Review of large deformation diffeomorphic metric mapping registration

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ABSTRACT This study investigates the development and clinical applications of Large Deformation Diffeomorphic Metric Mapping (LDDMM) in medical image registration. Through systematic comparison between conventional optimization-based methods and contemporary deep learning techniques, we evaluate their respective performance in registration accuracy, computational efficiency, and clinical utility. Our methodology encompasses a thorough examination of both mathematical foundations and neural network implementations in LDDMM. Results demonstrate that traditional approaches maintain superior precision for complex anatomical variations via rigorous variational optimization, whereas deep learning methods achieve substantial computational acceleration (reducing processing time from hours to seconds) through learned deformation patterns. Critical analysis reveals important trade-offs: while deep learning offers remarkable speed improvements, traditional methods preserve accuracy advantages in specialized clinical scenarios. We identify key challenges including computational complexity, implementation difficulties, and domain adaptation limitations, while proposing hybrid architecture and transfer learning as potential solutions. The study concludes that integrating the mathematical robustness of conventional LDDMM with the computational efficiency of deep learning presents the most viable path forward. Such synergistic approaches promise to advance medical image analysis pipelines and promote wider clinical implementation of sophisticated registration technologies.

KEYWORDS: LDDMM; Image registration; Deep learning
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INTRODUCTION

Image registration is fundamental in various applications, including medical imaging, computer graphics and remote sensing (Balakrishnan *et al*., 2019; Chen *et al*., 2021; Younes, 2019; Richardson & Younes, 2016; Zhang *et al*., 2019). Large Deformation Diffeomorphic Metric Mapping (LDDMM) is a typical approach, particularly in large deformations (Beg *et al*., 2005). The LDDMM theory has succeeded greatly in various image registrations (Zhang *et al*., 2019; Beg *et al*., 2005; Yang *et al*., 2017).

In 1990s, Griewank (1992) and Grenander (1994, 1998) introduced the concept of diffeomorphism, which is smooth and invertible transformations that preserve the structure of the original objects. Moreover, they defined distances in transformation space using the geodesic theory. These works laid the theoretical foundation for LDDMM.

Since the 2000s, LDDMM has been formalized as a computational framework for computational anatomy, especially in medical image registration (Beg *et al*., 2005; Joshi *et al*., 2004). Beg *et al.* (2005) proposed the LDDMM registration algorithm in which the diffeomorphism group was used to describe transformations. They developed variational optimization techniques, which are currently widely used to determine deformation paths. Using time-dependent velocity fields $v(t,x)$ that describe the rate and direction of change (motion) at every point in a spatial domain, they introduced a minimized energy function to combine the velocity field with a data-matching term. This framework formed the basis for shape analysis. The framework was extended to support different data types, as shown in Table 1.

Table 1. LDDMM in different types of data.

Data Type	Application
Curves (Glaunes *et al*., 2008; Yang *et al*., 2017)	Used for contour and shape data registration.
Surfaces (Vaillant *et al*., 2007; Hsieh & Charon, 2022; Charon & Trouvé, 2013; Hsieh & Charon, 2021; Goshtasby, 2012)	Adapted for 3D surface registration.
Landmarks (Joshi & Miller, 2000)	Applied to point set registration.
Tensors (Cao *et al*., 2005; Cao *et al*., 2006)	Used for DTI (diffusion tensor imaging) data.
Statistical Representations (Charon & Trouvé, 2013; Hsieh & Charon, 2021)	Introduced varifolds for multi-modal data registration.

Unlike other traditional methods including rigid, affine and elastic registration (Goshtasby, 2012), LDDMM can handle large and complex deformations, making it suitable for aligning images with significant anatomical differences (Younes, 2019; Beg *et al*., 2005; Griewank, 1992; Grenander, 1994; Grenander & Miller, 1998; Joshi *et al*., 2004; Glaunes *et al*., 2008; Yang *et al*., 2017). Foremost, by ensuring that the transformations are diffeomorphic, LDDMM preserves the topology of the images, which is crucial for maintaining the integrity of anatomical structures (Stouffer *et al*., 2022). The LDDMM has been extensively and successfully adapted to various types of images and different similarity metrics, providing flexibility in medical imaging registration scenarios.

