratt, D.C., 2018a. Adversarial deformation regularization for training image registration neural networks. In: Frangi, A.F., Schnabel, J.A., Davatzikos, C., Alberola-López, C., Fichtinger, G. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2018. Springer International Publishing, Cham, pp. 774–782.
Hu, Y., Modat, M., Gibson, E., Ghavami, N., Bonmati, E., Moore, C.M., Emberton, M., Noble, J.A., Barratt, D.C., Vercauteren, T., 2018b. Label-driven weakly-supervised learning for multimodal deformable image registration. In: 2018Del InsThinspace IEEE 15Th International Symposium on Biomedical Imaging (ISBI 2018), pp. 1070–1074.
Hu, Y., Modat, M., Gibson, E., Li, W., Ghavami, N., Bonmati, E., Wang, G., Bandula, S., Moore, C.M., Emberton, M., Ourselin, S., Noble, J.A., Barratt, D.C., Vercauteren, T., 2018c. Weakly-supervised convolutional neural networks for multimodal image registration. Med. Image Anal. 49, 1–13.
Hu, Y., Morgan, D., Ahmed, H.U., Pendsé, D., Sahu, M., Allen, C., Emberton, M., Hawkes, D., Barratt, D., 2008. A statistical motion model based on biomechanical simulations for data fusion during image-guided prostate interventions. In: Metaxas, D., Axel, L., Fichtinger, G., Székely, G. (Eds.), Medical Image Computing and Computer-Assisted Intervention – MICCAI 2008. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 737–744.
Hua, R., Pozo, J.M., Taylor, Z.A., Frangi, A.F., 2017. Multiresolution extended free-form deformations (XFFD) for non-rigid registration with discontinuous transforms. Med. Image Anal. 36, 113–122.
Huang, C., Chen, K., Huang, M., Kong, D., Yuan, J., 2024. Topology-preserving image registration with novel multi-dimensional beltrami regularization. Appl. Math. Model. 125, 539–556.
Huang, W., Yang, H., Liu, X., Li, C., Zhang, I., Wang, R., Zheng, H., Wang, S., 2021. A coarse-to-fine deformable transformation framework for unsupervised multi-contrast MR image registration with dual consistency constraint. IEEE Trans. Med. Imaging 40 (10), 2589–2599.
Jia, X., Thorley, A., Chen, W., Qiu, H., Shen, L., Styles, I.B., Chang, H.J., Leonardis, A., de Marvao, A., O'Regan, D.P., Rueckert, D., Duan, J., 2022. Learning a model-driven variational network for deformable image registration. IEEE Trans. Med. Imaging 41 (1), 199–212.
Joshi, A., Hong, Y., 2022. Diffeomorphic image registration using lipschitz continuous residual networks. In: Konukoglu, E., Menze, B., Venkataraman, A., Baumgartner, C., Dou, Q., Albarqouni, S. (Eds.), Proceedings of the 5Th International Conference on Medical Imaging with Deep Learning. PMLR, pp. 605–617.
Joshi, A., Hong, Y., 2023a. Metaregnet: metamorphic image registration using flow-driven residual networks. In: Qin, W., Zaki, N., Zhang, F., Wu, J., Yang, F., Li, C. (Eds.), Computational Mathematics Modeling in Cancer Analysis. Springer Nature Switzerland, Cham, pp. 160–170.
Joshi, A., Hong, Y., 2023b. R2net: Efficient and flexible diffeomorphic image registration using lipschitz continuous residual networks. Med. Image Anal. 89, 102917.
Jud, C., Giger, A., SandkÃ¼hler, R., Cattin, P.C., 2017a. A localized statistical motion model as a reproducing kernel for non-rigid image registration. In: Descoteaux, M., Maier-Hein, L., Franz, A., Jannin, P., Collins, D.L., Duchesne, S. (Eds.), Medical Image Computing and Computer-Assisted Intervention - MICCAI 2017. Springer International Publishing, Cham, pp. 261–269.
Jud, C., Möri, N., Bitterli, B., Cattin, P.C., 2016. Bilateral regularization in reproducing kernel hilbert spaces for discontinuity preserving image registration. In: Wang, L., Adeli, E., Wang, Q., Shi, Y., Suk, H.-I. (Eds.), Machine Learning in Medical Imaging. Springer International Publishing, Cham, pp. 10–17.
Jud, C., Sandkühler, R., Cattin, P.C., 2018. An inhomogeneous multi-resolution regularization concept for discontinuity preserving image registration. In: Klein, S., Staring, M., Durrleman, S., Sommer, S. (Eds.), Biomedical Image Registration. Springer International Publishing, Cham, pp. 3–12.
Jud, C., Sandkühler, R., Möri, N., Cattin, P.C., 2017b. Directional averages for motion segmentation in discontinuity preserving image registration. In: Descoteaux, M., Maier-Hein, L., Franz, A., Jannin, P., Collins, D.L., Duchesne, S. (Eds.), Medical Image Computing and Computer Assisted Intervention - MICCAI 2017. Springer International Publishing, Cham, pp. 249–256.
