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Deformable Image Registration: A Survey

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Abstract: Deformable image registration is a fundamental task in medical image processing. Among its most important applications, one may cite: i) multi-modality fusion, where information acquired by different imaging devices or protocols is fused to facilitate diagnosis and treatment planning; ii) longitudinal studies, where the development of phenomenon is studied over time; and iii) population modeling towards studying normal anatomical variability. In this research report, we attempt to give an overview of the deformable registration methods, putting emphasis on the most recent advances in the domain. Additional emphasis has been given to techniques applied to medical images. In order to study in depth image registration methods, their main components are identified and then studied independently. The most recent techniques are presented in a principled fashion.

Key-words: Deformable registration, bibliographical review

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Étude Bibliographique sur le Recalage Déformable d'Images

Résumé : Le recalage déformable d'images est une des tâches les plus fondamentales dans l'imagerie médicale. Parmi ses applications les plus importantes, on compte: i) la fusion d' information provenant des différents types de modalités afin de faciliter le diagnostic et la planification du traitement; ii) les études longitudinales, oú le d'eveloppement d'un phénomène est etudié en fonction du temps; et iii) la modélisation de la variabilité anatomique normale d'une population. Dans ce rapport de recherche, nous essayons de donner un aperçu des différentes méthodes du recalage déformables, en mettant l'accent sur les avancées les plus récentes du domaine. Nous avons particuliérement insisté sur les techniques appliquées aux images médicales. Afin d'étudier en profondeur les méthodes du recalage d'images, leurs composants principales sont d'abord identifiés puis étudiées de manière indeépendante, les techniques les plus récentes étant classifiées en suivant un schéma logique déterminé.

Mots-clés : recalage déformable, étude bibliographique

1 Introduction

Registration is defined as the process of establishing correspondences between two images. Registration, along with segmentation, is considered as one of the pillars of medical imaging. As a consequence, it is among the first problems researchers tried to tackle. Despite great efforts and some partial success, it is still considered an open problem.

Its importance becomes evident if one considers the span of clinical applications throughout which it occurs. One can imagine that the goal of automating medical diagnosis with the aid of computers would be out of consideration unless reliable registration methods exist. Apart from diagnostic settings, registration permits the study of the anatomical variability, as it is expressed along different members of a population or as it evolves, physiologically or not, for the same subject in time, and perform statistical group studies. Last but not least, it is crucial in order to plan or evaluate therapeutic procedures that are either based on surgery or medical treatment.

In order to demonstrate the clinical importance of registration, let us cite some characteristic examples of its application in biomedical tasks. First of all, in the side of computer aided diagnosis, one can cite the study of the cardiac motion towards revealing pathologies and the tumor localization problem. In the first case, spatio-temporal acquisitions are used for strain estimation and registration accounts for the motion of the organ [1]. The case of tumor localization is even more complex as registration on top of motion should also be able to account for the intensity changes inhibited by contrast-agents [2].

Doctors, in their effort to better understand the way the human body functions, need to fuse functional and anatomical information. Positron Emission Tomography (PET) is one imaging modality that allows the study of biological functions while Computer Tomography conveys anatomical information. Their fusion [3] has applications to numerous clinical examples such as the study of lung cancer. Functional Magnetic Resonance Imaging (fMRI) is an important technique that measures the neural activity of the brain. Most of the functional studies require a prior spatial normalization step that is important for the success of the subsequent statistical studies [4, 5].

Image registration plays a vital role in treatment planning. One can imagine registration between healthy subjects and ones with brain tumors in order to localize important brain structures to be taken into consideration for surgical planning [6, 7]. Registration is important even during the surgery itself as it allows for accurate localization of anatomical structures accounting for position shifts induced by surgical operations [8]. In terms of treatment planning, we should also note the impact that registration has in radiotherapy by localizing tumorous cells and thus limiting the destruction of healthy ones [9].

In general, in image registration two images are considered. One is usually referred to as source or moving image, while the other is referred to as target or fixed image. In this research report, the source image is denoted by $S : \Omega_S \subset \mathbb{R}^d \mapsto \mathbb{R}$, while the target image by $T : \Omega_T \subset \mathbb{R}^d \mapsto \mathbb{R}$, $d = \{2, 3\}$. The source image undergoes a transformation $\mathcal{T} : \Omega_S \mapsto \mathbb{R}^d$.

The goal of registration is to estimate the optimal transformation. This is often achieved by means of an energy minimization problem:

$$\arg\min_{\boldsymbol{\theta}} \mathcal{M}(T, S \circ \mathcal{T}(\boldsymbol{\theta})) + \mathcal{R}(\mathcal{T}(\boldsymbol{\theta})). \tag{1}$$

The previous energy (Eq. 1) comprises two terms. The first term, $\mathcal{M}$, quantifies the level of alignment between a target image T and a source image S under the influence of transformation $\mathcal{T}$ parametrized by $\boldsymbol{\theta}$. The notation $S \circ \mathcal{T}$ will be used interchangeably with $S \circ \mathbf{u}$ to denote that a moving image is deformed. The second term, $\mathcal{R}$, regularizes the transformation and accounts for the ill-posedness of the problem. In general, the transformation at every position $\mathbf{x} \in \Omega$

(Ω depicting the image domain) is given as $\mathcal{T}(\mathbf{x}) = \mathbf{x} + \mathbf{u}(\mathbf{x})$ where $\mathbf{u}$ is the deformation field. The velocity field, denoted as $\mathbf{v}$, is defined as $\mathbf{v} = \partial_t \mathbf{u} + \mathbf{v}^T \nabla \mathbf{u}$. An effort to keep the notation consistent throughout the document has been made. Hereafter, vectors are denoted in bold, while the upper-script is used to index their components. Due to the diversity of the models described, the meaning of some symbols may change. Whenever a change occurs, the signification of the symbol will be stated explicitly.

Image registration involves three main components: (i) a deformation model; (ii) an objective function; and (iii) an optimization strategy. Image registration is a problem that has been studied in great detail during the past few decades and many innovative ideas regarding these three main aspects have been proposed. General reviews of the field may be found in [10,11,12,13,14,15,16]. However due to the rapid progress of the field such reviews are to a certain extent outdated.

The aim of this research report is to provide a thorough overview of advances of the past decade in deformable registration. Nevertheless, some *classic* papers that have greatly influenced the advance of the ideas in the field are mentioned. Even though our primary interest is deformable registration, for the completeness of the presentation, references to linear methods are also included as many problems have been treated in this low degrees of freedom setting before being extended to the deformable case.

The research report is divided following the previous structural separation of registration algorithms in three components: (i) a deformation model; (ii) an objective function; and (iii) an optimization strategy.

2 Deformation Models

The choice of deformation model is of great importance for the registration process as it entails an important compromise between computational efficiency and richness of description. The parameters that registration estimates through the optimization strategy correspond to the degrees of freedom of the deformation model. Their number varies greatly, from around 10, in the case of global linear transformations, to millions, when non-parametric dense transformations are considered. The greater the dimension of the state space, the richer the descriptive power of the model though at the cost of more challenging and computational demanding inference. Furthermore, the choice of the deformation field often implies an assumption regarding the nature of the deformation to be recovered.

The rest of the section is organized following the classification of deformation models given by Holden [17]. More emphasis is put on aspects that were not covered by that review. According to [17], geometric transformations can be classified into two main categories:(i) those that are inspired by physical models; and (ii) those inspired by interpolation and approximation theory.

Of great importance for biomedical applications are the constraints that may be applied to the transformation such that it exhibits special properties. Such properties include, but are not limited to, inverse consistency, symmetry, topology preservation and diffeomorphicity. The value of these properties was made apparent to the research community and were gradually introduced as extra constraints.

- **Inverse consistency:** Despite common intuition, interchanging the order of input images could produce transformation changes, making the choice of template an important task and biasing the subsequent statistical analysis. Moreover, the composition of the forward and backward transforms (or the transforms that we obtain by interchanging the role of the images) is not the identity one. In some cases, the transformations may not even be invertible. To account for that counter intuitive result, inverse consistent algorithms have been developed.

- **Symmetry:** Taking one step further the previous idea, symmetric algorithms have been conceived that guarantee that the result does not change by swapping the inputs. The distinction between symmetric and inverse consistent algorithms lies in their primary aim. The first guarantee that the result is invariant to the order of the images, while the second approximates symmetry by imposing the inverse consistency constraint. Inverse consistent methods are only asymptotically symmetric.

- **Topology preservation:** The previous properties are desired and are usually imposed as soft constraints. Thus, the resulting transformation is not always one-to-one and crossings may appear in the deformation field. Such an effect in undesirable because it is quite often the case (especially when dealing with normal subjects) that we know that true correspondences can be obtained for every point of the image domain. What is more, the mapping from one anatomical structure to another should conserve the relative positions of points. Such a demand has motivated topology preserving algorithms whose deformation field is one-to-one or has a Jacobian determinant that is not zero.

- **Diffeomorphicity:** On top of the topology preservation constraint, ensures that the transformation field exhibits a certain level of smoothness.

In the following sections, the most important methods of the two classes are presented with emphasis on the approaches that endow the model under consideration with the previous desirable properties. One subsection is devoted to methods that employ task-specific constraints.

2.1 Geometric Transformations Inspired by Physical Models

Following [11], physical models can be further separated in five categories:

- Elastic model.
- Viscous fluid flow model.
- Diffusion model.
- Curvature registration.
- Flows of diffeomorphisms.

Elastic Model

In this case, the image under deformation is modeled as an elastic body. The Navier-Cauchy equation describes the deformation, or

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

where $\mathbf{F}(\mathbf{x})$ is the force that drives the registration based on an image matching criterion, μ refers to the rigidity that quantifies the stiffness of the material and λ is Lamé's first coefficient.

Image grid was modeled initially as an elastic membrane in [18]. Two different types of forces compete to reach an equilibrium. The external force tries to deform the image such that matching is achieved while the internal enforces the elastic properties of the material. The resulting equation is solved by deploying a finite difference scheme in an iterative manner.

Bajcsy and Kovacic [19] extended this approach in a hierarchical fashion where the solution of the coarsest scale is up-sampled and used as initialization for the finer one. Linear registration is used at the lowest resolution.

The linear elastostatic problem can be formulated in a variational setting where the displacement is given by minimizing:

$$E = \frac{1}{2}\int_V \boldsymbol{\sigma} : \boldsymbol{\epsilon} \, dV - \int_V \mathbf{F} \cdot \mathbf{u} \, dV - \int_S \mathbf{t} \cdot \mathbf{u} \, dS, \tag{3}$$

where $\boldsymbol{\epsilon}$ denotes the strain tensor, $\boldsymbol{\sigma}$ the stress tensor and $\mathbf{t}$ the tractions that are distributed over a surface S of a volume V. The inner product between two tensors is denoted as $\cdot : \cdot$. The first term in the equation entails the internal forces while the other two, the external body and surface ones.

In [20] the previous equation 3 was considered in a Bayesian setting allowing for the computation of the uncertainty of the solution as well as for confidence intervals. The Finite Element Method (FEM) is used where the displacements are inferred for the element nodes and interpolated elsewhere.

Linear elastic models have been also used when registering brain images based on sparse correspondences. In [21], a mapping between the cortical surface is established, two images are brought into correspondence by estimating a global transformation modeling images as inhomogeneous elastic objects. The elasticity parameters vary as a function of location in the brain image to compensate for the fact that certain structures tend to deform more than others. In addition, a non-zero initial strain was considered so that some structures expand or contract naturally.

In general, an important drawback of registration process is that when source and target volumes are interchanged, the obtained transformation is not the inverse of the previous solution. Christensen and Johnson [22] tried to overcome this shortcoming by estimating simultaneously both transformations while penalizing inconsistent transformations by adding a constraint to the objective function. The regularization constraint is that of linear elasticity though the transformation is parametrized by a $3D$ Fourier series.

To tackle the inconsistency problem Leow *et al.* [23] took a different approach. Instead of adding a constraint that penalizes the inconsistency error, they proposed a unidirectional approach that couples the forward and backward transformation and provides inverse consistent transformations by construction. This method considers only the forward mapping to minimize the symmetric energy:

$$\begin{aligned} E(\mathcal{T}) &= \\ &\underbrace{\int_{\Omega_T} \|S(\mathcal{T}(\mathbf{x})) - T(\mathbf{x})\|^2 d\mathbf{x} + \omega\mathcal{R}(\mathcal{T})}_{E_1} + \underbrace{\int_{\Omega_S} \|T(\mathcal{T}^{-1}(\mathbf{x})) - S(\mathbf{x})\|^2 d\mathbf{x} + \omega\mathcal{R}(\mathcal{T}^{-1})}_{E_2}. \end{aligned} \tag{4}$$

Minimizing the previous energy $E(\mathcal{T})$ in a gradient descent fashion would lead to the following update rule:

$$\mathcal{T} \to \mathcal{T} + \delta\eta_1 + \delta\eta_2, \ \mathcal{T}^{-1} \to \mathcal{T}^{-1} + \delta\xi_1 + \delta\xi_2 \tag{5}$$

where δ is the step, η_1 and ξ_1 are the gradient descent directions of E_1 when considering the forward and backward warping respectively. Similarly, η_2 and ξ_2 are defined for E_2. By taking into account that the composition of the two maps should give the identity, η_2 can be expressed as:

$$\eta_2 = -\nabla \cdot (\mathcal{T}(\mathbf{x}))\xi_2((\mathcal{T}(\mathbf{x})). \tag{6}$$

The previous formulation allows the minimization of the symmetric energy by considering only the forward mapping but at the same time imposing the transformation to be inverse consistent.

However, linear elastic models are limited as they can only handle efficiently the case of small deformations. In [24], a way to recover large deformations, that are inverse consistent is given by considering a sequence of small deformation transformations. Each incremental transformation is modeled by a linear elastic model. A periodic sequence of images is considered where the first (or last) and middle image are the source and target respectively. Each incremental transformation maps an image of the sequence to the one that proceeds it. The concatenation of all transformations maps one input image to another. The objective function to be minimized is the summation of the intensity similarity cost evaluated over two successive pairs of images.