Brain magnetic resonance imaging (MRI) (Beg *et al*., 2005; Vaillant *et al*., 2007; Stouffer *et al*., 2022; Hernandez, 2021a, 2021b, 2022), brain atlas (Joshi *et al*., 2004), Cardiac MRI registration (Ye *et al*., 2023), 3D cardiac computed tomography (CT) (Wang *et al*., 2020a, 2020b), animal ultrasound (US) heart images (Guan *et al*., 2020a, 2020b, 2024), 2D and 3D lung CT (Polzin *et al*., 2016; Polzin *et al*., 2020; Mang *et al*., 2023; Sakamoto *et al*., 2014).

For all LDDMM literature, the brain is the most frequently studied organ. However, LDDMM has several drawbacks. Specifically, it requires solving complex optimization problems, which are computationally intensive and time-consuming (Mang *et al*., 2023; Sakamoto *et al*., 2014). For instance, in the experiments of Sakamoto *et al*. (2014), a single registration task took nearly three hours to complete. Such computational demands make it difficult to apply LDDMM in real-time scenarios or on large-scale datasets. Since the 2010s, LDDMM has been increasingly combined with deep learning methods (Zhang *et al*., 2019; Yang *et al*., 2017; Yang *et al*., 2024; Hsieh & Charon, 2022; Amor *et al*., 2022; Guan *et al*., 2024). With these approaches, the computation time has been drastically reduced—from hours to just a few seconds (Amor *et al*., 2022; Guan *et al*., 2024)—thereby enabling broader practical applicability. In this paper, we introduce the development of both traditional LDDMM and deep learning–based LDDMM, followed by a discussion of the challenges and potential solutions.

METHODOLOGY CLASSIFICATION OF THE LDDMM METHODS

Based on their implementation approaches, LDDMM methods can be broadly categorized into traditional and deep learning-based methods.

Traditional Methods

Let I^1, I^0 denote fixed and moving images, respectively. The goal of the LDDMM is to find a diffeomorphic mapping ϕ so that the image $I^0 \circ \phi^{-1}$ is as close to the image I^1 as possible (Younes, 2019). At the same time, ϕ is as close to the identity mapping as close as possible. There are two major different classes called relaxation approaches (Beg *et al*., 2005; Polzin, 2018) and shooting approaches

(Polzin, 2018; Vialard *et al*., 2012; Singh *et al*., 2013). The relaxation model iteratively optimizes the entire time-dependent velocity field $v(t,x)$, and deformation path $\phi_t(x)$. The shooting model optimizes the initial velocity field $v(0,x)$, which obtains the full deformation path by solving geodesic equations. The geodesic equation, a differential equation, is used to describe the shortest path (or geodesic) between two points in a curved space or manifold. The problem of image registration comes down to minimizing the energy and obtaining the velocity field v by solving the variational problem. Considering the advantages and disadvantages of the two models (Polzin, 2018), a brief comparison is shown in Table 2. In Table 3, we compare the relaxation model and the shooting model in LDDMM, detailing their energy functions, optimality conditions, optimization variables, dimensionality, efficiency, complexity, integration requirements, and applications. In other words, the comparison between the two modes is summarized in Table 3. Related information is summarized in Table 2 and Table 3.

Table 2. Comparison between the shooting and relaxation model.

Model	Advantage	Disadvantage
Shooting model	With a good starting point, the convergence is faster than the relaxation methods.	The results highly depend on a good starting point.
	Compared with the relaxation methods, less memory is needed.	With fewer degrees of freedom, it is sensitive to changes.
	More suitable for extrapolation, it allows "to generate continuous evolution models."	It is sensitive to minor deviations and may be less accurate.
Relaxation model	With more degrees of freedom, it allows large and complex deformations. It can estimate the velocities for multiple points.	Compared with the shooting methods, more memory is needed.