Kabus, S., Franz, A., Fischer, B., 2005. On elastic image registration with varying material parameters. In: Meinzer, H.-P., Handels, H., Horsch, A., Tolxdorff, T. (Eds.), Bildverarbeitung Für Die Medizin 2005. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 330–334.
Keall, P.J., Joshi, S., Vedam, S.S., Siebers, J.V., Kini, V.R., Mohan, R., 2005a. Four-dimensional radiotherapy planning for DMLC-based respiratory motion tracking. Med. Phys. 32 (4), 942–951.
Keall, P.J., Joshi, S., Vedam, S.S., Siebers, J.V., Kini, V.R., Mohan, R., 2005b. Four-dimensional radiotherapy planning for DMLC-based respiratory motion tracking. Med. Phys. 32 (4), 942–951.
Kearney, V., Chen, S., Gu, X., Chiu, T., Liu, H., Jiang, L., Wang, J., Yordy, J., Nedzi, L., Mao, W., 2014. Automated landmark-guided deformable image registration. Phys. Med. Biol. 60 (1), 101.
Khor, H.G., Ning, G., Sun, Y., Lu, X., Zhang, X., Liao, H., 2023. Anatomically constrained and attention-guided deep feature fusion for joint segmentation and deformable medical image registration. Med. Image Anal. 88, 102811.
Kim, B., Kim, D.H., Park, S.H., Kim, J., Lee, J.-G., Ye, J.C., 2021. Cyclemorph: cycle consistent unsupervised deformable image registration. Med. Image Anal. 71, 102036.
Kim, M.-J., Kim, M.-H., Shen, D., 2008. Learning-based deformation estimation for fast non-rigid registration. In: 2008Del InsThinspace IEEE Computer Society Conference on Computer Vision and Pattern Recognition Workshops, pp. 1–6.
King, A.P., Buerger, C., Tsoumpas, C., Marsden, P.K., Schaeffter, T., 2012. Thoracic respiratory motion estimation from MRI using a statistical model and a 2-d image navigator. Med. Image Anal. 16 (1), 252–264.
Krebs, J., Delingette, H., Mailhé, B., Ayache, N., Mansi, T., 2018. Learning a probabilistic model for diffeomorphic registration. IEEE Trans. Med. Imaging 38, 2165 –2176.
Lai, X., Yang, W., Wang, L., Ying, S., 2023. Image registration with learned regularization. In: 2023 China Automation Congress (CAC), pp. 6592–6597.
Ledesma-Carbayo, M.J., Kybic, J., Desco, M., Santos, A., Suhling, M., Hunziker, P., Unser, M., 2005. Spatio-temporal nonrigid registration for ultrasound cardiac motion estimation. IEEE Trans. Med. Imaging 24 (9), 1113–1126.
Leow, A., Huang, S.-C., Geng, A., Becker, J., Davis, S., Toga, A., Thompson, P., 2005. Inverse consistent mapping in 3d deformable image registration: its construction and statistical properties. In: Information Processing in Medical Imaging: 19Th International Conference, IPMI 2005, Glenwood Springs, CO, USA, July 10Del-Ins–15, 2005. Proceedings 19. Springer, pp. 493–503.
Lester, H., Arridge, S.R., Jansons, K.M., Lemieux, L., Hajnal, J.V., Oatridge, A., 1999. Non-linear registration with the variable viscosity fluid algorithm. In: Kuba, A., Šáamal, M., Todd-Pokropek, A. (Eds.), Information Processing in Medical Imaging. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 238–251.
Li, Y., Chen, K., Chen, C., Zhang, J., 2024. A bi-variant variational model for diffeomorphic image registration with relaxed jacobian determinant constraints. Appl. Math. Model. 130, 66–93.
Little, J.A., Hill, D.L.G., Hawkes, D.J., 1997. Deformations incorporating rigid structures. Comput. Vision Image Understanding 66 (2), 223–232.
Liu, Y., Chen, J., Wei, S., Carass, A., Prince, J., 2024. On finite difference jacobian computation in deformable image registration. Int. J. Comput. Vis. 132 (9), 3678–3688.
Liu, Y., Gu, S., 2023. Co-learning semantic-aware unsupervised segmentation forÂ pathological image registration. In: Greenspan, H., Madabhushi, A., Mousavi, P., Salcudean, S., Duncan, J., Syeda-Mahmood, T., Taylor, R. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2023. Springer Nature Switzerland, Cham, pp. 537–547.
Loeckx, D., Maes, F., Vandermeulen, D., Suetens, P., 2003. Non-rigid image registration using a statistical spline deformation model. In: Taylor, C., Noble, J.A. (Eds.), Information Processing in Medical Imaging. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 463–474.
Loeckx, D., Maes, F., Vandermeulen, D., Suetens, P., 2004. Nonrigid image registration using free-form deformations with a local rigidity constraint. In: Barillot, C., Haynor, D.R., Hellier, P. (Eds.), Medical Image Computing and Computer-Assisted Intervention – MICCAI 2004. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 639–646.

