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Deformable Medical 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 temporal structural or anatomical changes are investigated; and iii) population modeling and statistical atlases used to study normal anatomical variability. In this 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 image registration methods, their main components are identified and then studied independently. The most recent techniques are presented in a systematic fashion. The contribution of this report is twofold: i) to serve as a tutorial on deformable medical image registration; and ii) to provide an extensive account of registration techniques in a systematic manner.

Key- words: Deformable registration, medical imaging, bibliographical review

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Étude Bibliographique sur le Recalage Déformable d'Images Médicales

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, où des changements structurels ou anatomiques sont étudiées en fonction du temps; et iii) la modélisation de la variabilité anatomique normale d'une population et les atlas statistiques. 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 particulièrement insisté sur les techniques appliquées aux images médicales. Afin d'étudier les méthodes du recalage d'images, leurs composants principales sont d'abord identifiés puis étudiées de manière indépendante, les techniques les plus récentes étant classifiées en suivant un schéma logique déterminé. La contribution de ce rapport de recherche est double: i) de servir comme didacticiel de recalage déformable d'images médicales; et ii) de fournir un compte rendu détaillé des techniques de recalage d'une manière systématique.

Mots-clés : recalage déformable, imagerie médicale, étude bibliographique

1 Introduction

Deformable registration/fusion has been, along with organ segmentation, one of the main challenges in modern medical imaging. The process consists of establishing functional and/or spatial anatomical correspondences between different image acquisitions. The term deformable (as opposed to linear or global) is often used to denote the fact that the observed signals are associated through a non-linear dense transformation, or a spatially varying deformation model.

An enormous amount of research has been dedicated to deformable registration research due to its potential clinical impact. It is often addressed through mathematical inference methods wherein the optimal solution is the lowest potential of a specifically designed cost function. Having said that, we should mention that image registration is a tedious task for a number of reasons:

- Ill-posedness is a challenge since the estimation of the deformation is under-constrained from a mathematical point of view. The theoretical number of parameters to be determined is superior to the constraints/information provided by the data.
- Non-linearity is another challenge. Depending on the type of images to be registered, often their comparison is done using non-linear functions with respect to the transformation parameters. Naturally, analytical direct estimation of the registration parameters becomes infeasible.
- Non-convexity is also an important concern to be addressed when solving deformable registration. Due to the dimensionality of the search space, the non-linearity of the designed objective function and the lack of a direct analytical solution, the often employed local search methods reach only a local minimum in the parameter space.
- Last but not least, the problem itself has an enormous number of different facets. The approach that one should take depends on the anatomical properties of the organ (for example, the heart and liver do not adhere to the same degree of deformation), the nature of observations to be registered (same modality versus multi-modal fusion), the clinical setting in which registration is to be used (*e.g.* off-line interpretation versus computer assisted surgery).

Moving from the algorithmic viewpoint to the clinical one, the consensus is that successful registration could have a tremendous clinical impact.

In a number of cases—in particular when considering organs that undergo severe periodic deformations (*e.g.* cardiac and respiratory motion)—the key element in diagnosis becomes their spatio-temporal behavior [1, 2]. Registration may be used to assess this motion through the efficient establishment of correspondences in time. Moreover, the patterns of spatio-temporal behavior that may be derived naturally as a byproduct of this process can be used in a differential diagnostic procedure to determine potential risk factors. One can go further and consider time-intensity curves in the case of functional imaging (*e.g.* perfusion imaging for cancer characterization and treatment) that convey great clinical information and have important diagnostic value [3, 4].

Successfully evaluating the progression of disease as well as the success of therapeutic strategies is another natural clinical use of deformable registration. In order to measure the evolution of physiological or pathological phenomena (*e.g.* tumor progression [5]), it is necessary to align longitudinal data into a common domain where comparisons are meaningful. Deformable registration provides the necessary insight to decide upon the nature and time of the therapeutic action to take.

Despite phenomenal progress in medical image resolution and the development of new modalities, one modality is often not sufficient to produce a precise diagnosis. This is natural since the physical principles behind different imaging modalities differ in the anatomical, tissue, organ and functional properties that they may capture, and the diagnosis of a number of diseases is based on leveraging complementary cross-modal information [6]. Simultaneous acquisition is often not possible and fusion in a deformable manner is required to agglomerate information and perform diagnoses. PET-CT fusion is the most natural example of such a need as demonstrated by the development of integrated scanners that can do parallel co-registered acquisitions of both modalities [7].