LDDMM operates in a high-dimensional space, which makes it prone to numerical instabilities and convergence issues (Yang *et al*., 2023). That can result in local minimum and suboptimal registration results. More sophisticated numerical techniques are then needed to ensure stability. The method consumes large amounts of memory, particularly in 3D image registration tasks (Yang *et al*., 2023; Polzin, 2018). Because storing and processing large deformation fields demand many memory resources. Polzin *et al*. (2016) adopted a multi-resolution strategy to improve memory efficiency. The registration process starts at a coarse resolution and progressively refines the deformation field at higher resolutions. This paper mainly focused on relaxation methods and was tailored specifically for lung CT images. A discretize-optimize approach was introduced by Polzin *et al*. (2020), which improves computational efficiency by discretizing the continuous optimization problem. It allows for faster and more accurate solutions, particularly for large-scale datasets.

Over the years, Hernandez and colleagues have progressively enhanced LDDMM frameworks in terms of computational efficiency and registration accuracy. In 2017, a primal–dual convex optimization LDDMM leveraging multi-GPU computing dramatically reduced runtime by over an order of magnitude while maintaining high accuracy, with Dice similarity coefficients on benchmark datasets differing by less than 1% and mean squared errors remaining statistically indistinguishable from standard LDDMM. In 2018, the combination of band-limited parameterization with Newton–Krylov PDE-constrained LDDMM achieved extremely fast convergence, with Dice coefficients above 0.87, PDE residuals below 1e-6, and mean squared errors minimized, demonstrating both numerical precision and efficiency. Similarly, Hernandez (2019) used the incremental adjoint Jacobi equations

Table 3. A summary of the shooting and relaxation model.

Aspect	**Relaxation model (Beg *et al.*, 2005; Polzin, 2018)**	**Shooting model (Polzin, 2018; Vialard *et al.*, 2012; Singh *et al.*, 2013)**
Energy	$\varepsilon^{\text{Beg}}(v,\phi)=\frac{1}{2\sigma^2}\lVert I^0\circ\phi_1^{-1}-I^1\rVert^2+\frac{1}{2}\int_0^1\langle Lv_t,\ Lv_t\rangle \text{dt}$	$\varepsilon^{\text{Shoot}}(M_0,I)=\frac{1}{2\sigma^2}\lVert I_1-I^1\rVert^2+\langle KM_0,\ M_0\rangle$
Optimality conditions	$\text{s.t.}\ \ \phi_0(\text{x})=\text{x},\overset{\square}{\phi}_t(\text{x})=v_t(\phi_t(\text{x}))$ $v_t-K(\frac{1}{\sigma^2}\lvert J_{\phi_{t,1}^{v}}\rvert(I^0\circ\phi_{t,0}^{v}-I^1\circ\phi_{t,1}^{v})\nabla(I^0\circ\phi_{t,0}^{v^*})=0$ $K=(L^{\dagger}L)^{-1}$	$\overset{g}{I}_t+\nabla I_t^{\text{T}}v_t=0,I_0=I^0,v_t=KM_t,K=(L^{\dagger}L)^{-1}$ $\overset{\square}{M}_t+J_{M_t}v_t+M_t\text{div}(v_t)+J_{v_t}^{\text{T}}M_t=0$ $-\overset{\square}{\lambda}{}_t^M+J_{v_t}\lambda_t^M-J_{\lambda_t^M}v_t+\lambda_t^v=0,\lambda_1^M=0$ $-\overset{\square}{\lambda}{}_t^I-\text{div}(\lambda_t^I v_t)=0,\lambda_1^I=\frac{1}{\sigma^2}(I^1-I_1)-J_{\lambda_t^M}^{\text{T}}M_t-J_{M_t}\lambda_t^M$ $-\text{div}(\lambda_t^M)M_t+\lambda_t^I\nabla I_t-L^{\dagger}L\lambda_t^v=0$
Optimization Variables	Entire velocity field $v(t,x)$.	Initial velocity field $v(0,x)$.
Dimensionality	Higher, as the velocity field is time-dependent.	Lower, as only the initial field is optimized.
Efficiency	Less efficient, iterative over the full trajectory.	More efficient, reduces problem dimensionality.
Complexity	Simpler to implement, but slower.	More complex, but computationally faster.
Integration	Required at every iteration.	Performed once for optimization.
Applications	Small-scale or precise control of deformations.	Large-scale problems requiring efficiency.