Lu, J., Jin, R., Wang, M., Song, E., Ma, G., 2023. A discontinuity-preserving regularization for deep learning-based cardiac image registration. Phys. Med. Biol. 68 (9), 095024.

Lu, Z., Yang, G., Hua, T., Hu, L., Kong, Y., Tang, L., Zhu, X., Dillenseger, J.-L., Shu, H., Coatrieux, J.-L., 2019. Unsupervised three-dimensional image registration using a cycle convolutional neural network. In: 2019Del InsThinspace IEEE International Conference on Image Processing (ICIP), pp. 2174–2178.

Luo, Z., Liu, D., Ai, D., 2023. Unsupervised medical image registration via dynamic adaptive total p-variation regularization. In: Proceedings of the 15Th International Conference on Digital Image Processing, pp. 1–8.

Ma, X., He, J., Liu, X., Liu, Q., Chen, G., Yuan, B., Li, C., Xia, Y., 2023. Hierarchical cumulative network for unsupervised medical image registration. Comput. Biol. Med. 167, 107598.

Mahapatra, D., Ge, Z., Sedai, S., Chakravorty, R., 2018. Joint registration and segmentation of xray images using generative adversarial networks. In: Shi, Y., Suk, H.-I., Liu, M. (Eds.), Machine Learning in Medical Imaging. Springer International Publishing, Cham, pp. 73–80.

Maillard, M., François, A., Glaunès, J., Bloch, I., Gori, P., 2022. A deep residual learning implementation of metamorphosis. In: 2022Del InsThinspace IEEE 19Th International Symposium on Biomedical Imaging (ISBI). IEEE, pp. 1–4.