Treatment planning is another situation in which registration is of critical importance. In the case of surgical planning, high-resolution anatomical and functional images are acquired, annotated and used to determine the optimal surgical procedure. This information is subsequently mapped to the patient's position in the operating room and serves as visual aid to the physician [8]. The same concept is also applicable during radiation treatment planning. High-resolution CT data are used to determine the optimal viewing angle and dose prior to treatment [9].

During treatment, the clinical situation of the patient undergoes significant and often abrupt changes either due to the treatment itself, the patient's motion or the elasticity of the anatomical organs. Thus, it is important to be able to reevaluate the clinical situation by considering imaging information acquired during treatment and mapping it to previously acquired high-resolution data. In the case of surgical operations, providing a continuous real-time mapping between interventional data (often 2D) and images used for planning (CT/MR) would have a great impact and help ensure the success of surgery [10, 11, 12]. In the case of radiation therapy, registration can be used to account for the patient's position and motion, allowing for the necessary adjustments to dose and aiming angles that maximize the therapeutic gain [13, 14, 15]. Current acquisition/navigation systems combine imaging with GPS sensors and fail to account for the motion/tissue shift of elastic organs. This could be addressed with efficient deformable registration methods and could be a major clinical breakthrough for both surgery and radiotherapy treatment.

Understanding disease, drug piloting and population studies are areas in which deformable registration/fusion goes beyond simple assistance in clinical diagnosis and treatment. Neurodegenerative diseases are an example where population studies are of great importance. The central idea is to combine anatomical and functional imaging within a large database of individuals and look for notable differences between healthy and unhealthy subjects that can be used as an indicator for potential future diagnosis [16]. Deformable registration and fusion are both required, the first to bring all subjects to the same reference space such that comparisons become meaningful/feasible and the second to establish correspondences between functional and anatomical data. The exact same concept is applicable when developing and evaluating new drugs where imaging studies need to be normalized and mapped to the same space towards interpretation [17].

The above mentioned examples compose a small subset of clinical problems where registration is critical but demonstrate the importance of this problem in the field and prove the clinical value of such computational methods. We will now review the algorithmic components/challenges of the problem.

In general, image registration involves two images. One is usually referred to as the source or moving image, while the other is referred to as the target or fixed image. In this report, the source image is denoted by $S : \Omega_S \subset \mathbb{R}^d \mapsto \mathbb{R}$, while the target image is denoted 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:

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

The previous energy (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 denoting 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 is denoted as \mathbf{v} .

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 [18, 19, 20, 21, 22, 23, 24]. However due to the rapid progress of the field such reviews are to a certain extent outdated.

The aim of this report is to provide a thorough overview of the advances of the past decade in deformable registration. Nevertheless, some *classic* papers that have greatly advanced 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 included as many problems have been treated in this low-degree-of-freedom setting before being extended to the deformable case.

The remainder of the report is organized following the previous structural separation of registration algorithms in three components: (i) deformation models, (ii) objective functions, and (iii) optimization strategies.

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. It also reflects the class of transformations that are desirable or acceptable, and therefore limits the solution to a large extent. 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, at the cost of more challenging and computationally demanding inference. Furthermore, the choice of the deformation model often implies an assumption regarding the nature of the deformation to be recovered.

The rest of the section is organized by following coarsely and extending the classification of deformation models given by Holden [25]. More emphasis is put on aspects that were not covered by that review. Geometric transformations can be classified into three main categories (see Fig. 1): i) those that are inspired by physical models, ii) those inspired by interpolation and approximation theory, and iii) knowledge-based deformation models that opt to introduce specific prior information regarding the sought deformation. Prior information can be inserted either through conditioning statistically image warping or by devising biomechanical/biophysical models that relate to anatomy/physiology more specifically than general physical models.

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/diffeomorphicity. The value of