in Gauss-Newton-Krylov PDE-constrained LDDMM schemes. This model was mainly performed in the shooting equations. Building on these developments, Hernandez (2021) proposed a conservation-constrained PDE-LDDMM framework incorporating Gauss–Newton–Krylov optimization, Semi-Lagrangian Runge–Kutta solvers, and band-limited parameterization; this approach preserved high numerical accuracy (Dice ≥ 0.88, PDE residuals < 1e-6) while reducing computational complexity, achieving 50–70% runtime reduction and 40–60% lower GPU memory usage compared with standard PDE-LDDMM implementations. Most recently, Hernandez (2025) introduced NODEO-LDDMM and NODEO-PDE-LDDMM, integrating neural ordinary differential equations with LDDMM. These deep learning-based approaches further improved non-rigid registration accuracy, achieving Dice coefficients of 0.90–0.92, reducing mean squared errors by 5–10%, and producing smoother deformation fields, outperforming both conventional and state-of-the-art deep learning registration methods. Collectively, these studies illustrate a clear trajectory of LDDMM evolution: accelerating computation while quantitatively preserving or enhancing registration accuracy.

Using the Fisher-Rao metric, Hsieh and Charon (2022) explored the integration of varifold-based representations with a metamorphosis framework. By combining varifolds with the Fisher-Rao metric, the method can enhance shape analysis and large deformations for objects like curves and surfaces. Besides, to study the well-posedness, relaxed optimal control formulations for computing optimal transformations were introduced. This article showed the potential for cases of partially missing data.

To reconstruct 3D anatomical coordinates from 2D measurements, Stouffer *et al.* (2022) proposed a projective LDDMM for mapping dense MRI atlases onto sparse histological measurements. As a diffeomorphic mapping technology, the method aligned dense human MRI atlases with sparse histological measurements using non-linear scattering transforms and a Gaussian mixture model to handle textures, tears, and distortions. It potentially integrated imaging data across different scales, which was significant to the development of Alzheimer's disease across imaging scales.

However, LDDMM's computational complexity makes it challenging to implement traditional methods. In addition, its mathematics requires a deep understanding, such as differential geometry, variational calculus, and some numerical optimization methods. To address these problems, deep learning-based methods are explored, which are high computational efficiency on GPU.

Deep Learning-based Methods

By introducing neural networks, deep learning methods were successfully used to reduce the run time (Balakrishnan *et al*., 2019; Yang *et al*., 2017; Yang *et al*., 2023). To predict the momenta directly from the images, Yang and Niethammer (2016) proposed a patch-based deep encoder-decoder network, which is a supervised mono-modal method for LDDMM. Retaining its theoretical properties, the method learned the mapping between image appearance and registration parameters. Compared to GPU optimization, 2D/3D registration is 1500 and 66 times faster, not to mention CPU. In addition, it is particularly pointed out that the prediction accuracy is better than that of direct prediction of the deformation field or velocity field. Yang *et al.* (2017a, 2017b) focused on both mono-modal and multi-modal registration frameworks called QuickSilver. It was an enhanced patch-based learning framework that predicted its momentum through neural networks utilizing a shooting model for registration. The patches from moving and fixed images were dealt with to encode spatial and contextual information. Additionally, a probabilistic framework evaluated deformation, and tested on atlas-to-image, image-to-image, and multi-modal registrations datasets in 2D and 3D. In their earlier work in 2016, the authors employed PyCA (Python for Computational Anatomy), a GPU-accelerated toolkit for diffeomorphic registration, to efficiently implement deformation field computations. Building on this, the 2017 QuickSilver framework adopted a U-shape CNN to directly learn and predict momentum from image patches, thereby capturing richer spatial and contextual representations. Compared with traditional optimization-based methods, these approaches (Yang & Niethammer, 2016; Yang *et al.*, 2017a, 2017b) not only demonstrated state-of-the-art accuracy in registration but also delivered substantial practical efficiency gains, markedly reducing computation time while maintaining or improving registration quality.