Mansi, T., Pennec, X., Sermesant, M., Delingette, H., Ayache, N., 2011. Ilogdemons: a demons-based registration algorithm for tracking incompressible elastic biological tissues. Int. J. Comput. Vis. 92, 92–111.

Mansilla, L., Milone, D.H., Ferrante, E., 2020. Learning deformable registration of medical images with anatomical constraints. Neural Networks 124, 269–279.

Matinkia, M., Ray, N., 2024. Learning diffeomorphism for image registration with time-continuous networks using semigroup regularization. arXiv:2405.18684.

Matkovic, L., Lei, Y., Fu, Y., Wang, T., Kesarwala, A.H., Axente, M., Roper, J., Higgins, K., Bradley, J.D., Liu, T., Yang, X., 2024. Deformable lung 4DCT image registration via landmark-driven cycle network. Med. Phys. 51 (3), 1974–1984.

Matl, S., Brosig, R., Baust, M., Navab, N., Demirci, S., 2017. Vascular image registration techniques: a living review. Med. Image Anal. 35, 1–17.

McEachen, J.C., Nehorai, A., Duncan, J.S., 2000. Multiframe temporal estimation of cardiac nonrigid motion. IEEE Trans. Image Process. 9 (4), 651–665.

Metz, C.T., Klein, S., Schaap, M., van Walsum, T., Niessen, W.J., 2011. Nonrigid registration of dynamic medical imaging data using nd+t b-splines and a groupwise optimization approach. Med. Image Anal. 15 (2), 238–249.

Min, Z., Baum, Z. M.C., Saeed, S.U., Emberton, M., Barratt, D.C., Taylor, Z.A., Hu, Y., 2023. Non-rigid medical image registration using physics-informed neural networks. In: Frangi, A., de Bruijne, M., Wassermann, D., Navab, N. (Eds.), Information Processing in Medical Imaging. Springer Nature Switzerland, Cham, pp. 601–613.

Min, Z., Baum, Z. M.C., Saeed, S.U., Emberton, M., Barratt, D.C., Taylor, Z.A., Hu, Y., 2024. Biomechanics-informed non-rigid medical image registration andÂ its inverse material property estimation withÂ linear andÂ nonlinear elasticity. In: Linguraru, M.G., Dou, Q., Feragen, A., Giannarou, S., Glocker, B., Lekadir, K., Schnabel, J.A. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2024. Springer Nature Switzerland, Cham, pp. 564–574.

Modersitzki, J., 2008. Flirt with rigidity-image registration with a local non-rigidity penalty. Int. J. Comput. Vis. 76, 153–163.

Mohamed, A., Zacharaki, E.I., Shen, D., Davatzikos, C., 2006. Deformable registration of brain tumor images via a statistical model of tumor-induced deformation. Med. Image Anal. 10 (5), 752–763. The Eighth International Conference on Medical Imaging and Computer Assisted Intervention - MICCAI 2005.

Mok, T. C.W., Chung, A. C.S., 2020. Large deformation diffeomorphic image registration with laplacian pyramid networks. In: Martel, A.L., Abolmaesumi, P., Stoyanov, D., Mateus, D., Zuluaga, M.A., Zhou, S.K., Racoceanu, D., Joskowicz, L. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2020. Springer International Publishing, Cham, pp. 211–221.

Mok, T. C.W., Chung, A. C.S., 2021a. Conditional deformable image registration with convolutional neural network. In: Medical Image Computing and Computer Assisted Intervention–MICCAI 2021. Springer, pp. 35–45.

Mok, T. C.W., Chung, A. C.S., 2021b. Fast symmetric diffeomorphic image registration with convolutional neural networks. arXiv:2003.09514.

Mok, T. C.W., Chung, A. C.S., 2021c. Large deformation image registration with anatomy-aware laplacian pyramid networks. In: Shusharina, N., Heinrich, M.P., Huang, R. (Eds.), Segmentation, Classification, and Registration of Multi-modality Medical Imaging Data. Springer International Publishing, Cham, pp. 61–67.

Mok, T. C.W., Chung, A. C.S., 2022. Unsupervised deformable image registration withÂ absent correspondences inÂ pre-operative andÂ post-recurrence brain tumor MRI scans. In: Wang, L., Dou, Q., Fletcher, P.T., Speidel, S., Li, S. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2022. Springer Nature Switzerland, Cham, pp. 25–35.

National Lung Screening Trial Research Team, 2011. The national lung screening trial: overview and study design. Radiology 258 (1), 243–253.

Nazib, A., Fookes, C., Salvado, O., Perrin, D., 2021. A multiple decoder cnn for inverse consistent 3d image registration. In: 2021Del InsThinspace IEEE 18Th International Symposium on Biomedical Imaging (ISBI), pp. 904–907.

Ng, E., Ebrahimi, M., 2020. An unsupervised learning approach to discontinuity-preserving image registration. In: Špiclin, Ž., McClelland, J., Kybic, J., Goksel, O. (Eds.), Biomedical Image Registration. Springer International Publishing, Cham, pp. 153–162.

Nie, Z., Yang, X., 2019. Deformable image registration using functions of bounded deformation. IEEE Trans. Med. Imaging 38 (6), 1488–1500.

Nielsen, R.K., Darkner, S., Feragen, A., 2019. Topaware: topology-aware registration. In: Shen, D., Liu, T., Peters, T.M., Staib, L.H., Essert, C., Zhou, S., Yap, P.-T., Khan, A. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2019. Springer International Publishing, Cham, pp. 364–372.

Niethammer, M., Hart, G.L., Pace, D.F., Vespa, P.M., Irimia, A., Van Horn, J.D., Aylward, S.R., 2011. Geometric metamorphosis. In: Fichtinger, G., Martel, A., Peters, T. (Eds.), Medical Image Computing and Computer-Assisted Intervention – MICCAI 2011. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 639–646.