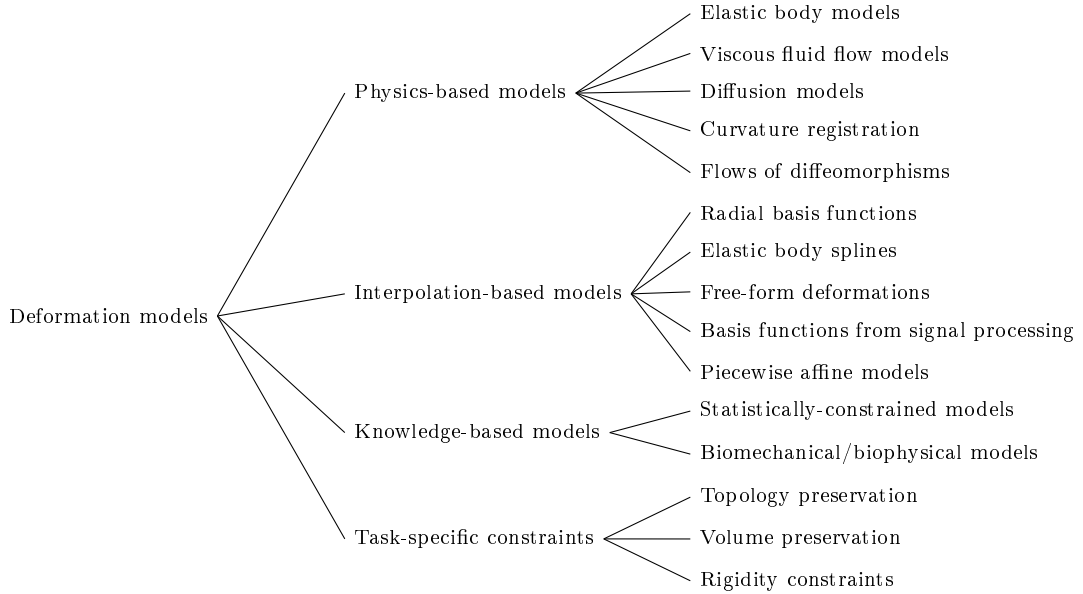


Figure 1: Classification of deformation models.

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 may produce transformation changes, making the choice of template an important task and biasing the subsequent statistical analysis. Inverse consistent algorithms constrain the forward and backward transformations to be inverse mappings of one another.
- **Symmetry:** Taking the previous idea one step further, symmetric algorithms have been devised 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. Inverse consistent methods are only asymptotically symmetric.
- **Topology preservation/Diffeomorphicity:** 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. Topology preserving/diffeomorphic algorithms produce a smooth deformation field that is one-to-one or has a Jacobian determinant that is greater than zero.

In the following three subsections, the most important methods of the three classes are presented with emphasis on the approaches that endow the model under consideration with the above desirable properties. Additionally, a fourth subsection is devoted to methods that employ task-specific constraints.

2.1 Geometric Transformations Inspired by Physical Models

Following [19], physical models can be further separated in five categories (see Fig. 1): i) elastic body models, ii) viscous fluid flow models, iii) diffusion models, iv) curvature registration, and v) flows of diffeomorphisms.

2.1.1 Elastic Body Models

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

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

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.

Broit [26] first proposed to model an image grid as an elastic membrane that is deformed under the influence of two forces that compete until equilibrium is reached. An external force tries to deform the image such that matching is achieved while an internal one 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 [27] extended this approach in a hierarchical fashion where the solution of the coarsest scale is up-sampled and used to initialize the finer one. Linear registration was used at the lowest resolution.

Gee and Bajcsy [28] formulated the elastostatic problem in a variational setting. The problem was solved under the Bayesian paradigm allowing for the computation of the uncertainty of the solution as well as for confidence intervals. The Finite Element Method (FEM) was used to infer the displacements for the element nodes, while an interpolation strategy was employed to estimate displacements elsewhere.

Linear elastic models have also been used when registering brain images based on sparse correspondences. In [29], after having established a mapping between the cortical surfaces using geometric characteristics, two images are brought into correspondence by estimating a global transformation that models the images as inhomogeneous elastic objects. The elasticity parameters were allowed to 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 is that when source and target volumes are interchanged, the obtained transformation is not the inverse of the previous solution. Christensen and Johnson [30] tried to overcome this shortcoming by simultaneously estimating both transformations while penalizing inconsistent transformations by adding a constraint to the objective function. The regularization constraint was that of linear elasticity though the transformation was parametrized by a 3D Fourier series.

Leow *et al.* [31] took a different approach to tackle the inconsistency problem. 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. The coupling was performed by modeling the backward transformation as the inverse of the forward. This fact was also exploited during the optimization of the symmetric energy by only following the gradient direction of the forward mapping.

An important limitation of linear elastic models lies in their inability to cope with large deformations. He and Christensen [32] proposed to tackle large deformations in an inverse consistent framework by considering a sequence of small deformation transformations, each modeled by a linear elastic model. The problem was symmetrized by considering a periodic sequence of images where the first (or last) and middle image are the source and target respectively. The symmetric objective function thus comprised terms that quantify the difference between any two successive pairs of images. The inferred incremental transformation maps were concatenated to map one input image to another.