A different way to produce inverse consistent transformations that can account for large deformations is proposed in [25]. They modeled the deformation process through the St Venant-Kirchoff elasticity energy:

$$\mathcal{R} = \int \frac{\mu}{4} Tr((\boldsymbol{\sigma} - \mathbf{I})^2) + \frac{\lambda}{8} Tr(\boldsymbol{\sigma} - \mathbf{I})^2. \tag{7}$$

Deformations that result in strain tensors that differ from the identity (or rigid transformation) are penalized by measuring the Euclidean matrix distance. Such an approach considers the trace of the squared difference of the strain tensor with the identity $Tr((\boldsymbol{\sigma} - \mathbf{I})^2)$. However, the Euclidean metric has been proven not good for the tensor space while its asymmetry results in the inverse-inconsistency problem. Such a limitation was dealt with the use of log-Euclidean metrics in the place of the Euclidean ones, resulting in the Riemannian elasticity energy which is inverse consistent:

$$\mathcal{R} = \frac{1}{4} \int Tr(\log(\boldsymbol{\sigma})^2). \tag{8}$$

In [26], fast diffeomorphic image registration was proposed based on either membrane, bending or linear elastic energy. The velocity field is assumed to be constant over time. The solution is thus given through integration over time by composing successive solutions. Given a pair number of steps, this can be performed efficiently by a scaling and squaring approach. Furthermore, the exponential of the flow field is considered to guarantee that then the mapping is diffeomorphic. The energy is optimized by using the Levenberg-Marquardt algorithm and a full multi-grid approach in order to compute efficiently its update step.

Viscous Flow Model

In this case, the image under deformation is modeled as a viscous fluid. The transformation is governed by the Navier-Stokes equation:

$$\mu_f \nabla^2 \mathbf{v} + (\mu_f + \lambda_f)\nabla(\nabla \cdot \mathbf{v}) + \mathbf{F} = 0. \tag{9}$$

Operating on velocities, such a model permits to recover large deformations. The first term of the Navier-Stokes equation (Eq. 9), constrains neighboring points to deform similarly by spatially smoothing the velocity field. The second term allows structures to change in mass while μ_f and λ_f are the viscosity coefficients.

Viscous fluid flow transformations were introduced in medical image registration in [27, 28]. In [27], a template is modeled as a viscous fluid allowing for large magnitude non-linear deformations. The Partial Differential Equation (PDE) is solved for small time intervals and the complete solution is given by an integration over time. For each time interval a successive over-relaxation scheme is used. The Jacobian is monitored and each time its value falls under 0.5, the template is re-gridded and a new one is generated that is subsequently used to estimate a transformation. The final solution is the concatenation of all successive transformations occurring for each re-gridding step. That way, the topology is guaranteed to be preserved. In a subsequent work [28], a hierarchical way to recover the transformations for brain anatomy is presented. Initially, global affine transformation is performed followed by a landmark transformation model. The result is refined by fluid transformation preceded by an elastic registration step.

Computational inefficiency is the main drawback of viscous fluid models and the reason they have not gained the popularity of the rest of transformation models. To circumvent this shortcoming, a massive parallel computer implementation has been proposed in [27] while Bro *et al.* [29] proposed a technique based on a convolution filter in scale-space. The filter is designed as the impulse response of the linear operator $L = \mu_f \Delta \mathbf{u} + (\mu_f + \lambda_f)\nabla(\nabla \cdot \mathbf{v})$ defined in its eigen-function basis. A multi-grid approach was proposed in [30] towards handling anisotropic data along with a multi-resolution scheme opting for recovering first coarse velocity estimations and refining them in a subsequent step.

An inverse consistent variant of fluid registration was proposed in [31] to register Diffusion Tensor images. Symmetrized Kullback-Leibler (KL) divergence was used as matching criterion. Inverse consistency was achieved by evaluating the matching and regularization criterion towards both directions. Fluid deformation models have also been used to tackle multi-modal registration [32] or in an atlas-enhanced registration setting [33].

Diffusion Model

In this case, the deformation is modeled by the diffusion equation:

$$\Delta \mathbf{u} + \mathbf{F} = 0, \tag{10}$$

that corresponds to the following regularization energy:

$$\mathcal{R} = \int \sum_{j=1}^{d} \|\nabla u^j(\mathbf{x})\|^2 d\mathbf{x}. \tag{11}$$

In the previous equation, the upper-script denotes order of the spatial dimension. Algorithms based on this transformation model exploit the fact that the Gaussian kernel is the Green's function of the diffusion equation Eq. 10 to provide for an efficient regularization step.

Thirion [34], inspired by Maxwell's Demons, was the first to propose diffusion models in image registration. In this work, object boundaries are modeled as membranes and the image is diffused through it under the influence of the Demons placed inside the membranes. The algorithm operates in two steps: (i) estimation of the displacements for every point, and (ii) a regularization step. The Demon force is calculated by considering the optical flow constraint that is valid for small displacements. Regularization is achieved through Gaussian smoothing.

Demons, as initially introduced, is an efficient algorithm able to provide dense correspondences but lacks a sound theoretical justification. Due to the success of the algorithm, a number of papers tried to give theoretical insight into its workings. Fischer *et al.* [35] gave a fast algorithm for image registration. The result was given as the solution of a diffusion PDE. An efficient scheme for its solution was proposed while a connection to Thirion's Demons algorithm was drawn.

The most successful attempt to shed light on Demons is described in [36]. Image registration is formulated as an energy minimization problem and the connection of the Demons algorithm with gradient descent schemes is shown. Thirion's image force based on optical flow is shown to be equivalent with a second order gradient descent on the Sum of Square Differences (SSD) matching criterion. As for the regularization, it is shown that the convolution of the global transformation with a Gaussian kernel corresponds to a single step of a first order gradient descent of a functional that penalizes the remainder of the transformation after having it convolved with a high-pass filter.

Vercauteren *et al.* [37] adopted the alternate optimization framework introduced by Cachier [38] to relate symmetric Demons forces with the Efficient Second-order Minimization (ESM) [39]. The transformation was computed by optimizing the global energy

$$E = \underbrace{\mathcal{M}(T, S \circ \mathbf{u}) + \mathcal{D}(\mathbf{u}, \mathbf{w})^2}_{Matching} \; \underbrace{\phantom{\mathcal{D}(\mathbf{u}, \mathbf{w})^2} + \mathcal{R}(\mathbf{w})}_{Regularization} . \quad (12)$$

Optimization can be achieved efficiently as the introduction of the auxiliary variable v decouples the problem into two parts that can be solved separately very fast. Matching was performed by minimizing the first term through ESM optimization while regularization was achieved by Gaussian smoothing.

In [40] Thirion's algorithm was endowed with the diffeomorphic property. Diffeomorphic transformations were parametrized by using stationary speed vector fields allowing for a fast computation of exponentials based on the scaling and squaring method.

To further facilitate the use of the Demons algorithm in anatomical computational studies, Demons were provided with the symmetric properties in [41]. Initially, it is shown how the complete spatial transformation can be represented in the log-domain. Subsequently, a symmetric extension is provided by averaging the forward and backward forces that have been computed separately.

Recently, efforts opting for a mathematical justification of the smoothing step in order to enable for deformations bearing different physical properties [42, 43, 44] have been considered.

Cahil *et al.* [42] showed that curvature and fluid registration can be formulated as two coupled diffusion equations. Their stationary solution may be approached via successive Gaussian convolutions, thus yielding a Demons algorithm for these cases. In a subsequent work [43], they showed how to extend the curvature regularization to consider local image gradient content. Again, a coupled PDE system was proposed whose stationary solution can be attained by consecutive convolutions with the Green's function of the diffusion equation. Another way to perform adaptive smoothing was presented in [45] where a non-stationary diffusion filter was used exploiting available knowledge regarding the deformability of tissues. In areas where greater deformations were expected, diffusion was scaled down. On the contrary, inside objects where coherence should be preserved, diffusion was scaled up.

Mansi et al. [44] introduced a physical constraint in the registration process to estimate the myocardium strain from Cine-MRI. The logDemons algorithm [41] was endowed with the incompressibility constraint by making the velocity field divergence-free. This was achieved by solving the Poisson equation under 0-Dirichlet boundary conditions within a subdomain of the image showing the myocardium.

A main drawback of this family of methods is that the Demons forces are usually calculated based on a SSD criterion and thus are appropriate for mono-modal image registration. Numerous efforts have been made towards extending Demons for multi-modal registration. Guimond *et al.* [46] proposed a method that alternates between Demons based registration and intensity correction. Other efforts include the encoding of similarity metrics such as Normalized Mutual Information [47, 48].

The application of the Demons algorithm is not limited to scalar images but has been extended to diffusion tensor images [49], multi-channel ones [50] as well as different geometries [51]. In [49], Demons forces were derived by considering the squared difference between each element of the Log-Euclidean transformed tensors while taking into account the reorientation introduced by the transformation. Multi-channel Demons were considered to register $4D$ Time-Series of Cardiac Images by enforcing trajectory constraints in [50]. Each time instance was considered as a different channel. In addition, the transformation between successive channels was considered as given. Finally, the Demons framework was employed to register cortical surfaces parametrized as spheres in [49]. To generalize Demons on the sphere, a way to measure the distance between two transformations and to regularize the transformation was introduced.

Curvature Registration

In this case, the deformation is modeled by the following equilibrium equation:

$$\Delta^2 \mathbf{u} + \mathbf{F} = 0. \tag{13}$$

The regularization part of the energy to be minimized in this specific case, is given by

$$\mathcal{R} = \int \sum_{j=1}^{d} (\Delta u^j(\mathbf{x}))^2 d\mathbf{x}. \tag{14}$$

The advantage of such a regularization scheme is that it does not penalizes affine linear transformations thus removing the need for a an additional affine linear pre-registration step.

Fischer and Modersitzki were the first to introduce this constraint in [52,53]. To solve equation Eq. 13, the Gâteaux derivatives with respect to the data and regularization term were calculated:

$$\int_{\Omega} \left\langle \mathbf{F}(\mathbf{x}, \mathbf{u}(\mathbf{x})) + \Delta^2 \mathbf{u}, \mathbf{v}(\mathbf{x}) \right\rangle_{\mathbb{R}^d} d\mathbf{x}. \tag{15}$$

To solve the resulting PDE a finite difference scheme was used by introducing an artificial time parameter while the following boundary conditions were considered:

$$\nabla u^j(\mathbf{x}) = \nabla \Delta u^j(\mathbf{x}) = 0,\ \mathbf{x} \in \partial\Omega,\ j = 1, \cdots d. \tag{16}$$

The use of the previous Neumann boundary conditions was motivated by the fact that the resulting matrix problem is highly structured and thus can be solved fast. While this is true, the resulting underlying function space penalizes the affine linear displacements as pointed out by Henn in [54]. Thus, Henn proposed to include second-order terms as boundary conditions in the energy and applied a semi-implicit time discretization scheme to solve the full curvature registration problem.

In [55], another way to solve the curvature based registration problem was proposed. Instead of devising a numerical scheme to solve the PDE that results from the equilibrium equation (Eq. 13), recursive convolutions with an appropriate Green's function were used following [29].

Flows of Diffeomorphisms

Last but not least, flows of Diffeomorphisms have been proposed to model the deformation. In this case, the deformation is modeled by considering its velocity over time according to the Lagrange transport equation [27, 56, 57]. The regularization constraint constrains the velocity field to be smooth:

$$\mathcal{R} = \int_0^1 \|\mathbf{v}_t\|_V^2 dt. \tag{17}$$

$\|\cdot\|_V$ is a norm on the space V of smooth velocity vector fields defined as $\|f\|_V = \|Lf\|_{L_2}$, where L is a differential operator and $\|\cdot\|_{L_2}$ is the L_2 norm of square integrable functions. Choosing appropriately the kernel that is associated with V allows for the modeling of different levels of spatial regularization. While most often a single Gaussian kernel is used, it is possible to use multiple kernels and smooth the deformations adaptively in different scales [58, 59]. Lastly, the fact that the velocity field varies over time allows for the estimation of large deformations [60].

The advantage of this framework, known as Large Deformation Diffeomorphic Metric Mapping (LDDMM), is that it allows for the definition of a distance between images or sets of points [61, 62]. The distance is defined as a geodesic according to a metric and can be used for studies of anatomical variability [63]. A number of theoretical aspects of this framework and especially the ones related with computational analysis were further developed in [64,65,66,67,68]. The interested reader is referred to [69] for an overview of the evolutions and the corresponding equations.

The LDDMM framework has been proven extremely versatile and has been extended to treat a number of problems, *e.g.* volume registration for scalar, vector- and tensor-valued data [60, 70, 71, 72, 73, 74], point-matching [61], point-matching on spheres [75], matching sets of unlabeled points [76, 77, 78], shape-matching [79, 58], curve-mapping [80, 81, 82, 83] and hybrid registration [84, 85].

Even though the LDDMM framework provides diffeomorphic transformations, it is not symmetric. To encode the symmetric property a number of approaches have been proposed [86,70,71]. Beg *et al.* [70] focused on providing symmetric data terms. Younes also discussed ways to render the alignment process symmetric in [86] while a symmetric LDDMM registration process driven by cross-correlation was presented in [71].

The mathematical rigorousness of the LDDMM framework comes at an important cost. The fact that the velocity field has to be integrated over time results in high computational and memory demands. Moreover, the gradient descent scheme that is usually employed to solve the optimization problem of the geodesic path estimation converges slowly. More efficient optimization techniques for the LDDMM have been investigated in [87, 88, 72].

Marsland *et al.* [87] formulated the problem in a PDE framework and a particle method was used to solve for the diffeomorphism. A similar approach that involves a particle mesh method was presented in [88] by Cotter *et al.* More recently, a Gauss-Newton implementation of the previous algorithm was given in [72]. These approaches are based upon the fact that knowing the initial velocity field suffices to calculate the intermediate and final deformation.

Instead of devising more sophisticated optimization schemes to calculate efficiently diffeomorphisms, one could simplify the problem by decreasing its degrees of freedom. Stationary velocity fields [89] have been used towards this direction. Despite being limited with respect to the diffeomorphisms that they can capture, stationary velocity fields are a common choice among many researchers [26, 90, 91, 92]. Hernandez *et al.* followed this approach and considered stationary Ordinary Differential Equations (ODEs) in the LDDMM framework [93].

2.2 Geometric Transformations Inspired by Interpolation Theory

Rather than being motivated by a physical model, the models of this class are derived either by interpolation theory or approximation theory. In interpolation theory, displacements, considered to be known for a restricted set of locations in the image, are interpolated for the rest of the image domain. In approximation theory, we assume that there is an error in the estimation of displacements. Thus, the transformation approximates smoothly the known displacements rather than taking the exact same values. The success of these models lies in the fact that they are rich enough to describe the transformations present in image registration problems while having low degrees of freedom facilitating the inference of the parameters.