Niethammer, M., Kwitt, R., Vialard, F.-X., 2019. Metric learning for image registration. In: Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition, pp. 8463–8472.

Nithiananthan, S., Schafer, S., Mirota, D.J., Stayman, J.W., Zbijewski, W., Reh, D.D., Gallia, G.L., Siewerdsen, J.H., 2012. Extra-dimensional demons: a method for incorporating missing tissue in deformable image registration. Med. Phys. 39 (9), 5718 –5731.

Onofrey, J.A., Papademetris, X., Staib, L.H., 2015a. Low-dimensional non-rigid image registration using statistical deformation models from semi-supervised training data. IEEE Trans. Med. Imaging 34 (7), 1522–1532.

Onofrey, J.A., Staib, L.H., Sarkar, S., Venkataraman, R., Papademetris, X., 2015b. Learning nonrigid deformations for constrained point-based registration for image-guided MR-TRUS prostate intervention. In: 2015Del InsThinspace IEEE 12Th International Symposium on Biomedical Imaging (ISBI), pp. 1592–1595.

Pace, D., Aylward, S., Niethammer, M., 2013. A locally adaptive regularization based on anisotropic diffusion for deformable image registration of sliding organs. IEEE Trans. Med. Imaging 32.

Pace, D.F., Enquobahrie, A., Yang, H., Aylward, S.R., Niethammer, M., 2011. Deformable image registration of sliding organs using anisotropic diffusive regularization. In: 2011Del InsThinspace IEEE International Symposium on Biomedical Imaging: From Nano to Macro, pp. 407–413.

Pal, S., Tennant, M., Ray, N., 2022. Towards positive jacobian: learn to post-process for diffeomorphic image registration with matrix exponential. In: 2022 26Th International Conference on Pattern Recognition (ICPR), pp. 3391 –3398.

Pan, L., Lima, J. A.C., Osman, N.F., 2003. Fast tracking of cardiac motion using 3d-HARP. In: Taylor, C., Noble, J.A. (Eds.), Information Processing in Medical Imaging. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 611–622.

Papenberg, N., Olesch, J., Lange, T., Schlag, P.M., Fischer, B., 2009. Landmark constrained non-parametric image registration with isotropic tolerances. In: Meinzer, H.-P., Deserno, T.M., Handels, H., Tolxdorff, T. (Eds.), Bildverarbeitung Für Die Medizin 2009. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 122–126.

PapieÅ¼, B.W., Heinrich, M.P., Fehrenbach, J., Risser, L., Schnabel, J.A., 2014. An implicit sliding-motion preserving regularisation via bilateral filtering for deformable image registration. Med. Image Anal. 18 (8), 1299–1311.

Periaswamy, S., Farid, H., 2006. Medical image registration with partial data. Med. Image Anal. 10 (3), 452–464.

Perperidis, D., Mohiaddin, R.H., Rueckert, D., 2005. Spatio-temporal free-form registration of cardiac MR image sequences. Med. Image Anal. 9 (5), 441–456. Medical Image Computing and Computer-Assisted Intervention - MICCAI 2004.

Pock, T., Urschler, M., Zach, C., Beichel, R., Bischof, H., 2007. A duality based algorithm for TV-l1-optical-flow image registration. In: Ayache, N., Ourselin, S., Maeder, A. (Eds.), Medical Image Computing and Computer-Assisted Intervention – MICCAI 2007. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 511–518.

Preiswerk, F., De Luca, V., Arnold, P., Celicanin, Z., Petrusca, L., Tanner, C., Bieri, O., Salomir, R., Cattin, P.C., 2014. Model-guided respiratory organ motion prediction of the liver from 2d ultrasound. Med. Image Anal. 18 (5), 740–751.

Preston, J.S., Joshi, S., Whitaker, R., 2016. Deformation estimation with automatic sliding boundary computation. Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics) 9902 LNCS, 72–80.

Qin, C., Wang, S., Chen, C., Bai, W., Rueckert, D., 2023. Generative myocardial motion tracking via latent space exploration with biomechanics-informed prior. Med. Image Anal. 83, 102682.

Qin, C., Wang, S., Chen, C., Qiu, H., Bai, W., Rueckert, D., 2020. Biomechanics-informed neural networks for myocardial motion tracking in MRI. In: Martel, A.L., Abolmaesumi, P., Stoyanov, D., Mateus, D., Zuluaga, M.A., Zhou, S.K., Racoceanu, D., Joskowicz, L. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2020. Springer International Publishing, Cham, pp. 296–306.

Qiu, A., Younes, L., Miller, M.I., 2012. Principal component based diffeomorphic surface mapping. IEEE Trans. Med. Imaging 31 (2), 302–311.

Qiu, H., Qin, C., Schuh, A., Hammernik, K., Rueckert, D., 2021. Learning diffeomorphic and modality-invariant registration using b-splines. In: Heinrich, M., Dou, Q., de Bruijne, M., Lellmann, J., SchlÃ¤fer, A., Ernst, F. (Eds.), Proceedings of the Fourth Conference on Medical Imaging with Deep Learning. PMLR, pp. 645–664.

Rabbitt, R.D., Weiss, J.A., Christensen, G.E., Miller, M.I., 1995. Mapping of hyperelastic deformable templates using the finite element method. In: Melter, R.A., Wu, A.Y., Bookstein, F.L., Green, W. D.K. (Eds.), Vision Geometry IV. International Society for Optics and Photonics. SPIE, pp. 252 – 265.

Ramon-Julvez, U., Hernandez, M., Mayordomo, E., 2024. Epdiff-jf-net: adjoint jacobi fields for diffeomorphic registration networks. In: 2024Del InsThinspace IEEE International Symposium on Biomedical Imaging (ISBI), pp. 1–5.