To simplify the geodesic regression model, Ding *et al.* (2019) proposed FPSGR, similar to Quicksilver. By predicting initial momenta based on geodesic distances, FPSGR captures longitudinal brain changes through pairwise image registrations. Correlations with clinical indicators were also analyzed, linking brain morphology with cognitive decline. LDDMM has been widely used in Alzheimer's disease research to track structural changes such as hippocampal atrophy and cortical thinning. Traditional LDDMM is computationally intensive, but FPSGR makes it feasible to analyze large longitudinal datasets efficiently. This enables early diagnosis, monitoring of disease progression, and evaluation of treatments, highlighting its real-world clinical impact.

Wang and Zhang (2020a, 2020b) proposed a framework called DeepFLASH, which predicts a low-dimensional Fourier representation of the velocity field using dual Rnet/Inet networks to separately estimate the real and imaginary components. This architecture enabled accurate decoupling of Fourier components, achieving Dice similarity coefficients of 0.88–0.91 and low mean squared errors of the velocity field compared with standard LDDMM. By employing a low-dimensional Fourier representation, DeepFLASH reduced training time by 60–70% and GPU memory usage by approximately 50%, demonstrating substantial improvements in efficiency while preserving registration accuracy.

Using gradient descent, Wu and Tang (2020) compared GPU- and CPU-based implementations of LDDMM-SSD. The GPU-based version achieved virtually identical registration accuracy, with Dice similarity coefficients differing by less than 1% (≈0.87–0.88) and minimal differences in mean squared error, while running approximately 94 times faster. In addition, Wu *et al.* (2021) proposed a multi-modal unsupervised LDDMM framework utilizing synthesized T2W images from T1W scans, though this approach proved unsuitable for general multi-modal datasets.

Amor *et al.* (2022) introduced Generative Adversarial Networks (GANs) to LDDMM. The aim was to enhance performance by combining deep learning with traditional LDDMM methods. Yang *et al.* (2024) presented LDDMM-Face, a framework that highlighted facial geometry in a diffeomorphic manner.

Since deep learning methods involve Large-scale data, most of the literature (Yang *et al.*, 2017a, 2017b; Yang *et al.*, 2024; Ding *et al.*, 2019; Wang & Zhang, 2020a, 2020b; Wu & Tang, 2020; Wu *et al.*, 2021; Wu & Gong, 2025) is about shooting methods. A summary of all reviewed learning-based registration methods is listed in Table 4 including the region of interest (ROI) and types of deep learning.

Table 4. Overview of deep learning-based registration methods.

Reference	Network	Modality	ROI	Dimension	Supervision
Yang *et al.* (2016)	PyCA	MRI	Brain	2D, 3D, mono-modal	Supervised
Yang *et al.* (2017a, 2017b)	U-shape CNN	MRI	Brain	3D, multi-modal	Supervised
Ding *et al.* (2019)	CNN	MRI	Brain	3D, mono-modal	Supervised
Wang & Zhang (2020a, 2020b)	CNN	MRI	Brain	2D, 3D, mono-modal	Supervised
Wu *et al.* (2021)	GANs	MRI	Brain	2D, multi-modal	Unsupervised
Wu & Gong, 2025	PyTorch	MRI	Brain	3D, multi-modal	Unsupervised
Ramon *et al.* (2022)	GANs	MRI	Brain	3D, mono-modal	Unsupervised
Yang *et al.* (2024)	HRNet	Photograph	Face	2D	Weakly-supervised
Amor *et al.* (2022)	ResNet	Surface	Brain, heart, hand	3D, mono-modal	Unsupervised

Compared with traditional registration methods, the runtime of the registration method based on deep learning has made significant progress. Besides, the deep learning-based methods have also achieved good results in various indicators. It fully illustrates the feasibility of the registration method based on deep learning.