Radial Basis Functions

One of the most important families of interpolation strategies are the Radial Basis Functions (RBFs), where the value at an interpolation point $\mathbf{x}$ is given as function of its distance r from the known sample $\mathbf{p}$, or

$$\mathbf{u}(\mathbf{x}) = \sum_{i=1}^{N} \omega_i \phi(\|\mathbf{x} - \mathbf{p}_i\|). \tag{18}$$

An evaluations study comparing RBFs used as transformation functions in non-rigid image registration was first given in [94]. A more thorough presentation and an analysis with respect to their property to preserve topology was given more recently in [95]. The advantage of the RBFs is that they are able to interpolate a deformation field from irregularly placed known values. Their main disadvantage lies in the fact that they often have a global support. As a result, knowing the displacement at one point influences the values that points in the whole image domain will take. This behavior is undesirable when local transformations are to be recovered.

One of the first RBFs that has been used in the field, and still of great importance, is Thin-Plate Splines (TPS) [96, 97]. Given N control points p whose displacement is known, the displacement field is given by:

$$\mathbf{u}(\mathbf{x}) = \mathbf{A}\mathbf{x} + \mathbf{b} + \sum_{i=1}^{N} \xi_i \phi(\|\mathbf{x} - \mathbf{p}_i\|), \tag{19}$$

where $\phi(r) = r^2 \log r$ in the $2D$ case and $\phi(r) = r$ in the $3D$ case. r is the distance $r = \|\mathbf{x} - \mathbf{p}_i\|$. The weighting factors ξ_i as well as the matrices $\mathbf{A}$ and $\mathbf{b}$ are calculated by solving a linear equations system. In the $2D$ case, TPS minimize the bending energy:

$$\mathcal{R} = \int \frac{\partial^2 \mathbf{u}}{\partial x^2} + 2\frac{\partial^2 \mathbf{u}}{\partial x \partial y} + \frac{\partial^2 \mathbf{u}}{\partial y^2} dx dy, \tag{20}$$

assuming infinite boundary conditions.

TPS are known to exhibit certain shortcomings. The transformation from one image domain to another is not inverse consistent. Moreover, their support is global not allowing to recover local image warping. Furthermore, TPS do not take into consideration possible errors in the estimation of the displacements in the landmark positions. Lastly, as the number of points increase, the interpolation becomes computationally demanding. A number of researchers have worked towards lessening the importance of these drawbacks [98, 99, 100, 101, 102].

In [98], Johnson and Christensen tackled the inverse inconsistency problem. They considered the minimization of the energy Eq. 20 under cyclic boundary conditions in an effort to account for the great consistency error that they observed in the boundary of the images. Additionally, a term that penalizes the consistency error was introduced in the objective function to render the registration inverse consistent.

The problem with the global nature of TPS was treated in [100]. TPS were constructed in such a way that their support is restricted locally. In a subsequent work, Yang *et al.* [101] defined the support of each point in an adaptive way by taking into consideration the distribution of the points in the image domain.

Rohr *et al.* [99] proposed to take into consideration the landmark localization error when estimating the dense deformation field through the use of approximating Thin-Plate Splines.

The proposed method is able to handle both isotropic and anisotropic errors in the estimation of the landmark position.

Three ways to address the computational problems related with the presence of a great number of landmarks were studied by Donato *et al.* [102]. The straightforward approach of subsampling the points was compared to more elaborated ones that use either a subset of the basis functions or matrix approximation techniques.

Clamped-Plate Splines [62, 103] minimize the same energy as TPS though under specific boundary conditions. Following the LDDMM framework, the energy is solved so that the resulting dense deformation field is diffeomorphic and thus this type of splines is referred to as Geodesic Interpolating Splines [104]. An extension to combine them with affine transformations was given in [105] while two ways to calculate them were presented by Mills *et al.* [106].

Another family of RBFs that has global support is the multi-quadratics [107]

$$\phi(r) = \left(r^2 + d^2\right)^{\frac{\mu}{2}}. \tag{21}$$

d is a parameter that controls the smoothness of the deformation and may vary for different points allowing for an adaptive smoothness based on their spatial distribution. μ a nonnegative scalar. The previous approach has been extended to treat the presence of a rigid object by Little *et al.* [108].

Gaussian functions is another class of RBFs that can be used to parametrize the deformation [109]. They are defined as:

$$\phi(r) = e^{-\frac{r^2}{\sigma^2}}, \tag{22}$$

Their advantage is that, despite having a global support, their spatial influence may be controlled by choosing appropriately the Gaussian kernel σ. By choosing a small size for the Gaussian kernel, their influence can be restricted greatly and thus local displacements may be recovered. A recent example of the use of this deformation model can be found in [110], where it has been used in the brain registration problem.

An approximative method to create a dense deformation field from a set of sparse displacements is by calculating their weighted average [94]. The weights at each interpolation point for all control points sum to one. Their support is global, though by choosing appropriately the function that determines the weights, the locality of their support can be adapted.

In medical imaging it is pretty often the case that we search to recover local deformations. In such cases, the previous functions that have global support, and thus all landmarks influence the estimation of the transformation, are not well suited. To be able to treat successfully such cases, interpolation methods where control points have spatially limited influence in the image domain are appropriate.

Fornefett *et al.* [111] investigated the use of Wendland functions [112, 113], that exhibit the desired locality property, for elastic registration.

Other local support radial basis functions are the C^2 smooth Wu functions [114] or the functions proposed by Buhmann [115]. Rohde *et al.* [116] applied the Wu functions in image registration and derived bounds for the basis function's coefficients so that the Jacobian of the computed transformation remains positive.

More recently, a new radial basis function was proposed in [117]. It is defined by using the cosine function and contrary to what claimed in the paper, it is not positive definite [118]. Lowitzsch [119] introduced a special class of matrix valued RBFs that are divergence free.

In [95], the previous locally constrained radial basis functions were compared using transformations on random point sets, artificial images, and medical images. In most cases, in the presence of both local and global deformation, the locally constrained TPS and Buhmann functions were found to perform better than the rest.

Elastic Body Splines

Splines, though mainly inspired by interpolation and approximation theory, may also be inspired by physical models. Such is the case of Elastic Body Splines (EBS) that were introduced by Davis *et al.* [120]. As the name implies, they are solutions of the Navier-Cauchy equilibrium equation for an homogeneous isotropic elastic body subjected to forces. In the case that the applied forces are either polynomial or rational one can solve analytically the equation.

The previous work was extended in [121] by considering a different type of forces acting upon the elastic body. Instead of assuming forces given as a polynomial or rational function, a Gaussian function was considered. As a result, the transformation model can cope better with local deformations. Moreover, the size of the kernel of the Gaussian can be used to parametrize the compactness of the model's support. Again, the authors were able to obtain an analytic solution of the equilibrium equation.

Wörz and Rohr further extended Gaussian Elastic Body Splines in [122]. Instead of opting for an exact interpolation, an approximation strategy was employed to account for errors in the landmark displacements. The PDE was extended to incorporate Gaussian forces that were weighted by the localization uncertainty. The uncertainties, depending on their isotropic or anisotropic nature, were represented as either scalar weights or matrices. An analytic solution was obtained for the extended equation. The error-aware method performed better than the two previous ones.

Free Form Deformations

Free-form Deformations (FFDs) is one of the most common transformation models in medical imaging. A rectangular grid $G = K \times L$ is superimposed upon the image (size $M \times N$, $K \ll M$, $L \ll N$) that gets deformed under the influence of the control points. The dense deformation is given as a summation of tensor products of univariate splines. FFDs were first popularized in the computer graphics community [123, 124] but gained vast acceptance in the medical imaging community when coupled with cubic-B splines [125, 126, 127, 128].

The deformation in $2D$ is given as:

$$\mathbf{u}(\mathbf{x}) = \sum_{k=1}^{K} \sum_{l=1}^{L} B_k(\mu) B_l(\nu) \mathbf{d}_{kl}, \tag{23}$$

where $\mathbf{d}$ denotes displacement, $k = \lfloor x/\delta_x \rfloor$, $l = \lfloor y/\delta_y \rfloor$, $\mu = x/\delta_x - \lfloor x/\delta_x \rfloor$, and $\nu = y/\delta_y - \lfloor y/\delta_y \rfloor$. B_l represents the lth basis function of the B-spline and $\delta_x = \frac{M}{K-1}, \delta_y = \frac{N}{L-1}$ denote the control point spacing. The advantage of the transformation model lies in its simplicity, smoothness, efficiency and ability to describe with few degrees of freedom local deformations.

While in general the transformations that result from cubic B-spline FFDs are smooth, the preservation of topology is not guaranteed. Rueckert *et al.* [129] imposed the hard constrains proven in [130] to produce diffeomorphic deformation fields. The required condition is that the maximum displacement should not be greater than 0.4 the grid spacing.

Many extensions of FFDs have been proposed in the literature. For example in [131], an inverse consistent method based on FFDs is proposed that does not need the inversion of the deformation field. Moreover, the fact that the gradient and Hessian can be computed analytically in this framework can be exploited by the optimizer to achieve faster and more accurate convergence. While, FFDs are usually uniform, non-uniform rational B-splines have been used in medical image registration in an adaptive focus approach [132].

FFDs have been extended to treat multiple image registration where hard constraints are employed to define a reference domain [133, 134, 135]. Last but not least, the transformation model has been extended to the spatio-temporal domain [136,137,138] where B-splines are also used for the temporal axis.

Basis functions from signal representation

Inspired by the mathematical tools that are available to represent and analyze signals, many researchers have used Fourier and Wavelet analysis to model the transformation. Maybe the most important reason to use them is the fact that they can provide naturally a multi-resolution decomposition of the displacement field. A necessary property for the coarse-to-fine schemes that are commonly applied in medical image registration to ease the computations and handle large deformations.

Maybe one of the most well known registration algorithms that employs a Fourier based transformation scheme is the consistent registration framework introduced by Christensen [22]. The advantage of the Fourier series representation of the transformation is that it results in a simplification of the used linear elasticity constraint. Moreover, it allows for an efficient numerical implementation.

Fourier basis functions are well localized in the frequency domain. On the contrary, they are not localized at all in the spatial domain. Wavelet basis functions, being localized in both domains, bear the important advantage that they can model local deformations often present in deformable image registration.

A wavelet is a square integrable function $\psi \in \mathbf{L^2}(\mathbb{R})$ with zero mean $\int_{-\inf}^{+\inf} \psi(t)dt = 0$, normalized $\|\psi\| = 1$ and centered at zero. A family of wavelet functions that generate an orthonormal base in $\mathbf{L^2}(\mathbb{R})$ can be obtained by scaling and translation. The construction of this basis is related to the multi-resolution signal approximation that can obtained by an orthogonal projection to a family of nested subspaces $V_{j+1} \subset V_j$, such that $V_{j+1} \oplus W_{j+1} = V_j$, where W_{j+1} is the necessary additional detail. V_j and W_j are created by projecting the function to orthogonal scaling and wavelet functions. For higher dimensions, tensor products of $1D$ wavelet functions are used.

Wu *et al.* [139] used a wavelet-based deformation model. The Cai-Wang wavelet was employed to generate a multi-resolution description in Sobolev space yielding intrinsically smooth deformations. Based on this model, the authors were able to treat global and local information simultaneously in a coarse-to-fine approach. Gefen *et al.* [140] modeled the deformation field by a finite-supported, semi-orthogonal wavelet. The Marquardt-Levenberg optimization scheme was used to minimize a functional that comprises of two terms. The first term penalizes surface distances while the second term regularizes the deformation according to a linear elasticity model.

Musse *et al.* [141] presented a topology preserving multi-resolution approach. Non-orthogonal Riesz basis of polynomial splines were used due to their compactness. The topology was preserved by controlling the Jacobian through hard linear constraints. The approach was extended to the $3D$ domain in [142] and was further validated in [143]. In the $3D$ case, the same multi-resolution framework was used, though no linear constraints can be derived to preserve the topology. To guarantee the desired property, a constrained optimization problem, where the Jacobian is enclosed between two user-defined bounds, was solved. Optimization was performed with a block-wise descent scheme. Cathier [144] used the same wavelet basis as in [139] to decompose the transformation in a multi-resolution fashion. An L_1 penalty on the wavelet coefficients was used to regularize the registration problem. This regularization leads to sparse transformations with respect to the wavelet basis and thus facilitates their storage in the disk.

Piecewise Affine

One of the simplest ways to deform an image is to consider a piecewise linear deformation model. The image is mosaicked by a set of triangles or tetrahedra depending on its dimension. The deformation is parametrized by the nodes of the mesh and an affine interpolation takes place inside each region. Efficiency and invertibility are the main strengths of this method, while lack of smoothness is its main limitation.

Some of the most recent approaches where a piecewise affine model was used include, but are not limited to, the following. Hellier *et al.* [145] proposed a multi-resolution and multi-grid approach. The image was partitioned adaptively to cubes and an affine transformation was inferred for each one. A regularization energy term encouraged neighboring pairs to deform similarly. Zhang *et al.* A similar approach was employed in [146] to tackle diffusion tensor registration by taking into consideration tensor reorientation. The images were separated into contiguous blocks and an affine transformation was recovered for each one of them. Regularization on the interface of regions ensured the global smoothness of the transformation.

Pitiot *et al.* [147] reconstructed $3D$ volumes of biological images by employing a piecewise affine transformation model. The images were separated into independent components through hierarchical clustering. In a subsequent step, affine registration was performed for each pair of regions. The final transformation was estimated by considering the affine transformation for each region and applying a non-linear interpolation in-between the regions. A similar approach was presented in [148] with the difference that a regularization step followed to improve the smoothness in the interpolated areas. The final transformation was composed in such a way that its invertibility was ensured.

Two more recent application of piecewise affine model were presented in [149, 150]. Cootes [149] favored the use of piecewise affine transformations as they can be easily inverted. Buerger *et al.* [150] proposed a hierarchical framework to separate adaptively the images in regions. Splitting was formulated as an energy minimization problem.

Most of the approaches that employ piecewise linear strategies, consider the affine transformations independently. As a result, singularities may occur and the transformation is not globally invertible. To account for the previous drawback, sophisticated methods have been introduced. A transformation model that is affine at the center of a region and reduces to identity as the distance from the center increases was introduced in [151]. The novel transformation model has a closed form and can be computed efficiently. Moreover, constraints were given in the form of bounds on the translation so that invertibility is ensured.