Raveendran, V., Spieker, V., Braren, R.F., Karampinos, D.C., Zimmer, V.A., Schnabel, J.A., 2024. Segmentation-guided medical image registration. In: Maier, A., Deserno, T.M., Handels, H., Maier-Hein, K., Palm, C., Tolxdorff, T. (Eds.), Bildverarbeitung Für Die Medizin 2024. Springer Fachmedien Wiesbaden, Wiesbaden, pp. 33–38.

Reinhardt, J.M., Ding, K., Cao, K., Christensen, G.E., Hoffman, E.A., Bodas, S.V., 2008. Registration-based estimates of local lung tissue expansion compared to xenon CT measures of specific ventilation. Med. Image Anal. 12 (6), 752–763.

Reithmeir, A., Felsner, L., Braren, R., Schnabel, J.A., Zimmer, V.A., 2024a. Data-driven tissue- andÂ subject-specific elastic regularization forÂ medical image registration. In: Linguraru, M.G., Dou, Q., Feragen, A., Giannarou, S., Glocker, B., Lekadir, K., Schnabel,

J.A. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2024. Springer Nature Switzerland, Cham, pp. 575–585.
Reithmeir, A., Schnabel, J.A., Zimmer, V.A., 2024b. Learning physics-inspired regularization for medical image registration with hypernetworks. In: Medical Imaging 2024: Image Processing. Vol. 12926. SPIE, pp. 625–635.
Ringel, M., Heiselman, J., Richey, W., Meszoely, I., Miga, M., 2023. Regularized kelvinlet functions to model linear elasticity for image-to-physical registration of the breast. In: Greenspan, H., Madabhushi, A., Mousavi, P., Salcudean, S., Duncan, J., Syeda-Mahmood, T., Taylor, R. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2023. Springer Nature Switzerland, Cham, pp. 344–353.
Risholm, P., Samset, E., Talos, I.-F., Wells, W., 2009. A non-rigid registration framework that accommodates resection and retraction. In: Prince, J.L., Pham, D.L., Myers, K.J. (Eds.), Information Processing in Medical Imaging. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 447–458.
Risholm, P., Samset, E., Wells, W., 2010. Bayesian estimation of deformation and elastic parameters in non-rigid registration. In: Biomedical Image Registration: 4th International Workshop, WBIR 2010, LÜbeck, Germany, July 11Del-Ins–13, 2010. Proceedings 4. Springer, pp. 104–115.
Risser, L., Baluwala, H., Schnabel, J.A., 2011. Diffeomorphic registration with sliding conditions: application to the registration of lungs CT images. In: Fourth International Workshop on Pulmonary Image Analysis, MICCAI, pp. 79–90.
Risser, L., Vialard, F.-X., Baluwala, H.Y., Schnabel, J.A., 2013. Piecewise-diffeomorphic image registration: application to the motion estimation between 3d CT lung images with sliding conditions. Med. Image Anal. 17 (2), 182–193.
Rohlfing, T., 2012. Image similarity and tissue overlaps as surrogates for image registration accuracy: widely used but unreliable. IEEE Trans. Med. Imaging 31 (2), 153–163.
Rohlfing, T., Maurer, C.R., Bluemke, D.A., Jacobs, M.A., 2003. Volume-preserving non-rigid registration of MR breast images using free-form deformation with an incompressibility constraint. IEEE Trans. Med. Imaging 22, 730–741.
Ruan, D., Esedoglu, S., Fessler, J.A., 2009. Discriminative sliding preserving regularization in medical image registration. In: 2009Del InsThinspace IEEE International Symposium on Biomedical Imaging: From Nano to Macro, pp. 430–433.
Ruan, D., Fessler, J.A., Esedoglu, S., 2008. Discontinuity preserving regularization for modeling sliding in medical image registration. In: 2008Del InsThinspace IEEE Nuclear Science Symposium Conference Record, pp. 5304–5308.
Ruan, D., Fessler, J.A., Roberson, M., Balter, J., Kessler, M., 2006. Nonrigid registration using regularization that accommodates local tissue rigidity. In: Medical Imaging 2006: Image Processing. Vol. 6144. SPIE, pp. 346–354.
Rudin, L.I., Osher, S., Fatemi, E., 1992. Nonlinear total variation based noise removal algorithms. Physica D 60 (1), 259–268.
Rueckert, D., 1999. Nonrigid registration using free-form deformations: application to breast mr images. IEEE Trans. Med. Imaging 18.
Rueckert, D., Schnabel, J.A., 2010. Medical image registration. In: Biomedical Image Processing. Springer, Berlin, Heidelberg, pp. 131–154.
Rühaak, J., Polzin, T., Heldmann, S., Simpson, I.J.A., Handels, H., Modersitzki, J., Heinrich, M.P., 2017. Estimation of large motion in lung ct by integrating regularized keypoint correspondences into dense deformable registration. IEEE Trans. Med. Imaging 36 1746–1757.
Sabour, S., Frosst, N., Hinton, G.E., 2017. Dynamic routing between capsules. Adv. Neural Inf. Process. Syst. 30.
Saddi, K.A., Chefd'hotel, C., Cheriet, F., 2007. Large deformation registration of contrast-enhanced images with volume-preserving constraint. In: Pluim, J. P.W., Reinhardt, J.M. (Eds.), Medical Imaging 2007: Image Processing. International Society for Optics and Photonics. SPIE, p. 651203.
Sandkühler, R., Jud, C., Pezold, S., Cattin, P.C., 2018. Adaptive graph diffusion regularisation for discontinuity preserving image registration. In: Klein, S., Staring, M., Durrleman, S., Sommer, S. (Eds.), Biomedical Image Registration. Springer International Publishing, Cham, pp. 24–34.
Sang, Y., Cao, M., McNitt-Gray, M., Gao, Y., Hu, P., Yan, R., Yang, Y., Ruan, D., 2022. Inter-phase 4d cardiac MRI registration with a motion prior derived from CTA. IEEE Trans. Biomed. Eng. 69 (6), 1828–1836.
Sang, Y., Ruan, D., 2020. Enhanced image registration with a network paradigm and incorporation of a deformation representation model. In: 2020Del InsThinspace IEEE 17Th International Symposium on Biomedical Imaging (ISBI), pp. 91–94.
Sang, Y., Ruan, D., 2021. 4D-cbct registration with a fbct-derived plug-and-play feasibility regularizer. In: Medical Image Computing and Computer Assisted Intervention–MICCAI 2021: 24th International Conference, Strasbourg, France, September 27–October 1, 2021, Proceedings, Part IV 24. Springer, pp. 108–117.
Sang, Y., Xing, X., Wu, Y., Ruan, D., 2020. Imposing implicit feasibility constraints on deformable image registration using a statistical generative model. J. Med. Imaging 7 (6), 064005.
Schmidt-Richberg, A., Ehrhardt, J., Werner, R., Handels, H., 2009. Slipping objects in image registration: improved motion field estimation with direction-dependent regularization. In: Yang, G.-Z., Hawkes, D., Rueckert, D., Noble, A., Taylor, C. (Eds.), Medical Image Computing and Computer-Assisted Intervention – MICCAI 2009. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 755–762.
Schmidt-Richberg, A., Werner, R., Handels, H., Ehrhardt, J., 2012. Estimation of slipping organ motion by registration with direction-dependent regularization. Med. Image Anal. 16 (1), 150–159.