CHALLENGES AND SOLUTIONS

The study of the LDDMM method has identified some challenges. Below are the challenges and the proposed solutions.

Complexity of Implementation

It is definitely difficult to implement the LDDMM because of its complex mathematical formulation. Without a strong background in differential geometry and computational mathematics, it is challenging to apply the LDDMM theory. These frameworks, for example, QuickSilver (Yang *et al*., 2017a, 2017b), FPSGR (Ding *et al*., 2019) and DeepFLASH (Wang & Zhang, 2020a), can be modified for further applications. Therefore, the focus of LDDMM should be on developing open-source software and comprehensive tutorials based on known frameworks.

Clinical Applications

Recent advances show that LDDMM-based modeling and image registration can support patient-specific cardiac surgery planning by quantifying remodeling (Guan *et al*, 2024), enabling accurate 2D/3D reconstructions (Guan *et al*, 2020a), and incorporating microstructural features into functional predictions (Guan *et al*., 2020b). While some studies have extended LDDMM into deep learning frameworks (e.g., ultrasound heart imaging; Guan *et al*, 2020a, 2020b, 2024), clinical adoption remains limited due to tool immaturity, computational burden, and poor interpretability. Building collaborative platforms between researchers and clinicians will be key to translating these methods into real-world surgical practice.

Generalization Challenges

The generalization of the existing registration model needs to be improved. For most medical images, there is a significant degradation in the performance of the model when migrating specific organs or modalities to another. In other words, most of the existing registration methods design a special network structure for a single task (Stouffer *et al*., 2022; Hernandez, 2017, 2018, 2019, 2021a, 2021b, 2025). How to make the model applicable in different domains has become an urgent problem that needs to be solved. For different modality medical images (e.g., MRI, CT, US), it is an excellent way to develop modality-specific cost functions combined with multi-modal similarity measures, enhancing the robustness and applicability of LDDMM across various domains. Using the transfer learning method (Guan *et al*., 2020a, 2020b), the registration model showed strong generalization in the registration tasks of different anatomical parts such as the brain, lungs, and liver.

FUTURE TRENDS

This review summarized the development from traditional to deep learning for the LDDMM, discussing both challenges and potential solutions. Most deep learning–based LDDMM methods have not yet surpassed traditional approaches in accuracy (Wu & Tang, 2020; Wu *et al*., 2021). Since much of the literature (Yang *et al*., 2017a, 2017b; Yang *et al*., 2024; Yang *et al*., 2022; Ding *et al*., 2019; Wang & Zhang, 2020a, 2020b; Wu & Tang, 2020; Wu *et al*., 2021) has focused on shooting methods, traditional frameworks—capable of handling both relaxation and shooting formulations—still provide a complete theoretical foundation. Nevertheless, deep learning–based registration with GPU acceleration enables direct estimation and offers clear advantages in computational efficiency compared with traditional LDDMM. Thus, combining LDDMM with deep learning remains a major research focus to improve feature extraction, parameter tuning, and robustness. At the same time, accuracy, generalization, and realistic deformation continue to be critical for clinical applicability.

Looking forward, emerging trends include the integration of physics-informed neural networks and biomechanical constraints to ensure physiologically plausible deformations, the development of interpretable deep learning frameworks to improve clinician trust, and the creation of collaborative platforms that bridge computational methods with clinical workflows. These directions not only aim to overcome current methodological limitations but also to strengthen the translational impact of LDDMM, accelerating its adoption in real-world applications such as personalized diagnosis and surgical planning.

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