Arsigny *et al.* [152] introduced a poly-rigid/affine transformation model. Based on a finite set of points whose transformation is known, the global transformation at each point is given by integrating over time a distance-weighted sum of infinitesimal velocities at the known points. No closed form exists but a computationally more expensive integration of ODEs is necessary. [153] extended the poly-affine transformation so that its inverse is also poly-affine. Moreover, the fusion of affine transformations was rendered invariant to affine changes of the coordinate system.

2.3 Constraints

Image registration is principally an ill-posed problem as the number of unknowns is greater than the number of available constraints. In order to account for that, regularization is necessary. Moreover, regularization allows us to introduce any prior-knowledge we may have for the physical properties of the underlying anatomical structure and helps optimization to avoid local minima.

There are two possible ways to regularize the problem, either explicitly or implicitly. Explicit regularization may be achieved through the addition of a smoothing term in the energy that penalizes non-regular configurations. This is mostly the case when physically motivated models are used. Implicit regularization may be achieved by parameterizing the deformation field with smooth functions. That does not exclude the use of explicit regularization but that may be used now to achieve complementary goals, usually tailored for the specific problem at hand.

One of the most important properties that a registration algorithm should exhibit is the preservation of topology. Apart from the framework of flows of diffeomorphisms that delivers naturally such results, the rest of deformation models don not exhibit these properties. In that case, smoothness and invertibility of the resulting deformation field may be guaranteed through the use of constraints. The Jacobian of the deformation field is very informative regarding the local properties of the deformation field. Thus, by tracking its values, singularities may be avoided by creating intermediate templates and reinitializing the process [27].

This technique is efficient but the way the preservation of topology is guaranteed seems rather awkward. A more elegant way would be to incorporate an appropriate term acting upon the Jacobian in the objective function. In [22], a term that penalizes small and large Jacobian values for both the forward and backward transformation was added to the objective function. Similarly, Droske and Rumpf [154] used a regularization term that considers the length, area and volume deformation. This approach has the disadvantage that it depends greatly upon the way the different energy terms are weighted. If the weight for the regularization term is not important enough, singularities may appear. Whereas, if the weight for the regularization is too great, the optimization may be hindered.

A different and probably more appropriate strategy is to cast the problem as a constrained optimization problem. In [141], linear inequality constraints were derived so that the topology is preserved. The optimization was solved by employing a fast method that bears a resemblance to sequential linear programming. In its $3D$ variant [142], the energy was optimized under the constraint that the Jacobian will stay in-between user specified bounds. Interval analysis techniques were used in order to solve the optimization problem. Inequality constraints were also used by Haber and Modersitzki [155]. A variant of a log-barrier method was used to solve the optimization problem. Instead of solving the initial constrained problem, a sequence of unconstrained ones was considered. The weight for the barrier terms increased gradually for each unconstrained problem that was optimized by applying a variant of the Gauss-Newton's method.

Sdika [128] also proposed a constrained optimization framework to ensure that the transformation, parametrized by cubic B-splines, is invertible. Two constraints were proposed. The first constrains the Jacobian of every pixel to be greater than a threshold. As this constraint does not control the value of the Jacobian between the voxels, a second constraint was proposed that relates the Jacobian with its derivative. In that way, the Jacobian is restricted to be within a range of values. Moreover, when approaching values close to the bounds, its derivatives are constrained to be close to zero. In [156], a simpler penalty was devised for the case of B-splines. The penalty takes into consideration the difference between two adjacent nodes and is memory efficient.

In many applications, on top of ensuring that the topology will be preserved, we are also interested in volume preservation. Such a constraint is of particular interest in cases that we know that the imaged anatomical structure is not compressible and all changes are due to either motion or intensity changes provoked by the action of a contrast agent. The simplest case would be to consider a rigid part of the body such as bone structures. More complicated cases would include deformable structures that preserve their volume such as breast, myocardium and liver.

In [157], such a strategy was employed to register contrast-enhanced MR breast images. Along with the image matching term a second term that penalizes volume changes was considered. The penalty integrates the absolute logarithm of the Jacobian determinant and is zero only when local volume is preserved. A sequential approach was proposed in [158]. First, a standard registration was performed. Based on its result, areas whose volume should be preserved were identified. Once found, the displacement of the control points of the FFD model that influence these areas were fixed to the mean of their previous ones and the registration was solved again for the rest of the variables. A constrained optimization approach to preserve volume was presented by Haber *et al.* [159]. An energy comprising a matching and regularization term was minimized under the constraint that the determinant of the transformation is equal to one ($det(\mathbf{I} + \nabla \mathbf{u}) - 1 = 0$). Staggered grids were used to discretize the problem and Sequential Quadratic Programming to solve it.

Another type of problems that call for an incompressibility constraint are those where the deformation of the myocardium is studied as it is known to be a nearly incompressible material. Bistoquet *et al.* [160] approximated the previous constraint by $\nabla \cdot \mathbf{u} = 0$. This constraint was enforced by the use of divergence-free radial basis functions as deformation model [119]. In addition, a hard constraint was introduced in the objective function to penalize deviations from incompressibility. The determinant of the Jacobian was constrained to be close to one in a predefined region by using Lagrange multipliers in [161]. A different approach was taken by Mansi *et al.* [44] where the velocity field $\mathbf{v}$ was constrained to be divergence-free. The method was based upon the fact that the integration over time of divergence-free velocities results in incompressible deformations.

Last but not least, as in medical images rigid structures are present, it would be beneficial for the quality of the registration result to incorporate rigidity constraints in order to treat them according to its physical properties. Loeckx *et al.* [162] constrained locally a non-rigid FFD registration method by penalizing deviations of the Jacobian from orthogonality. In [163] rigidity was imposed by introducing three conditions. The first condition enforces the second derivatives of the transformation to be zero. The second condition enforces the orthonormality of the rotation matrix while the third condition imposes the determinant of the Jacobian to be equal to one. Local rigidity has also been considered in a variational setting by Modersitzki [164]. Along with the matching and the regularization term, a third one was introduced in the objective function. The third term controls the rigidity of the transformation by enforcing its Jacobian to be linear, orthogonal and orientation preserving. A Gauss-Newton optimizer was used.

3 Objective Functions

Images can be aligned either by evaluating a criterion based on intensities over the whole image domain (iconic methods) or by establishing point correspondences (geometric methods). There is also a third class of methods, a hybrid one, that opts for combining both types of information in an effort to get the best of both worlds.

3.1 Iconic Methods

Iconic registration methods offer accuracy by providing dense correspondences between the considered image domains at the cost of considerable computational expense. Due to the fact that all image points are considered equally, salient points might fail to get the importance they deserve. In addition, initial conditions influence greatly the quality of the obtained result. In the presence of large deformations, typical in longitudinal and population studies, the quality of the solution is often degraded.

The matching term integrates the evaluation of a dissimilarity criterion over all image elements:

$$\mathcal{M} = \int_{\Omega_T} \rho(S \circ \mathcal{T}(\mathbf{x}), T(\mathbf{x})) d\mathbf{x}. \tag{24}$$

Devising an appropriate criterion ρ is an important and difficult task as the criterion should be able to account for different physical principles behind the acquisition of the two images and thus for the intensity relation between them. Moreover, the properties of the objective function (*e.g.* its convexity) may influence the difficulty of the inference and thus the quality of the obtained result. An ideal criterion would take low values, when points belonging to the same tissue class are considered and great values, when points from different tissue classes are compared. Moreover, it should be convex allowing for accurate inference.

At this point, two cases should be discerned: i) the mono-modal case, considering images from one modality, and ii) the multi-modal case, considering images from multiple modalities.

Mono-modal registration

The mono-modal case is the easiest one and historically the first to be studied. Since the same imaging device is used to image both volumes it is often assumed that same anatomical structures correspond to similar intensity values. This assumption leads naturally to the use of Sum of Squared or Absolute Differences (SSD and SAD respectively) as a matching criterion. The choice between the two depends on the assumption on the noise that corrupts the image intensities. In a more sophisticated setting when a linear relation is assumed between the signal intensities, the optimal criterion is Cross Correlation (CCor) and Correlation Coefficient (CCoef) [13, 165, 71].

Intensity information by itself is considered a poor feature that often leads to ambiguous matching and is one of the main reasons for the presence of local minima in the objective function. Trying to minimize the effect of these local minima and establish more accurate correspondences, a number of researchers have proposed to increase the dimensionality of the feature space by introducing local information through the use of attributes that represent the geometric structure of the underlying anatomy. These approaches are often referred to as feature- or attribute-based approaches.

In their seminal work, Shen and Davatzikos [110] proposed the use of an attribute vector including Geometric Moment Invariants in an attempt to capture local anatomical information at different spatial scales. The motivation is that a rich enough attribute vector will be able to differentiate between voxels that would be considered the same based only on their intensity information. Thus, fewer local minima will be present and better accuracy may be achieved. To further reduce the effect of the local minima, they proposed a hierarchical scheme that approximates successively the objective function through the use of an increasing number of voxels where the matching is evaluated.

The success and importance of the previous method becomes evident in view of the number of approaches that have been proposed to improve its performance. One drawback of the previous method is that it requires a pre-segmentation step in order to introduce local spatial information. To remove the previous requirement, the use of Daubechies wavelets to populate the attribute vector was proposed in [166]. The attribute vector was constructed in a multiscale fashion and is translation and rotation invariant. It was shown that the wavelet-based attribute vector is more discriminative when compared to the geometric moments. Another approach to tackle the previous shortcoming is by using local histograms and boundary information as attributes [167]. In [168], a learning approach was proposed to improve the result in two ways. First, the optimal scale for the geometric features for each voxel was determined leading to increased discriminative power. The hierarchical scheme was improved by deciding upon which voxels drive the registration process based on their saliency and the consistency of their description across the training data.

Another way to incorporate local information using attribute vectors is through the use of local frequency representations being the responses of Gabor filters [169, 170]. Gabor features have proven successful for both mono-modal and multi-modal image registration as they are able to capture information across different scales and orientations. Ou *et al.* [169] optimized the Gabor features to be more distinctive and introduced the notion of mutual saliency to let the most reliable points drive the registration process. Liao and Chung [171] however argued that frequency spectrums of MRI brain images often exhibit non-Gaussian behavior and thus the choice of Gabor filters is not optimal. They proposed the use of symmetric alpha stable filters and showed experimentally that they outperform Gabor features in non-rigid MRI brain registration. A new feature for non-rigid registration, named uniform spherical region descriptor, was proposed in [172]. It is invariant with respect to rotation as well as monotonic gray-level transformation and thus is able to account for the presence of bias field.

Multi-modal registration

Multi-modal registration is more challenging as the choice of an appropriate objective function is harder a task. Two main approaches have been proposed to solve the problem:

1. Use information theoretic measures.
2. Reduction of multi-modal problem to a mono-modal problem by:
   (a) simulating one modality from another, or
   (b) mapping both modalities to a common domain.

Here, we are going to focus primarily on information theoretic approaches as they constitute the most frequently used way to tackle the challenges posed by multi-modal registration. Reduction techniques will also be briefly discussed.

Information theoretic approaches: Information theoretic approaches were popularized by Viola, Wells, Colignon and Maes [173,174,175,176]. They proposed to use as objective criterion, the mutual information (MI):

$$I(XY) = H(X) + H(Y) - H(X,Y). \tag{25}$$

That is, the MI between two random variables X and Y is defined as the difference of their marginal entropies $H(X)$ and $H(Y)$ with their joint entropy $H(X,Y)$. The difference between the two approaches is the way entropy is estimated. In [173, 174] a non-parametric estimator was used while in [175,176] histograms were applied. The advantage of MI is its generality since it does not assume any relationship between the image intensities. For a survey on MI-based registration methods, the interested reader is referred to [177].

The widespread use and study of MI has revealed some of its shortcomings. One of the main shortcomings is that it is not overlap invariant. Thus, in certain cases it may be possible for mutual information to be maximized when the images get misaligned. To remedy that, a Normalized version of Mutual Information (NMI) was proposed in [178]. Recently, Cahill and co-workers elaborated upon the idea of overlap invariance and showed that neither NMI, MI, CR, CCor nor CCoef are invariant to changes of overlap and introduced appropriate invariant versions of the previous similarity measures in [179].

The success of MI paved the way for the introduction of an important number of statistical criteria in image registration. Roche *et al.*. [180] argued that the generality of mutual information can be a drawback when a reasonable hypothesis can be made regarding the relationship between the intensities. They proposed to use the Correlation Ratio (CR) as appropriate similarity measure when the assumption of functional dependence between the image intensities is valid.

Pluim *et al.* [181] compared the performance of a number of f-information measures in medical image registration. Given two probability distributions P and Q, the quantification of their difference can be given by a measure of divergence. An f-divergence measure is defined as:

$$f(P\|Q) = \sum_i q_i f(\frac{p_i}{q_i}). \tag{26}$$

For different functions f, different divergence measures may be defined. In the context of registration, what is measured is the difference of the joint distribution of the intensities with respect to the joint distribution that would arise when images are independent.

The idea to use divergence measures to compare joint intensity distributions has attracted significant attention and numerous divergence measures have been proposed for multi-modal image registration. Kullback-Leibler divergence (KLD) was used in [182, 183] to register multi-modal images. The joint intensity distribution is either learned from aligned pairs of images or by segmenting corresponding anatomical structures. Images get aligned by minimizing the divergence between the observed and estimated distributions. In a similar setting [184], in the sense that learned distributions are used, Jensen-Shannon Divergence (JSD) was used and shown to be better that KLD being symmetric, bounded and true metric.

Another family of information theoretic approaches is built upon Renyi entropy (RE),

$$RE_\alpha(P) = \frac{1}{1-\alpha} \log \sum_i p_i^\alpha, \;\; \alpha > 0 \; and \; \alpha \neq 1. \tag{27}$$

Based on this entropy, the Jensen-Renyi divergence can be defined. Its advantage lies in the fact that it is symmetric and generalizable to any finite number of probability distributions. The Jensen-Renyi divergence is convex for $\alpha \in (0,1)$ and is maximum when the distributions are degenerate. Its use for image registration was proposed in [185, 186]. In [187, 188], a Minimum Spanning Tree (MST) was used to estimate the RE and the optimal transformation was estimated by minimizing it. Spanning graphs were also used by Sabuncu and Ramadge [189]. The latter demonstrated the superiority of the entropic graph estimator with respect to standard estimators. A generalization of KLD was introduced in [190]. The new divergence measure is based on modified Bessel functions of the second kind and allows for an efficient recursive computation. The generalization of KLD was shown to perform better than the standard measures of divergence.