Sdika, M., 2008. A fast nonrigid image registration with constraints on the jacobian using large scale constrained optimization. IEEE Trans. Med. Imaging 27 (2), 271–281.
Sha, Q., Sun, K., Xu, M., Li, Y., Xue, Z., Cao, X., Shen, D., 2024. Hierarchical symmetric normalization registration using deformation-inverse network. In: Linguraru, M.G., Dou, Q., Feragen, A., Giannarou, S., Glocker, B., Lekadir, K., Schnabel, J.A. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2024. Springer Nature Switzerland, Cham, pp. 662–672.
Shen, D., Sundar, H., Xue, Z., Fan, Y., Litt, H., 2005. Consistent estimation of cardiac motions by 4d image registration. In: Duncan, J.S., Gerig, G. (Eds.), Medical Image Computing and Computer-Assisted Intervention – MICCAI 2005. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 902–910.
Shen, Z., Han, X., Xu, Z., Niethammer, M., 2019a. Networks for joint affine and non-parametric image registration. In: Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition, pp. 4224–4233.
Shen, Z., Vialard, F.-X., Niethammer, M., 2019b. Region-specific diffeomorphic metric mapping. Adv. Neural Inf. Process. Syst. 32.
Shuaibu, A.L., Simpson, I. J.A., 2024. Hyperpredict: estimating hyperparameter effects for instance-specific regularization in deformable image registration. Mach. Learn. Biomed. Imaging 2 (Image Registration), 686–716.
Song, L., Ma, M., Liu, G., 2023. Ts-net: two-stage deformable medical image registration network based on new smooth constraints. Magn. Reson. Imaging 99, 26–33.
Sotiras, A., Davatzikos, C., Paragios, N., 2013. Deformable medical image registration: a survey. IEEE Trans. Med. Imaging 32 (7), 1153–1190.
Spieker, V., Eichhorn, H., Hammernik, K., Rueckert, D., Preibisch, C., Karampinos, D.C., Schnabel, J.A., 2024. Deep learning for retrospective motion correction in MRI: a comprehensive review. IEEE Trans. Med. Imaging 43 (2), 846–859.
Staring, M., Klein, S., Pluim, J. P.W., 2007a. Nonrigid registration with tissue-dependent filtering of the deformation field. Phys. Med. Biol. 52 (23), 6879.
Staring, M., Klein, S., Pluim, J. P.W., 2007b. A rigidity penalty term for nonrigid registration. Med. Phys. 34 (11), 4098–4108.
Stefanescu, R., Pennec, X., Ayache, N., 2004. Grid powered nonlinear image registration with locally adaptive regularization. Med. Image Anal. 8 (3), 325–342.
Suh, J.W., Wyatt, C.L., 2011. Registration under topological change for CT colonography. IEEE Trans. Biomed. Eng. 58 (5), 1403–1411.
Sun, D., Roth, S., Black, M.J., 2010. Secrets of optical flow estimation and their principles. In: 2010Del InsThinspace IEEE Computer Society Conference on Computer Vision and Pattern Recognition. IEEE, pp. 2432–2439.
Talwalkar, J.A., 2008. Elastography for detecting hepatic fibrosis: options and considerations. Gastroenterology 135 (1), 299–302.
Tang, S., Cong, W., Yang, J., Fu, T., Song, H., Ai, D., Wang, Y., 2018. Local statistical deformation models for deformable image registration. Neurocomputing 303, 1–10.
Tanner, C., Hipwell, J.H., Hawkes, D.J., 2009. Using statistical deformation models for the registration of multimodal breast images. In: Pluim, J. P.W., Dawant, B.M. (Eds.), Medical Imaging 2009: Image Processing. International Society for Optics and Photonics. SPIE, p. 72590P.
Tanner, C., Samei, G., SzÃ©kely, G., 2013. Investigating anisotropic diffusion for the registration of abdominal MR images. In: 2013Del InsThinspace IEEE 10Th International Symposium on Biomedical Imaging, pp. 484–487.
Tanner, C., Schnabel, J.A., Chung, D., Clarkson, M.J., Rueckert, D., Hill, D.L.G., Hawkes, D.J., 2000. Volume and shape preservation of enhancing lesions when applying non-rigid registration to a time series of contrast enhancing MR breast images. In: Delp, S.L., DiGoia, A.M., Jaramaz, B. (Eds.), Medical Image Computing and Computer-Assisted Intervention – MICCAI 2000. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 327–337.
Thirion, J.P., 1998. Image matching as a diffusion process: an analogy with maxwell's demons. Med. Image Anal. 2 (3), 243–260.
Tian, L., Greer, H., Kwitt, R., Vialard, F.-X., Estepar, R. S.J., Bouix, S., Rushmore, R., Niethammer, M., 2024. unigradICON: A foundation model for medical image registration. arXiv:2403.05780.
Tian, L., Greer, H., Vialard, F.-X., Kwitt, R., Estépar, R. S.J., Rushmore, R.J., Makris, N., Bouix, S., Niethammer, M., 2023. GradICON: approximate diffeomorphisms via gradient inverse consistency. In: Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition, pp. 18084–18094.
Trouvé, A., Younes, L., 2005. Local geometry of deformable templates. SIAM J. Math. Anal. 37 (1), 17–59.
Tzitzimpasis, P., Ries, M., Raaymakers, B.W., Zachiu, C., 2024. Generalized div-curl based regularization for physically constrained deformable image registration. Sci. Rep. 14 (1), 15002.
Vandemeulebroucke, J., Rit, S., Kybic, J., Clarysse, P., Sarrut, D., 2011. Spatiotemporal motion estimation for respiratory-correlated imaging of the lungs. Med. Phys. 38 (1), 166–178.
Vercauteren, T., Pennec, X., Perchant, A., Ayache, N., 2009. Diffeomorphic demons: efficient non-parametric image registration. Neuroimage 45.
Viergever, M.A., Maintz, J.B.A., Klein, S., Murphy, K., Staring, M., Pluim, J. P.W., 2016. A survey of medical image registration - under review. Med. Image Anal. 33, 140–144.
Vishnevskiy, V., Gass, T., Székely, G., Goksel, O., 2014. Total variation regularization of displacements in parametric image registration. In: International MICCAI Workshop on Computational and Clinical Challenges in Abdominal Imaging. Springer, pp. 211–220.
Vishnevskiy, V., Gass, T., Szekely, G., Tanner, C., Goksel, O., 2017. Isotropic total variation regularization of displacements in parametric image registration. IEEE Trans. Med. Imaging 36 (2), 385–395.
Wang, A.Q., Evan, M.Y., Dalca, A.V., Sabuncu, M.R., 2023a. A robust and interpretable deep learning framework for multi-modal registration via keypoints. Med. Image Anal. 90, 102962.
Wang, A.Q., Saluja, R., Kim, H., He, X., Dalca, A., Sabuncu, M.R., 2024. Brainmorph: A foundational keypoint model for robust and flexible brain MRI registration. arXiv:2405.14019.
Wang, H., Ni, D., Wang, Y., 2023b. Modet: learning deformable image registration via motion decomposition transformer. In: International Conference on Medical Image Computing and Computer-Assisted Intervention. Springer, pp. 740–749.
Wang, J., Xing, J., Druzgal, J., Wells, W.M., Zhang, M., 2023c. Metamorph: learning metamorphic image transformation withÂ appearance changes. In: Frangi, A., de Bruijne,