Most of the previous approaches share a common drawback; they are based upon a single pixel joint probability model. As a consequence, by changing the positions of the pixels in a random way and evaluating the statistical criterion, the same similarity is obtained [191]. To rectify the previous shortcoming, local context should be introduced in the used criterion.

One way to relax the global way the statistical criteria are considered is by means of computing them locally and thus cope with the fact that the relation between the intensities of the two images is non stationary. This approach was investigated by Hermosillo *et al.* and Karaçali. Hermossilo *et al.* [192] derived the Euler-Lagrange equations for MI, CR and CCoef based on locally estimated probability distribution functions. Karaçali [193] followed a deterministic rationale to express in closed form mutual information, joint entropy and the sum of marginal entropies over small spherical regions.

Local evaluation of mutual information has also been proposed by other researchers. For instance, [194] introduced Regional Mutual Information (RMI). The proposed objective function is a linear weighted sum of local evaluations of MI and aims to reduce the error caused by local intensity changes. Loeckx *et al.* [195] proposed to condition the evaluation of MI upon the position. More recently, locally evaluated MI in combination with standard global MI was used in [196]. Moreover, the local evaluation of the probability distribution function considers pixels relatively to their distance with respect to the FFD control points.

An alternative way to introduce local context is by inserting spatial information. This has been mainly achieved by considering additional features that capture local geometric information resulting in higher order entropic measures.

In one of the first attempts to exploit spatial information Pluim *et al.* [197] used intensity image gradient as an additional cue. The proposed algorithm sought not only to maximize NMI but also intensity gradient information. This was simply achieved by multiplying NMI with a measure that takes into consideration both the intensity gradient magnitude and its orientation in an effort to encourage the alignment of strong intensity gradients. Intensity gradient information drove the registration to more accurate results but most importantly rendered it more robust.

Approximately at the same time, Rueckert *et al.* [191] proposed to use second-order MI encoding local information by considering co-occurrences of intensities between neighboring voxels. That approach requires a $4D$-histogram to estimate the information measures. To account for the high dimension of the histogram and the curse of dimensionality, the number of bins was reasonably small. More robust and accurate registration with respect to standard MI was obtained.

Russakoff *et al.* [198] introduced the Regional Mutual Information that pushed forward the previous idea by considering co-occurrences between regions. Moreover, an efficient way to deal with the curse of dimensionality was presented. Assuming a high-dimensional distribution, the data points were transformed so that they were independent in each dimension. Then, the entropy was estimated by summing the distributed $1D$ entropies. In [199], NMI between blocks of image elements was studied. The high-dimensional NMI was estimated by using random lines and reducing the number of bins. Recently, a similar approach was presented by Yi and Soatto [200]. Their approach is based upon learning a dictionary of image patches. Each image patch is represented by the label of its closest dictionary element. Then, higher-order mutual information can be estimated by using this label representation while accounting for the euclidean transformation that maps the patch to the label.

Instead of taking into account explicitly neighboring voxels, a more compact way to consider local information would be by extracting features that describe concisely regional characteristics. In [201], Gaussian scale space derivatives were employed and considered as an additional information channel in a higher dimensional MI criterion. On top of the intensity, one more channel of information was also used in [202] resulting in a multi-dimensional NMI. A novel spatial field, named Maximum Distance-Gradient (MDG), was introduced. First, a set of special points located in important gradient areas was created. Based on that, a vector field that contained both local and global information was created. For every voxel, in addition to the local gradient, the distance, the direction and the intensity difference with respect to its source was retained. The magnitude of the MDG vector field formed the supplementary channel while its orientation was used as a second element in the objective function.

The curse of dimensionality is an important limitation of the previous approaches as it hinders the evaluation of higher dimensional statistical criteria. To be able to handle such calculations, most researchers resort to crude implementation approximations such as limiting the number of histogram bins. Nevertheless, ways to estimate high dimensional entropies have been proposed and used to perform image registration.

In [203], spatial information through the construction of feature vectors was adopted. The resulting high dimensional entropy was estimated with the use of the MST estimator. Entropic graphs were also used in [204] to tackle high dimensional α-MI registration of ultrasound images. Both previous approached coped with global linear registration. Most recently, deformable registration of Cervical MRI using high-dimensional MI was presented in [205]. Features were used to describe local geometric information and a k-nearest neighbor graph to estimate the multi-dimensional MI.

Spatial information is not the only type of information that can be used to endow registration with increased robustness and accuracy. Assuming that a prior step of segmentation has been performed, tissue classification information may also help disambiguate between voxels that belong to different tissues but share common appearance properties.

In [206], regions were segmented by thresholding and connected component labeling. The labels were used as an additional channel and the objective function considered the difference between the three entropies and the joint entropy.

Knops *et al.* [207] performed a k-means clustering before registration. Based on this clustering, voxels that share similar intensity profiles but belong to different anatomical structures were mapped to different intensity bins during the construction of the histogram. The new remapped intensities along with the initial one contributed to an NMI based similarity criterion. The new objective function performed better than the standard MI approach.

Voxel class probabilities were considered in the objective criterion by D'Agostino *et al.* [208] for the labeled-to-labeled and intensity-to-labeled image registration. For the labeled-to-labeled case, KLD was used to compare the distribution of the joint classes whereas for the intensity-to-label registration, a version of MI was used with the difference that one of the features is a class probability and not intensity.

Reduction to mono-modal registration: An alternative way to proceed with multi-modal registration is by reducing the problem to a mono-modal one where the solution can be obtained in a simpler and more accurate way. There are two possible ways to perform such a task, either to simulate one modality from another so that at the end both images come from the same modality, or to map them both to a third domain where the registration will take place.

Simulating one modality from another can be achieved by taking advantage of the knowledge that is available with respect to the physical properties of the imaging device and trying to model the imaging process. An alternative way is to exploit available co-registered pairs of images and use machine learning techniques to capture the relation between the intensities.

The first approach, that is task specific, was first proposed by Roche *et al.* [209] towards registering rigidly US images to MR ones. In [209], US intensities are predicted by exploiting MR intensities and MR gradient magnitude information. Complex phenomena such as US signal attenuation and speckle are neglected, leading to images that only roughly resemble to actual US images. A more sophisticated model was proposed in [210] to tackle the problem of CT-to-US registration problem. Based on the physical principles of ultrasound, the authors were able to simulate an US image that was then used along with a locally evaluated statistical criterion to drive the registration.

In [211], mixture of experts were used to learn the conditional probability of the target intensity given a source patch. The conditional probability was then used to drive a Markov Random Field to regularize the simulated image. An SSD criterion, evaluated by considering the simulated and target image, was shown to outperform MI.

The most common approach out of the two is to map both modalities to a common space. As both modalities image the same anatomical structure, it is logical to assume that the local geometry would be helpful to establish meaningful correspondences. Thus, in principle, most methods apply filters that extract geometrical information and then use it in a mono-modal registration setting.

For instance, Maintz *et al.* [212] used morphological tools to create new gray-value intensity images. Their method basically uses morphological opening and closing to extract edge information and then cross-correlation to align the images. It resembles to a surface registration with the difference that instead of having binary values, real ones are used. Haber *et al.* [213] assumed that borders of anatomical structures correspond to intensity changes and thus opted to exploit intensity gradient information. An intermediate image domain was created by considering the normalized intensity gradient field that conveys purely geometric information and accounts for the fact that the gradient magnitude may vary among different modalities. As objective criterion, the difference in angles between the normalized gradient vectors was considered. In [154], following the mathematical morphology theory that states that an image can be characterized uniquely by the entity of its level sets, the Gauss map of the images was considered as common space. The registration was formulated in a variational framework where a morphological, contrast invariant, matching criterion was minimized under the influence of an appropriate regularization term.

Butz *et al.* [214] also experimented with edge related information. They used an edgeness operator that considers the local edge variance to map both images to a common space. Mutual information driven registration was then performed coupled with a multi-scale genetic optimization. Depending on the nature of the images, other operators may be applied. In [215], the probability of vessel presence was used along with normalized cross-correlation to register MRI with ultrasound images.

Richer descriptions of local structure based on Gabor filtering can also be used to perform registration [170, 169]. In [170], local frequency that is robust to edge strength and contrast differences was used. It was estimated by calculating the local phase gradient of the most significant Gabor filter response. Then, the integral squared error was chosen as matching criterion. The responses of Gabor filters were used in [169] to construct a rich vector descriptor. The images were aligned by minimizing a weighted sum of the vector differences. In [216], the authors took a different direction to estimate the local frequency information. Instead of using Gabor filters, the Riesz transform was used.

In [217], a pseudo-modality was created by remapping intensity values based on the conditional distributions of the intensities. This step was performed in order to apply simpler criteria than MI when the size of patches is small and its estimation compromised. Recently, Wachinger *et al.* [218] proposed two techniques that derive from information theory and manifold learning to create the intermediate structural representation. The first one considered the entropy of a patch centered around the voxel to assign a new intensity value. The second method used Laplacian Eigenmaps to embed the patches in a lower-dimensional manifold that preserves local distances.

A supervised technique was presented in [219] to learn the similarity measure for multi-modal image registration. The approach was formulated in a discriminative setting where the goal is to optimize a similarity function so that correct correspondences are assigned high values and erroneous ones low. Support vector machine regression was employed to learn the metric. The optimal metric performed better than the standard NMI.

Another supervised technique was presented in [220, 221] to learn a similarity metric that discerns between corresponding and non-corresponding points. This technique maps both modalities to a Hamming metric space where true correspondences are more probable to have the same code while wrong ones are not likely to. The embedding was constructed by using AdaBoost. The proposed method was proven experimentally to outperform CR, MI and NMI.

It should also be noted that some of the techniques that were previously presented under the *information theoretic* class of methods learn a similarity measure. The difference is that a generative framework is employed. Given co-registered data, the joint distribution of the intensities is learned. Then, either a maximum likelihood approach [222] or a divergence criterion [182, 183, 184, 189] is used to compare the estimated and learned distribution.

3.2 Geometric Methods

Geometric registration establishes sparse correspondences between a subset of the image voxels. The voxels are placed in salient image locations considered to correspond to meaningful anatomical locations. The underlying assumption is that saliency in the image level is equivalent to anatomical regions of interest. Geometric registration is able to overcome some of the limitations of the iconic registration being robust with respect to the initial conditions and the existence of large deformations. The solution of the registration problem is obtained in a relative straightforward way once landmarks have been extracted. However, locating reliable landmarks is an open problem and active field of research. Most importantly, the sparse set of directly obtained correspondences gives rise to the need for interpolation which results in decrease of the accuracy as the distance from the landmarks increases. This, as well as the advance of technology permitting to meet both the memory and computational demands of iconic registration have boosted research towards that direction, stripping off the geometric methods from the interest they enjoyed during previous decades. Nevertheless, for some task specific applications geometric registration is the most reliable choice.

Detecting points of interest

The first step in geometric registration is to detect points of interest. Images that contain sufficient details facilitate point detection. Medical images are not as rich in details as natural images. That is why, point detection has mainly drawn the interest of the computer vision community and thus is well-studied in the case of $2D$ images and not in the case of $3D$ images mostly found in medical imaging.

A full overview of the point detectors that have been proposed for computer vision related problems is out of the scope of this review. Nonetheless, let us give a brief description of the most important ones. Maybe the most well-known, point of interest detector is the Harris corner detector proposed in [223]. Harris *et al.* proposed to identify corners by exploiting the information conveyed by the structure tensor A. Specifically, points of interest are determined by considering the following quantity: $det(A) - \alpha\, Tr(A)^2$. In similar lines, Shi and Tomasi [224] proposed the use of the minimal eigenvalue of the structure tensor in order to tract points of interest.

Many extensions to the Harris detector have been proposed in the literature. Their main aim is to impose a certain invariance. One may cite the approach proposed in [225] and affine-invariant Harris and Hessian [226]. Affine invariance is important as it enables the detection of points under affine transformations and a lot of efforts have been concentrated in defining such detectors. An evaluation study comparing the most important methods was presented by Mikolajczyk *et al.* [227]. A historical review of point detection methods can be found in [228,225], while evaluation studies of point and corner detectors can be found in [228] and [229], respectively.

An alternative way to determine point of interest is by performing scale-space analysis and detecting blob-like regions. One of the first methods to perform such a task is the Laplacian of Gaussian. The image is convolved with different scales of a Gaussian kernel and at each level the Laplacian operator is applied. By tracking across scales the local maxima/minima of its response, key-points are detected [230]. Lowe [231] proposed to use the Difference of Gaussians that is an approximation of the Laplacian. From this scale-space representation, local minima/maxima are extracted in order to detect feature points and the local Hessian information is used to reject spurious ones. Lowe's Scale Invariant Feature transform has been proven extremely successful and has been extended in the $3D$ domain so as to be applied in medical imaging in [232]. A more recent technique for blob detection was proposed by Matas *et al.* [233]. Image regions, created by thresholding in the intensity domain, are tracked and selected based on their area's stability as the threshold value varies.

In medical imaging, such generic approaches have not been explored. On the contrary, feature detection is performed in a task specific manner, usually as product of a segmentation preprocessing step. In brain image registration, sulci information has been used in [234, 82, 235, 236]. The cortical surface information has also served as feature in [236, 237, 238].

Another case where geometric registration has been proven successful is the retina image registration. In this case, intensities are homogeneous while important information is conveyed by the vasculature. In [239] branching and crossover points of the blood vessel structure were used as feature points. While Stewart *et al.* [240] used in addition the centerlines of the segmented vasculature. For each centerline point, its location, tangent direction and width were retained. Vascular structures are also important in brain sift correction [241], pulmonary CT images [242] and liver registration [243]. That is why a number of task-tailored detectors have been devised [244, 245, 246, 247].

In a more general setting, points of interest can be found based on the maximal response of Gabor features weighted by a mutual saliency criterion in [248]. Lastly, markers that are often used in medical imaging such as fiducial ones can be used to guide image registration. Some resent studies regarding the errors in the process are given in [249, 250, 251].

Following the previous, two sets of points ($K = \{\kappa_1, \cdots, \kappa_n\}$ and $\Lambda = \{\lambda_1, \cdots, \lambda_m\}$, $m \geq n$) are created. The first contains points belonging to the source domain Ω_S, while the second points that belong to the target one Ω_T. These constitute the set of known variables. The set of unknown variables usually comprises: i) the correspondence, and ii) the transformation. Based on how these variables are treated, three different classes of methods can be discerned:

- Methods that infer only the spatial transformation.
- Methods that infer only the correspondence.
- Methods that infer both variables.

Methods that infer only the spatial transformation

Two categories of methods should be considered. The first one assumes that the correspondences are known in an exact or inexact way. This problem is known as *exact or inexact landmark matching*. In the exact case, a smooth transformation is sought so that the correspondence are respected exactly or a regularization energy is optimized under correspondence constraints. In the inexact case, a compromise between matching and smoothing the deformation is preferred.

Procrustes analysis is a popular method for shape analysis and is useful when homologies between point-sets are given [252, 253, 254, 149]. In Procrustes analysis, a least-squares distance is minimized. Given the correspondences, an analytical solution, that consists of translating, rotating and scaling [253], exists. In the affine case, the solution is usually given by numerical optimization [255]. Recently, an algebraic way to solve for the affine registration of planar sets based on complex numbers was presented in [256].

During the last decade, it became possible to estimate non-rigid transformation based on point correspondences. As we saw in the previous section (Sec. 2.2), radial basis functions are able to produce dense deformation fields for any spatial distribution of points. Moreover, inspired by approximation theory, non-interpolating splines are able to account for the uncertainty in the estimated correspondences [99, 122]. What is more, both the exact and inexact landmark matching have been solved for the case of diffeomorphic deformations [257]. This is achieved by introducing a time parameter t and considering the transport equation:

$$\frac{\partial \mathcal{T}(\mathbf{x}, t)}{\partial t} = \mathbf{v}(\mathcal{T}(\mathbf{x}, t), t), \tag{28}$$

under the constraint that $\mathcal{T}(\mathbf{p}_i, 1) = \mathbf{q}_i$ or that the given correspondence is respected. The previous method has been extended to the case where the domain is a sphere [75]. This is of interest as surfaces are often mapped to spheres in order to facilitate their study.

The second subclass opts for estimating the transformation without concerning itself with the establishment of correspondences. These methods are more robust to missing correspondences and outliers. One of the most recent methods belonging to this category is the one proposed in [258]. The point sets are transformed into their canonical forms by considering second order statistics. This results in reducing the estimation of the affine matrix to determining an orthonormal one which is subsequently estimated by using third order moments. Affine transformation of point sets without correspondences can also be achieved by considering the convex hull and Hausdorff distance. For instance, Gope *et al.* [259] proposed to obtain an affine invariant representation of the point sets based on the convex hull. The transformation was optimized based on a variant of the Hausdorff distance that takes into consideration some pairing distance. Another way to perform such a task is to consider robust ways to calculate the distance between the points [260].

Initially, such methods were able to estimate only linear transformations. Recently, methodological advances have permitted the handling of non-rigid transformations. The breakthrough was achieved by representing the point sets as probability distributions and minimizing a distance measure between the two distributions. One of the first attempts in that direction was proposed by Glaunes *et al.* [77]. The authors extended the large diffeomorphic deformation framework in the case of distributions and unlabeled point sets. Point sets were modeled as a weighted sum of Dirac measures and a kernel-based error measure was used. Tsin and Kanade [261] proposed to register point sets based on a measure called *kernel correlation*. The proposed measure is proportional to the correlation of two kernel density estimates. A similar approach based on kernel density correlation was presented in [262].

Gaussian Mixture Models (GMMs) are a common way to model distributions. In [263], each point set was modeled using GMMs and a L_2 distance was used to compare them. In [264], registration was recast as a probability density estimation problem. The points of the first set were considered as the centroids of the GMMs which were fitted to the data (or points of the second set) by likelihood maximization. Special care was taken so that the centroids move in a coherent way. Roy *et al.* [265] modeled each feature of each shape as GMM. A mixture model was used to represent the shape by assuming that features are independent and identically distributed. A closed-form distance between the two distributions was used along with a TPS parametrization of the transformation. A similar model was used in [266] where the problem of the simultaneous registration of multiple point sets is tackled. Jensen-Shannon divergence was used as similarity metric. The drawback of this approach is that no closed-form solution exists. Thus, a computationally and memory demanding estimation based on the law of large numbers is required. In a subsequent work, Wang *et al.* [267] alleviated the previous shortcoming by using the generalized L_2-divergence that allows for a closed-form solution. Lastly, a GMM was also used in [268] with the difference that the Gaussians are not isotropic. The Havrda-Charvat-Tsallis (HCT) divergence was used along with directly manipulated free form deformation.

It should be noted that another way to perform non-rigid registration of shapes and points without caring to establish correspondences, is to embed them in a higher dimensional space and perform classic image-based registration there [76, 78, 269, 270].

Methods that infer only the correspondences

Inferring the correspondences or matching the features is a task that is inherently coupled with the way the features are described. To better disambiguate between close potential candidates rich descriptors should be used. Moreover, as the image undergoes some sort of deformation, it is to be expected that the appearance of the features will vary between images. To account for this fact, descriptors should be invariant to such changes.

Constructing rich invariant descriptors is an active field of research though mainly oriented towards computer vision applications. We are going to present briefly some of the most important feature descriptors that have been proposed and discuss briefly some of the ones that have been applied in medical imaging. For a comparison of the performance of different feature descriptors, the interested reader is referred to [271, 272].

Lowe in his seminar article [231] proposed a feature descriptor (SIFT) based on the gradient information at the scale a point of interest was detected. For every pixel in a neighborhood of the key-point the gradient magnitude is computed. Its value is weighted depending on its distance from the key-point. From these values, gradient orientation histograms are computed and normalized to account for photometric variations. Many variants of SIFT have been proposed. Among them PCA-SIFT [273], Gradient Location and Orientation Histogram (GLOH) [271] and Speeded-Up Robust Features (SURF) [274]. For a comparison between the original SIFT and its variants see [275]. An affine invariant version of SIFT was proposed by Morel and Guoshen [276]. Invariance is introduced by simulating latitude and longitude angles, the two parameters of the camera for which the original SIFT is not invariant.

A number of descriptors have been applied in medical imaging. The SIFT descriptor for example has been used to match points in a hybrid registration framework in [277]. Gabor features have proven their value in a number of applications [169, 248]. Wavelet filters and Steerable filters [278, 279] have been used in [166] and [280] respectively. The list is not complete but indicative of the importance of the feature descriptors in medical imaging.

Having established a discriminative and ideally deformation invariant description of the key-points, correspondences may be established either by i) relying solely on the closeness of the descriptions; or ii) by incorporating structural constraints.

In the first case, the information contained by the descriptor is used to determine the correspondences. There is an implicit assumption that the descriptors are constructed so that the use of the Euclidean distance is sufficient to rank potential matches. This construction can be achieved by appropriate rescaling of the feature vector values. Based on an established ranking, different matching strategies may be considered. The simplest one is by thresholding. The definition of the threshold can be achieved through ROC analysis. A better strategy would be to assign each point to its closest candidate. As the probability of detecting a false positive is significant, a threshold is still needed to control it. The third strategy is to consider the ratio between the distance with the nearest and the second nearest neighbor in the feature space. For an evaluation of these strategies, the interested reader is referred to [271].

While being intuitive and efficient, the previous approaches discard any information regarding the spatial location of the key-points in the image. The incorporation of such a knowledge aims to constrain better the matching problem and reduce further the number of erroneous correspondences.

A popular way to introduce structural constraints is by formulating the problem as graph matching. Leordeanu *et al.* [281] proposed a spectral technique to solve the matching problem. Pairwise constraints were used to preserve pairwise geometry. Berg *et al.* [282] formulated the problem of recovering feature correspondences as an integer quadratic programming problem. Changes in the length and the direction of vectors defined by pairs of features were penalized. Pairwise constraints were also employed in [283] to model local spatial coherence. Moreover, the authors showed that is possible to handle outliers during the optimization. In medical imaging, [248] presented recently a method to detect mutually-salient pairs in brain images.

Despite the success pairwise constraints have enjoyed in many applications, they are limited with respect to the relations they can model. Recently, a number of researchers have tried to tackle the graph matching problem with higher order constraints. The spectral matching method of [281] was generalized to higher order constraints by Duchenne *et al* [284]. A tensor power iteration method was employed to solve the matching problem. A similar formulation was also proposed by Zass and Shashua in [285] favoring the use of a different optimization method. Wang *et al.* [286] proposed a higher-order graph matching formulation incorporating learned structural constraints in a segmentation framework. The inference was performed by a dual decomposition based method [287].

Methods that infer both the correspondences and the transformation

The last class of methods aims to estimate the correspondences and the transformation at the same time. This is usually performed in an iterative way, where one component is estimated first and then, based on this estimation, the second is refined.

On of the most well known approaches is the Iterative Closest Point (ICP) method [288]. The advantage of this algorithm lies is its simplicity and speed. Correspondences are defined based on a closest (in a geometric sense) neighbor principle. Based on this estimation, the transformation is calculated. Then, a new closest neighbor is assigned to each key-point and the process continues till convergence.

ICP has drawn a lot of attention and a number of researchers have tried to ameliorate the method over the years ([289] presents an overview of the improvements over ICP). The performance of the ICP depends greatly on the initial conditions. In general, a good overlap of the two point-sets is necessary for the method to converge to a good minimum. This stems from the assumption that the closest point is a good approximation of the true correspondence. Thus, Sharp *et al.* [290] investigated the use of invariant features in addition to the positional information in order to make the method more robust.

Penney *et al.* [291] also tried to improve on the precision and robustness of the algorithm. To achieve that, Gaussian noise was added to the positions of the points in one set before each iteration of the original ICP. The magnitude of the noise was decreased as the process advanced. [292] tried to render the algorithm more robust by allowing for anisotropic noise in both target and source point sets. The problem was cast in the form of a Generalized Total Least Square problem. [289] improved on the robustness and accuracy of the algorithm for free form deformation shapes by considering collinearity and closeness constraints.

One of the most important works in the domain was introduced by Chui *et al.* [293]. The proposed TPS-RPM algorithm iterates between estimating the correspondence with the softassign method and computing the transformation field with a TPS model. [236] further refined the latter approach by iteratively solving a clustering and matching problem. Stewart *et al.* [240] proposed a dual-bootstrap ICP method to register retinal images. The method operates initially on small regions where accurate correspondences can be obtained. Based on these correspondences low order transformations are estimated. In the subsequent steps, the size of the regions as well as the order of the transformation model are refined. The region refinement is based on the uncertainty of the transformation.

The iterative refinement between the estimation of the correspondences and transformation can be naturally formulated in an Expectation-Maximization fashion. In [294], an approach named multi-scale EM-ICP was proposed. The method is similar to standard ICP with a Mahalanobis distance. The principal difference lies in the estimation of the transformation step where multiple matches weighted by Gaussian weights are considered. [295] aimed to render spectral methods for matching more robust to noise and outliers. Towards this end, the use of an extension of EM [296] along with a spectral method to compute the correspondence probabilities was investigated. Finally, an EM approach was presented in [297] where correspondences are found between scale-invariant salient region features. Based on the set of all pairs of correspondences, a global transformation is estimated. Then, the set of correspondences is refined by considering the increase of global aligned-ness.

As previously seen, Procrustes analysis is a useful tool when the correspondences are known [252]. When that is not the case, iterative methods can be used to enhance the performance of the Procrustes method. In [298], the use of the Dual-Step EM algorithm is studied. Rangarajan *et al.* [299] proposed the softassign Procrustes method treating the problem from an optimization point of view.

3.3 Hybrid Methods

Iconic and geometric registration methods bear certain advantages while suffering from some shortcomings. Hybrid methods try to capitalize on their advantages by using both complementary information in an effort to get the best of both worlds. Among the methods that belong to this class, the following distinct subclasses may be distinguished based on the way the geometric information is exploited, that is:

- As initialization.
- As constraint.
- Coupled.

Geometric information as initialization

The first subclass treats each type of information separately and sequentially. Registration is decomposed into two independent steps, each one acting principally on a different type of information. Typically, geometric registration precedes providing a rough alignment of the two images. Subsequently, iconic registration is performed to refine the result. The energy comprises two terms, a matching term, $\mathcal{M}$, and a regularization term, R, or:

$$E_{\text{hyb}}(\mathcal{T}) = \mathcal{M}_{\text{ico}}(S \circ \mathcal{T} \circ \mathcal{T}_{\text{geo}}, T) + \mathcal{R}_{\text{ico}}(\mathcal{T} \circ \mathcal{T}_{\text{geo}}), \tag{29}$$

Notice that the estimate transformation $\mathcal{T}$ acts as an update upon the transformation $\mathcal{T}_{\text{geo}}$ that has been estimated in a preceding step.

Johnson and Christensen initialized their consistent intensity algorithm with the result of a consistent landmark approach in [300]. The landmark and intensity registration were solved independently in an iterative way till a criterion was met. Landmark information was also used in [301] to provide a coarse registration that was used as initialization for a multi-scale deformable image registration. In [237], a hybrid algorithm that combines surface and volume information to register cortical structures was proposed. The algorithm was initialized with the result of a volumetric approach [110] and was subsequently refined using a surface warping method. Postelnicu *et al.* [302] on the contrary, started from the geometric registration, propagated the result to the whole volume using a biophysical model of the brain and refined with a non-linear optical flow registration algorithm. Recently, a similar approach was presented in [303]. Moreover, Auzias *et al.* in [85], tested their diffeomorphic sulcal-based cortical registration (DISCO) in collaboration with an intensity method (DARTEL [26]) in a sequential manner to further improve their results. In [304], geometric registration of anatomical structures preceded the iconic registration in order to make CT-PET registration more robust to initialization and local minima. Similar methods have also been proposed in the case of CT abdominal [305] and retinal [306] images.

Geometric information as constraint

Using one type of information independently of the other to initialize the following step usually results in an increase of the robustness of the registration procedure. However, there is no guarantee that the correspondences that were established during the previous step will be preserved. To overcome this limitation, a number of researchers have proposed to use the correspondences that are recovered during a first step of geometric registration as a constraint in the objective function that the iconic registration seeks to optimize. In general, the objective function takes the following form:

$$E_{\text{hyb}}(\mathcal{T}) = \mathcal{M}_{\text{ico}}(S \circ \mathcal{T}, T) + \mathcal{R}_{\text{ico}}(\mathcal{T}) + \mathcal{D}(\mathcal{T}, \mathcal{T}_{\text{geo}}), \tag{30}$$

where $\mathcal{T}_{\text{geo}}$ denotes the geometric transformation that can be either sparse or dense and $\mathcal{D}$ measures a distance between the two. The influence of the constraint varies from point-wise to global.