M., Wassermann, D., Navab, N. (Eds.), Information Processing in Medical Imaging. Springer Nature Switzerland, Cham, pp. 576–587.
Wang, M., Li, P., 2019. A review of deformation models in medical image registration. J. Med. Biol. Eng. 39, 1–17.
Wang, P., Yan, Y., Qian, L., Suo, S., Xu, J., Guo, Y., Wang, Y., 2023d. Context-driven pyramid registration network for estimating large topology-preserved deformation. Neurocomputing 521, 65–78.
Wang, Y., Qiu, H., Qin, C., 2023e. Conditional deformable image registration with spatially-variant and adaptive regularization. In: 2023Del InsThinspace IEEE 20Th International Symposium on Biomedical Imaging (ISBI), pp. 1–5.
Wasserthal, J., Breit, H.-C., Meyer, M.T., Pradella, M., Hinck, D., Sauter, A.W., Heye, T., Boll, D.T., Cyriac, J., Yang, S., Bach, M., Segeroth, M., 2023. Totalsegmentator: robust segmentation of 104 anatomic structures in CT images. Radiology: Artif. Intell. 5 (5).
Wei, D., Ahmad, S., Guo, Y., Chen, L., Huang, Y., Ma, L., Wu, Z., Li, G., Wang, L., Lin, W., Yap, P.-T., Shen, D., Wang, Q., 2022. Recurrent tissue-aware network for deformable registration of infant brain MR images. IEEE Trans. Med. Imaging 41 (5), 1219–1229.
Wiputra, H., Chan, W.X., Foo, Y.Y., Ho, S., Yap, C.H., 2020. Cardiac motion estimation from medical images: a regularisation framework applied on pairwise image registration displacement fields. Sci. Rep. 10 (1), 18510.
Wodzinski, M., Ciepiela, I., Kuszewski, T., Kedzierawski, P., Skalski, A., 2021. Semi-supervised deep learning-based image registration method with volume penalty for real-time breast tumor bed localization. Sensors 21 (12).
Wodzinski, M., Jurgas, A., Marini, N., Atzori, M., Müller, H., 2023. Unsupervised method forÂ intra-patient registration ofÂ brain magnetic resonance images based onÂ objective function weighting byÂ inverse consistency: contribution toÂ theÂ braTS-reg challenge. In: Bakas, S., Crimi, A., Baid, U., Malec, S., Pytlarz, M., Baheti, B., Zenk, M., Dorent, R. (Eds.), Brainlesion: Glioma, Multiple Sclerosis, Stroke and Traumatic Brain Injuries. Springer Nature Switzerland, Cham, pp. 241–251.
Wodzinski, M., Skalski, A., 2018. Resection-based demons regularization for breast tumor bed propagation. In: Image Analysis for Moving Organ, Breast, and Thoracic Images: Third International Workshop. Springer, pp. 3–12.
Wouters, J., D'Agostino, E., Maes, F., Vandermeulen, D., Suetens, P., 2006. Non-rigid brain image registration using a statistical deformation model. In: Medical Imaging 2006: Image Processing. Vol. 6144. SPIE, pp. 338–345.
Xie, Y., Chao, M., Xiong, G., 2011. Deformable image registration of liver with consideration of lung sliding motion. Med. Phys. 38 (10), 5351–5361.
Xu, T., Jiang, T., Li, X., 2023. Ic-cvit: inverse-consistent convolutional vision transformer for diffeomorphic image registration. In: 2023 International Joint Conference on Neural Networks (IJCNN), pp. 1–10.
Xu, Z., Lee, C.P., Heinrich, M.P., Modat, M., Rueckert, D., Ourselin, S., Abramson, R.G., Landman, B.A., 2016. Evaluation of six registration methods for the human abdomen on clinically acquired CT. IEEE Trans. Biomed. Eng. 63 (8), 1563–1572.
Xu, Z., Luo, J., Lu, D., Yan, J., Frisken, S., Jagadeesan, J., Wells, W.M., Li, X., Zheng, Y., Tong, R. K.-y., 2022. Double-uncertainty guided spatial andÂ temporal consistency regularization weighting forÂ learning-based abdominal registration. In: Wang, L., Dou, Q., Fletcher, P.T., Speidel, S., Li, S. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2022. Springer Nature Switzerland, Cham, pp. 14–24.
Xu, Z., Niethammer, M., 2019. Deepatlas: joint semi-supervised learning of image registration and segmentation. In: Shen, D., Liu, T., Peters, T.M., Staib, L.H., Essert, C., Zhou, S., Yap, P.-T., Khan, A. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2019. Springer International Publishing, Cham, pp. 420–429.
Xue, Z., Shen, D., Davatzikos, C., 2006. Statistical representation of high-dimensional deformation fields with application to statistically constrained 3d warping. Med. Image Anal. 10 (5), 740–751.
Yan, Z., Ji, J., Ma, J., Cao, W., 2024. Hgcmorph: joint discontinuity-preserving and pose-learning via gnn and capsule networks for deformable medical images registration. Phys. Med. Biol. 69 (7), 075032.
Yang, J., Wu, Y., Zhang, D., Cui, W., Yue, X., Du, S., Zhang, H., 2022. Ldvoxelmorph: a precise loss function and cascaded architecture for unsupervised diffeomorphic large displacement registration. Med. Phys. 49 (4), 2427–2441.
Ye, M., Yang, D., Huang, Q., Kanski, M., Axel, L., Metaxas, D.N., 2023. Sequencemorph: a unified unsupervised learning framework for motion tracking on cardiac image sequences. IEEE Trans. Pattern Anal. Mach. Intell. 45 (8), 10409–10426.
Yin, Y., Hoffman, E.A., Lin, C.-L., 2010. Lung lobar slippage assessed with the aid of image registration. In: Jiang, T., Navab, N., Pluim, J. P.W., Viergever, M.A. (Eds.), Medical Image Computing and Computer-Assisted Intervention – MICCAI 2010. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 578–585.
Younes, L., 2010. Shapes and diffeomorphisms. Vol. 171. Springer.
Zeng, K., Sotiras, A., Davatzikos, C., 2018. Statistically-constrained robust diffeomorphic registration. In: 2018Del InsThinspace IEEE 15Th International Symposium on Biomedical Imaging (ISBI 2018), pp. 1083–1087.
Zhang, J., 2018. Inverse-consistent deep networks for unsupervised deformable image registration. arXiv:1809.03443.
Zhang, J., Chen, K., Yu, B., 2016. An improved discontinuity-preserving image registration model and its fast algorithm. Appl. Math. Model. 40 (23), 10740–10759.
Zhang, L., Ning, G., Zhou, L., Liao, H., 2023. Symmetric pyramid network for medical image inverse consistent diffeomorphic registration. Comput. Med. Imaging Graph. 104, 102184.
Zhao, B., Christensen, G.E., Hyun Song, J., Pan, Y., Gerard, S.E., Reinhardt, J.M., Du, K., Patton, T., Bayouth, J.M., Hugo, G.D., 2016. Tissue-volume preserving deformable image registration for 4DCT pulmonary images. In: Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition Workshops, pp. 41–49.
Zheng, Y., Sui, X., Jiang, Y., Che, T., Zhang, S., Yang, J., Li, H., 2022. Symreg-GAN: symmetric image registration with generative adversarial networks. IEEE Trans. Pattern Anal. Mach. Intell. 44 (9), 5631–5646.
Zhou, H., Leung, H., Balaji, B., 2023. Ar-unet: a deformable image registration network with cyclic training. IEEE/ACM Trans. Comput. Biol. Bioinf. , 1–10.
Zhu, Y., Lu, S., 2022. Swin-voxelmorph: a symmetric unsupervised learning model forÂ deformable medical image registration using swin transformer. In: Wang, L., Dou, Q., Fletcher, P.T., Speidel, S., Li, S. (Eds.), Medical Image Computing and Computer Assisted Intervention – MICCAI 2022. Springer Nature Switzerland, Cham, pp. 78–87.
Zhu, Z., Li, Q., Wei, Y., Song, R., 2024. Hierarchical multi-level dynamic hyperparameter deformable image registration with convolutional neural network. Phys. Med. Biol. 69 (17), 175007.