Hellier and Barillot proposed to couple dense and landmark-based approaches for non-rigid brain registration in [235]. In a first step, sulci were extracted and modeled as active ribbons. Then, a matching point algorithm was used to establish geometric correspondences that were subsequently used in a robust function as constraints with local spatial support. In [307], sulcal constraints were also used. A robust point matching method was used to account for outliers. The objective function was enhanced by an additional term. The latter ensured that the estimated deformation field adhered to the point correspondences as well as minimized the normalized mutual information. Normalized mutual information combined with geometric cues was used to tackle brain registration in [308]. Two kinds of geometric cues were employed, landmarks and surfaces. The correspondences for the landmarks were fixed while the surface correspondences were estimated in an ICP fashion. The ratio between the iconic and geometric terms was calculated automatically based on their derivatives.

Adherence to point correspondences was also considered by Rohr *et al.* [309]. The local correlation coefficient was combined with landmarks, detected using a model fitting approach, to register pairs of electrophoresis images. The mean landmark distance was also incorporated in a multi-modal diffeomorphic demons approach to tackle the problem of diffusion weighted imaging distortion in [310]. Registration between preoperative and intra-operative images has also been attempted with the use of hybrid approaches [311]. Avants *et al.* [84] added a landmark inexact matching term in the LDDMM framework in order to compare human and chimpanzee cortices. Landmarks were provided manually to establish either anatomical or functional correspondences between the two species.

A dense deformation field was created in [312] by considering both landmark correspondences and their localization uncertainties. The solution of the registration problem was a compromise between matching the image data, being regular and close to the landmark-based deformation field. A similar approach was presented in [313]. The difference was that a local measure of mutual information was used as an intensity criterion. A dense deformation field was also created from user provided landmark correspondences and TPS interpolation in [314]. The transformation was given as an adaptive combination of intensity- and landmark-fitting. Point information was weighted more in landmarks's vicinity. The advantage of this method is its ability to incorporate any intensity-based algorithm though it cannot guarantee convergence.

While most methods establish geometric correspondences and then encourage the intensity driven deformation field to comply with them without guaranteeing their preservation, Joshi *et al.* [315] imposed geometric correspondences as hard constraints. First correspondences were established between the cortical gray/white matter and gray/CSF surfaces using sulcal constraints. The correspondences were then propagated to the whole cortical volume with the use of an harmonic map. Following, the dense deformation field was refined by considering image intensity information under the hard constraint that the deformation is zero for the previously registered surfaces.

Coupled approach

The disadvantage of the previous approaches is that the flow of information is towards one direction. By treating the problems in a decoupled way, iconic registration may profit from geometric either by being initialized closer to the solution or by being driven by an extra force of adherence to correspondences. However, the geometric registration, being treated independently, does not benefit from the iconic one. In an ideal case, the two problems should be considered in a unified way and solved by minimizing a single objective function simultaneously. The advantage of such a setting would be a more consistent and accurate registration relieved from the previous limitations and endowed with the advantages of both classes of methods. A coupled registration objective function may be defined as follows:

$$E_{\text{uni}}(\mathcal{T}_{\text{ico}}, \mathcal{T}_{\text{geo}}) = \underbrace{\mathcal{M}_{\text{ico}}(S \circ \mathcal{T}_{\text{ico}}, T) + \mathcal{R}_{\text{ico}}(\mathcal{T}_{\text{ico}}) + \mathcal{H}(\mathcal{T}_{\text{ico}}, \mathcal{T}_{\text{geo}})}_{iconic} \underbrace{+ \mathcal{M}_{\text{geo}}(K \circ \mathcal{T}_{\text{geo}}, \Lambda) + \mathcal{R}_{\text{geo}}(\mathcal{T}_{\text{geo}})}_{geometric}, \quad (31)$$

where K (respectively Λ) is the set of landmarks in the source S (respectively target T) image domain. $\mathcal{H}$ is a consistency term defined on $\mathcal{T}_{\text{ico}}$ and $\mathcal{T}_{\text{geo}}$. It has the following form:

$$\mathcal{H}(\mathcal{T}_{\text{ico}}, \mathcal{T}_{\text{geo}}) = \int_{\Omega} \delta(\mathcal{T}_{\text{ico}}(\mathbf{x}), \mathcal{T}_{\text{geo}}(\mathbf{x})) d\mathbf{x}. \quad (32)$$

The minimization of the coupled objective function results in the estimation of both the iconic and geometric registration, which should ideally be identical upon convergence.

Such a universal energy for the problem of deformable registration was first proposed by Cachier *et al.* [234]. However, they considered a slightly different energy: the coupling was performed through the introduction of an auxiliary smooth deformation field. The authors proposed to extract sulci modeled as point distributions and use them in the coupled formulation to solve brain registration. The previous universal formulation (Eq. 31) was solved by iterating between three steps: i) solve for the deformation that minimizes the iconic criterion; ii) solve the geometric one by establishing correspondences between the closest points of the geometrical structures; iii) and finally opt for a smooth deformation that respects both iconic and geometric constraints.

More recently, the previous universal formulation was solved by formulating the problem as a first-order Markov Random Field in [316]. There, a graph is constructed for each problem and the consistency constraint is imposed by appropriately adding edges to connect the two graphs. The advantage of this approach is that is able to encompass any iconic objective function due to the discrete nature of the formulation, to provide diffeomorphic deformation through the use of hard constraints, consider in an adaptive and local way the landmark information and solve the problem in a one-shot minimization process. The disadvantage of this approach is that the coupling constraint was approximated in order to be modeled by pairwise relations.

Some of the limitations of the previous work have been addressed in subsequent ones. In [317] for example, the exact L_2 distance was used to couple the geometric and iconic information developed to be modeled by pairwise relations. In [318], learned higher-order relations are used for the graph that models the geometric problem alleviating the need for a global linear registration. Moreover, the landmarks are matched by using an optimized similarity metric.

In the same context, the method proposed by Joshi *et al.* [319] should also be referred to. In surface registration, it is often the case that both surfaces are mapped to a common domain, usually a sphere, where registration is performed. Joshi *et al.* proposed to also map the interior brain volumes to the interior of the spheres through harmonic maps. Then, correspondences may be established by considering the complete sphere domain or both the surface and iconic information at the same time.

4 Optimization Strategies

While most research efforts have been concentrated on devising better similarity metrics as well as transformation models and regularization terms, little attention has been paid to the last component of registration, optimization. It is usually treated as a black-box and techniques are used in a plug and play fashion. Even though few methods have been designed specifically for the registration problem, it would not be an exaggeration to say that almost all optimization methods have been tested to tackle it.

Optimization methods may be discerned based on the nature of the variables that try to infer in two categories: i) *continuous*, and ii) *discrete*. The first class of methods treats real valued variables while in the second case, the variables take values from a discrete set. The two previous classes of methods are constrained with respect to the nature of the objective function as well as the structure to be optimized. *Heuristic* and *metaheuristic* methods bear not the previous limitations. Following, some typical exemplars of each class of methods that have found applications in image registration are going to be presented. Particular emphasis will be put on Markov Random Field (MRF) formulations for image registration. An approach that has gained significant attention during the past few years.

4.1 Continuous Optimization

Typically, continuous optimization methods are constrained to problems where the variable take real values and the objective function is differentiable. In medical image registration, it is often the case that both the previous constraints are satisfied. Moreover, being rather intuitive and easy to implement, continuous optimization methods have been applied to numerous registration problems. Let $\boldsymbol{\theta}$ denote the vector of parameters of the transformation and t index the number of iteration. Continuous optimization methods estimate the optimal parameters following an update rule of the following form:

$$\boldsymbol{\theta}_{t+1} = \boldsymbol{\theta}_t + \alpha_t \mathbf{g}_t(\boldsymbol{\theta}_t), \tag{33}$$

where α_t is generally referred to as step size or gain factor, while g defines the search direction.

There are various ways to define the previous parameters. For example, the step size may be constant, decrease with the iterations or so that it minimizes the objective function along the search direction (exact or inexact line search). The search direction can be specified by considering only first-order information or, for example, by also taking into consideration second-order one. It is the choice with respect to the previous parameters that discriminates different methods between them. The approaches the most frequently used in medical image registration are:

- Gradient Descent (GD).
- Conjugate Gradient (CG).
- Powell's conjugate directions.

- Newton-type methods.
- Levenberg-Marquardt (LM).
- Stochastic gradient descent.

A comparison study between some algorithms of the previous categories along with their description was presented in [320].

The simplest approach is to optimize the objective function by following the direction that decreases the energy or its negative gradient. In other words, the direction is given as $\mathbf{g} = -\nabla_\theta(\boldsymbol{\theta})$. In [320], two variants of gradient descent are tested. The first employs a decaying with the iterations function of the step size while the second is based upon the inexact line search algorithm of Moré and Thuente [321]. Other line strategies include keeping the step size fixed, monotone line search [322], line search and golden section search [323]. Gradient descent has been used by numerous researchers to solve a registration problem. In the LDDMM framework, usually posed in a variational setting, gradient descent is often used to solve the problem [60, 68, 73]. Johnson's consistent registration approach [300] as well as Rueckert's FFD registration algorithm [126] were also based upon a gradient descent optimization scheme. Without trying to give a full account for all registration methods that employ gradient descent, a task that can be deemed impossible, let us also cite two more variational approaches [154, 269] .

While gradient descent is intuitive and easy to compute it is known to suffer from slow convergence. Therefore, techniques that have better convergence rates have been tested. Conjugate gradient descent methods try to exploit the knowledge conveyed by the previous gradients so that to proceed not down to the new gradient but instead, towards a direction that is conjugate to the previous. Thus, the direction now is given as $\mathbf{g}_t = f(\nabla_\theta(\boldsymbol{\theta}_t), \mathbf{g}_{t-1})$, where f usually depicts a linear combination $\mathbf{g}_t = \nabla_\theta(\boldsymbol{\theta}_t) + \beta_t \mathbf{g}_{t-1}$. Different ways to define the weighting factor β_t have been proposed. Some examples of registration methods that use conjugate gradient descent as an optimizer are [64, 315, 75, 302]. An interesting tailored approach for FFD image registration using a preconditioned gradient scheme was presented in [324].

A similar in spirit optimization approach that has been used in an important number of registration problems is Powell's or Direction Set method [323]. Powell's method aims to minimize the objective function by following conjugate directions but contrary to the previous method, no gradient information is used to produce them. The basic procedure that Powell proposed sets the initial direction to the basis vectors $\mathbf{g}^i = \mathbf{e}^i,\ i = 1, \cdots, N$, optimizes along each parameter axis independently from the rest, performs the replacement $\mathbf{g}_t^i = \mathbf{g}_{t-1}^{i+1}$ while adding $\mathbf{g}_t^N = \boldsymbol{\theta}_{t-1} - \boldsymbol{\theta}_0$ and iterates till convergence. Despite being less efficient than the previous method, being gradient free, Powell's method has been applied in many registration tasks [176, 181, 182, 197, 202].

Another class of optimization methods that has been tested in an important number of registration applications is the Quasi-Newton (QN) methods [323]. This class of methods, like the two previous ones, aims to accumulate information from the previous iterations and take advantage of it in order to achieve better convergence. More specifically, their goal is to estimate the inverse Hessian matrix $H^{-1}(\boldsymbol{\theta})$ and use it to define the search direction. Thus, the search direction is defined as $\mathbf{g} = -\hat{H}^{-1}(\boldsymbol{\theta})\nabla_\theta(\boldsymbol{\theta})$, where the ˆ denotes that an approximation is used (the true Hessian is used in the case of Newton's or Newton-Raphson method). Two main algorithms exist in this category, the *Davidon-Fletcher-Powell (DFP)* and the *Broyden-Fletcher-Goldfarb-Shanno (BFGS)*. BFGS is considered to be slightly better than DFP. A version of BFGS that uses less memory (L-BFGS) was tested in [320]. Other efforts where researchers have experimented with Quasi-Newton methods can be found in [266, 91, 195, 138]

An optimization method of the same family is the Gauss-Newton (GN) algorithm. It is devised to solve optimization problems where sum of squared function values are considered.

This is of particular interest for image registration as such objective functions are common when aligning images from the same modality. The advantage of this algorithm is that it does not require the computation of second derivatives. Instead, the Hessian is approximated by ignoring derivatives higher than first order as $\hat{H} = 2J^TJ$ where J denotes the Jacobian. The search direction is now given as $\mathbf{g} = -(J^T(\boldsymbol{\theta})J(\boldsymbol{\theta}))^{-1}\nabla_\theta(\boldsymbol{\theta})$. The Gauss-Newton optimizer has been used in [72, 155, 164]. The Gauss-Newton algorithm is the optimizer that is most frequently used in the demons registration framework to tackle mono-modal registration [40, 37, 49, 90, 51]. In the demons registration setting, an extension of Gauss-Newton [39] was employed to derive the symmetric demons forces [41, 44]. This algorithm exploits more knowledge with respect to the problem at hand. More specifically, it takes advantage of the fact that when the images are aligned, the gradient of the source can be approximated by the gradient of the target. Recently, Zikic *et al.* [325] proposed a preconditioning scheme that improves the convergence speed of registration algorithms. The scheme is based upon normalizing the length of the point force vectors.

A related to the previous method that has been successfully applied to the problem of image registration is the Levenberg-Marquardt algorithm. The search direction in this case is given by: $\mathbf{g} = -\left(\hat{H}^{-1}(\boldsymbol{\theta}) + \zeta\mathbf{I}\right)\nabla_\theta(\boldsymbol{\theta})$. $\mathbf{I}$ is the identity matrix and ζ is a weighting factor that regulates the performance of the optimizer with respect to its speed and stability. By decreasing its value, greater speed may be achieved. At the limit, when ζ equals to zero, we fall to the previous algorithm. On the contrary, when its value increases, the stability increases as well. For some applications of the LM approach the interested reader is referred to [26, 127, 139, 140]. Based on the LM algorithm, Thevanez *et al.* [326] proposed an efficient optimizer for mutual information driven registration. [127] compared the LM algorithm with GD, GD with a quadratic step size estimation and CG to find that it performs the best for a FFD registration task.

The previous techniques cover the *deterministic* gradient methods that are used most often to solve the optimization problems that arise when tackling image registration. In medical image registration, the computation of the derivative information can be computationally demanding. Thus, in order to alleviate the computational burden, many researchers have experimented with *stochastic* gradient approaches. The update rule for the stochastic gradient approaches is based upon an approximation of the gradient,

$$\boldsymbol{\theta}_{t+1} = \boldsymbol{\theta}_t + \alpha_t\hat{\mathbf{g}}_t(\boldsymbol{\theta}_t). \tag{34}$$

The only difference with respect to the deterministic approaches is that an approximation $\hat{\mathbf{g}}_t(\boldsymbol{\theta})$ of the gradient is used.

The variants of the stochastic gradient approach differ with respect to the way the gradient is approximated. In [320], three approaches were considered. The first one, referred to as Kiefer-Wolfowitz (KW) [327], approximates the gradient by a finite difference scheme. The second one, known as Simultaneous Perturbation (SP) [328], estimates the gradient perturbing it not along the basis axis but instead along a random perturbation vector $\boldsymbol{\Delta}$ whose elements are independent and symmetrically Bernoulli distributed. The last method that was studied is the one proposed by Robbins and Monro (RM) [329]. It is more general, in the sense that it only assumes that an approximation of the gradient exists. This method uses a step-size that decreases with time in order to decrease the inaccuracy. [320] estimated the gradient by using a subset of the image voxels sampled uniformly. Their conclusion is that the RM method performs better than the rest. This method was extended in two subsequent works [330, 331] by considering adaptive image-driven strategies. In [330], an adaptive step mechanism was presented while in [331] an edge-driven importance sampling was proposed to improve the gradient approximation. For some applications of stochastic gradient see [134, 174, 173, 205].

All the previous approaches aim to solve an *unconstrained* optimization problem. As we have seen in Sec. 2.3, *constrained* optimization problems often arise when trying to impose task-specific conditions on the deformation field. The solution of such optimization problems is more challenging. The optimization strategies that are usually employed transform the constrained to an unconstrained one that can be solved efficiently. For example, in [155], a log-barrier method was used. Most often, the transformation is achieved by augmenting the dimensionality of the problem using the method of Lagrange multipliers [159, 161].

4.2 Discrete Optimization

The main drawback of the previous methods is that they proceed by performing local search in the parameter spacing. As a consequence, they are sensitive to the initial conditions and tend to get trapped in local minima. Moreover, the fact that they rely on the computation of the gradient of the objective function limits their use in two ways. On the one hand, not all objective functions are differentiable. On the other hand, their practical use is hindered by the fact that they are not modular with respect to the objective criterion and the transformation model. Last but not least, they are often computationally inefficient.

On the contrary, discrete methods, performing a global search, are robust to initial conditions while exhibiting better convergence rates in comparison to the continuous methods. Furthermore, their modularity permits their use in various settings. Their limitation stems from the quantization of the search space and the lack of precision that is thus introduced. This implies an important precision versus computational efficiency trade-off. The more densely the solution space is sampled, the better accuracy we may achieve, though at a higher computational cost. We should also note that the quantization of the search space allows us to introduce our knowledge with respect to where the solution should lie by sampling appropriately. Such a control mechanism is not available in the continuous optimization methods.

Let us attempt a brief historical overview of the methods used to solve the discrete optimization problems arising from Markov Random Field (MRF) formulations that are typically employed in the case of image registration. Even though a thorough presentation of all methods is neither possible nor of interest here, the principal classes of methods along with their basic ideas are going to be traced. More emphasis will be put on the methods that were used in a registration framework and the registration methods themselves.

Before describing any methods, let us introduce some notation. In general, a graph $\mathcal{G}$, consisting of set of vertices $\mathcal{V}$ and a set of edges $\mathcal{E}$ ($\mathcal{G} = \{\mathcal{V}, \mathcal{E}\}$), is going to be considered. Depending on the case, the graph may be directed or undirected. The corresponding energy is the sum of all unary potentials $\mathcal{U}_p$ of the nodes p (*i.e.* data cost) along with the pairwise potentials $\mathcal{P}_{pq}$ (*i.e.* regularization cost) modeled by the edges connecting nodes p and q.

$$E_{MRF} = \sum_{p \in \mathcal{V}} \mathcal{U}_p(l_p) + \sum_{pq \in \mathcal{E}} \mathcal{P}_{pq}(l_p, l_q) \tag{35}$$

The random variables take values in a discrete label set $\mathcal{L}$. Minimizing the previous energy result in an optimal labeling $\mathbf{l}^\star$ or in assigning to each random variable p a label l_p.

The first attempts to solve the difficult combinatorial problem were based on *heuristic* and *metaheuristic* strategies. In the first case, one may cite Iterated Conditional Modes (ICM) [332] and Highest Confidence First (HCF) [333, 334]. In the second case, a method inspired by metallurgy, Simulated Annealing [335] should be referred. These methods suffer from lack of optimality guarantees and slow convergence.

The interest on the field was revitalized during the nineties with the introduction of the graph-cut [336] and belief propagation methods [337]. If we would like to class the methods according to the techniques they employ, three different categories should be discerned:

- Graph-based methods.
- Message passing methods.
- Linear-programming (LP) approaches.

The first class of methods is based on the max-flow min-cut principle [338] that states that the maximum amount of flow that can pass from the source to the sink is equal to the minimum cut that separates the two terminal nodes. The two terminal nodes are defined as source and sink depending on the direction of their edges. The cost of a cut is given by the sum of the weights of the edges that were removed.

Among the most efficient implementations one can distinct the push-relabel [339] and the graph-cut method [336]. Of particular interest due to its application in medical image registration is the α-expansion [340]. α-expansion is the extension to the multi-label case of the method presented in [336]. In [336], it is shown how to calculate the exact maximum a posteriori estimation for the case of the Ising model through a single graph cut computation. Boykov et al. [340] extend the previous technique in the multi-dimensional case by iteratively applying binary graph cuts. The algorithm starts from an initial labeling and then checks every label to see if the energy may be decreased by allowing any set of nodes to change their label to the one under study. The optimal labeling is estimated each time by performing a single graph cut. The method is guaranteed to finish in a finite number of iterations though, most often, it terminates earlier as the energy stops decreasing.

The advantage of these methods is their computational efficiency, especially when regular grids are concerned. Unfortunately, they are limited with respect to the type of energies that they can solve [341]. Several variants of these methods, like fusion moves [342] or dynamic graph-cuts [343] were introduced to further improve convergence at the expense of becoming problem specific.

In medical image registration, α-expansion is the optimizer used in [344, 345, 346, 347, 172]. A graph the size of the image is constructed assuming a 6-connectivity scheme and the solution space is sampled densely resulting in a large set of candidate solutions. The size of the graph as well as the large label set result in computational times that almost prohibit the use of this method in any reasonable clinical setting. Moreover, the registration setting that is used is not able to guarantee the diffeomorphicity of the transformation as the regularization only penalizes the first derivatives of the transformation.

The second class of methods, the so-called belief propagation methods [337], is based on local message exchange between the nodes of the graph and then backtracking towards recovering the best solution to the problem. The message, a vector of size equal to the cardinality of the set of solutions or labels, conveys the belief of a node regarding each solution to its neighboring one. For each label, the message transmitted from a node p to a node q is equal to the minimum of an energy given the label. Belief propagation methods can provide exact inference for chain and tree-structured graphs. Though such a property is not true in the case of graphs that contain loops, they have been shown to converge to satisfactory solutions [348,349] (in this case, normally they are referred to as Loopy Belief Propagation). Their main strength is their ability to copy with non-submodular pairwise interactions.

Maybe, the most notable drawback of these methods is the computational burden of the message calculation. To alleviate the computational burden, efficient techniques to perform belief propagation were proposed in [350]. The most interesting of the proposed techniques shows how to decrease the complexity of the message computation by reinterpreting the process as a distance transform calculation. The methods proposed in [350] apply to the linear and quadratic case of pairwise interactions. An extension to arbitrary pairwise functions appropriate for parallel architectures was most recently introduced in [351].

The previous methods are rather generic as they are appropriate for any MRF problem. On the contrary, Shekhovtsov et al. [352] proposed an efficient MRF deformation model for non-rigid $2D$ image matching by decomposing the original graph into two layers. The latent variables of each layer model the displacement along each axis. Nodes placed at corresponding positions at each layer are connected with an edge that models the data matching term. In each layer, nodes are connected with each-other following a 4-connectivity scheme. These edges encode the regularization term. For this model, the operations needed to update the messages are greatly reduced. The previous model was extended to the $3D$ case in [353]. Similarly to the previous model, the original graph is decomposed into three layers. Intra-layer edges model the smoothing term while ternary interactions between the nodes are necessary to model the data cost.

In [354], the previous decomposed model was used along with loopy belief propagation to calculate the SIFT-flow. SIFT-flow, similarly to optical flow, aims to match SIFT-descriptors along the flow vectors. A similar approach that matches dense local descriptors using a higher-order smoothness prior was presented in [355].

More recently, techniques based on Linear Programming, endowed with better theoretical properties, have been proposed to solve the optimization problem. These techniques instead of trying to solve the original problem, that is in general NP-hard, opt for a solution of its LP relaxation. We are going to present briefly two methods that have been used in registration tasks, Fast-PD [356, 357] and TRW-S [358].

Fast-PD casts the original problem as a linear integer program. Then, solutions are derived based on the primal and dual LP relaxations so that the primal-dual gap decreases. The advantages of this optimization technique lie in its generality (it only requires that the pairwise potentials are non-negative), its optimality guarantees, the fact that it provides per-instance approximation factors and, last but not least, its extreme speed.

TRW-S or sequential tree-reweighted message passing is also based on an LP relaxation. The algorithm aims to solve the dual of the relaxation that provides a lower bound of the optimal MRF energy. Hence, the goal is to maximize this lower bound. The lower bound in this case is given by a convex combination of trees. Practically, the algorithm first decomposes the graph into a set of trees. Then, in a sequential order for every node, performs belief propagation in each tree that contains it, followed by an averaging operation. That way, the lower bound is guaranteed to increase. The algorithm iterates till the lower bound ceases to increase (within some precision) or a user-defined maximum number of iterations is reached.

FastPD was first used for image registration in [359]. There, it was used to infer the displacements of a grid-based deformation model. Hard constraints on the set of solutions imposed the diffeomorphic property on the deformation field despite the use of a simple first-order regularization term. On top of the efficient optimizer, a computationally efficient, though approximative scheme, was used for the calculation of the data cost. As a consequence, it was made possible to obtain results for both intra- and inter-modal registration tasks in low computational times. Thereafter, the optimizer have been applied to deformable registration with prior [360], feature-based deformable registration [169], hybrid registration [361], single- and multi-channel group-wise registration [362, 363], diffusion tensor registration [364] and linear registration [365].

TRW-S has also been used in a number of registration tasks. For example, it was the optimizer that was preferred to optimize the efficient decomposed MRF deformation model in [352]. Moreover, because of its ability to deliver good quality solutions in reasonable computational time for difficult optimization problems, it was used in [316]. Last, Lee *et al.* [366] used TRW-S to solve the optical flow estimation problem based on an adaptive convolution kernel prior.

Discrete graphical models and the algorithms that are used to perform inference on them are efficient when first-order relations between the variables are considered. On the contrary, their efficiency is more limited when more complex interactions are concerned as that entails inference in higher-order graphs. Nevertheless, research efforts have begun to bear fruit and registration algorithms with a higher-order spatial prior have been presented in [367, 355].

4.3 Miscellaneous

The previous methods are limited regarding to what objective function and structure they can optimize. *Heuristic* and *metaheuristic* methods, on the contrary, are able to handle a wide range of problems and explore large solution spaces. Nevertheless, they are not able to provide any guarantee with respect to the optimality of the solution.

A heuristic often used in image registration is to make at each step the locally optimal choice. This greedy strategy needs at each step the definition of a set of plausible solutions and a score function. Being gradient free and intuitive, it has been applied to tackle the problem of feature-driven image registration where the cost function is based on the comparison of feature vectors and thus is not differentiable. The candidate sets are constructed in a multi-resolution fashion. Moreover, the features as well as the score function can also be designed to reflect information at different resolutions. More information about the practical implementation of this strategy can be found in [110, 166, 168, 167, 237].

Evolutionary algorithms is a strategy that has been used quite often in medical image registration [368], though most of the times limited to linear registration. These algorithms derive from the theory of evolution and natural selection. These algorithms start from an initial set of solutions. The individual solutions are ranked according to a fitness measure and a subset of them is chosen in a stochastic fashion to generate a new set of solutions. The new set of solutions is generated by adapting the current set following a nature-motivated strategy such as mutation. In [320], the covariance matrix adaptation method was considered [369] and found to converge slowly. For a more elaborated presentation and comparison of state-of-the-art evolutionary methods for image registration the interested reader is referred to [368]. 7

5 Discussion

In this report, we have studied in a systematic way image registration. The main emphasis of this study is the recent advances in deformable medical image registration. Most notable contributions in the field include, but are not limited to, the evolution of diffeomorphic deformation models, the study of information theoretic measures to tackle multi-modal registration or the introduction of discrete optimization methods to infer the optimal transformation parameters.

We may safely conclude that the field has greatly matured over the past decade. Nonetheless, there are important problems yet to be solved in order to further promote its use in clinical practice. One may identify the following important challenges to be tackled: i) the violation of the one-to-one correspondence assumption in clinical practice; ii) the important time constraints; iii) tailored similarity criteria and optimization methods; and iv) quality assessment and validation.

Despite the enormous efforts to construct diffeomorphic registration frameworks, in various clinical setting missing correspondences are encountered. One should not expect correspondences between pre- and post-operative images, between normal brain images and ones in tumor or lesion presence, or between volumes images depicting the evolution of degenerative disease. To cope with such challenging cases both new deformation models and similarity criteria should be devised.

Clinical practice entails important time constraints that, despite the progress in the computational power of modern computers, cannot be easily met by sophisticated registration methods. The development of the Graphic Processing Unit (GPU) technology seems a a prominent direction towards accelerating deformable registration. To fully harness the computational power of parallel architectures, new registration algorithms that are hardware aware should be conceived. Moreover, tailored optimization strategies could lead to faster convergence rated and better quality results.

The development of new imaging techniques has resulted in a great number of available image modalities, each conveying complementary information. Data fusion is necessary to fully exploit them in treatment planning and diagnosis. Information theoretic approaches have provided consistently reliable solutions in this context. Nonetheless, their generality is also their shortcoming. Task-specific similarity criteria devised by using machine learning techniques could capture better the dependencies between the intensity distributions of different modalities and thus lead to more accurate results.

Lastly, maybe the most important direction of research is the one related to the evaluation of the quality of registration methods. On the one hand, publicly available benchmark datasets with associated ground-truth evaluation are necessary so that a comprehensive comparison of the current methods may take place. In such a setting, the shortcomings of each method can be studied and motivate the introduction of novel techniques. On the other hand, clinicians need an accurate estimation of the quality of the provided solution so as to moderate their judgement based on the certainty of the registration result.

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