A theoretically more elegant approach to account for large deformations was proposed in [33]. The authors dropped the linearity assumption by modeling the deformation process through the

St Venant-Kirchoff elasticity energy that extends the linear elastic model to the nonlinear regime. Moreover, the use of log-Euclidean metrics instead of Euclidean ones resulted in a Riemmanian elasticity energy which is inverse consistent.

In [34], fast diffeomorphic image registration was proposed based on either membrane, bending or linear elastic energy. The velocity field was assumed to be constant over time. The solution was thus given through integration over time by composing successive solutions. Given an even number of steps, this was performed efficiently by a scaling and squaring approach. Furthermore, the exponential of the flow field was used to guarantee that the inferred mapping is diffeomorphic. The energy was optimized using the Levenberg-Marquardt algorithm coupled with a full multi-grid approach to efficiently compute its update step.

2.1.2 Viscous Flow Models

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

$$\mu_f \nabla^2 \mathbf{v} + (\mu_f + \lambda_f) \nabla(\nabla \cdot \mathbf{v}) + \mathbf{F} = 0. \quad (3)$$

These models allow for the recovery of large deformations since they operate on velocities. The first term of the Navier-Stokes equation (3), 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 [35, 36]. In [35], a template was modeled as a viscous fluid allowing for large magnitude non-linear deformations. The Partial Differential Equation (PDE) was solved for small time intervals and the complete solution was given by an integration over time. For each time interval a successive over-relaxation scheme was used. To guarantee the preservation of topology, the Jacobian was monitored and each time its value fell under 0.5, the template was re-gridded and a new one was generated to estimate a transformation. The final solution was the concatenation of all successive transformations occurring for each re-gridding step. In a subsequent work [36], a hierarchical way to recover the transformations for brain anatomy was presented. Initially, global affine transformation was performed followed by a landmark transformation model. The result was refined by fluid transformation preceded by an elastic registration step.

Computational inefficiency is an important drawback of viscous fluid models and a significant reason they have not gained the popularity of the other transformation models. To circumvent this shortcoming, a massive parallel computer implementation was proposed in [35] while Bro and Gramkow [37] proposed a technique based on a convolution filter in scale-space. The filter was 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 [38] towards handling anisotropic data along with a multi-resolution scheme opting for first recovering coarse velocity estimations and refining them in a subsequent step.

An inverse consistent variant of fluid registration was proposed in [39] to register Diffusion Tensor images. Symmetrized Kullback-Leibler (KL) divergence was used as the matching criterion. Inverse consistency was achieved by evaluating the matching and regularization criteria towards both directions. Fluid deformation models have also been used to tackle multi-modal registration [40] and in an atlas-enhanced registration setting [41].

2.1.3 Diffusion Models

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

$$\Delta \mathbf{u} + \mathbf{F} = 0. \quad (4)$$

Algorithms based on this transformation model exploit the fact that the Gaussian kernel is the Green's function of the diffusion equation (4) to provide an efficient regularization step.

Thirion [42], inspired by Maxwell's Demons, was the first to introduce diffusion models in image registration. In this work, object boundaries were modeled as membranes and the image was diffused through it under the influence of the Demons placed inside the membranes. The algorithm operated in two steps: (i) estimation of the displacements for every point, and (ii) a regularization step. The Demons force was calculated by considering the optical flow constraint that is valid for small displacements, while regularization was achieved through Gaussian smoothing.

The use of Demons, as initially introduced, was an efficient algorithm able to provide dense correspondences but lacked a sound theoretical justification. Due to the success of the algorithm, a number of papers tried to give theoretical insight into its workings. Fischer and Modersitzki [43] provided 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 the Thirion's Demons algorithm [42] was drawn.

The most successful attempt to shed light on Demons was described in [44]. Image registration was formulated as an energy minimization problem and the connection of the Demons algorithm with gradient descent schemes was shown. Thirion's image force based on optical flow was shown to be equivalent with a second order gradient descent on the Sum of Square Differences (SSD) matching criterion. As for the regularization, it was 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 convolving it with a high-pass filter.

Vercauteren *et al.* [45] adopted the alternate optimization framework introduced by Cachier [46] to relate symmetric Demons forces with the Efficient Second-order Minimization (ESM) [47]. In this framework, an auxiliary variable was used to decouple the matching and regularization terms. Matching was performed by minimizing the data term through ESM optimization while regularization was achieved by Gaussian smoothing.

In [48] Thirion's algorithm was endowed with the diffeomorphic property. Diffeomorphic transformations were parametrized using stationary speed vector fields that allow 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 property in [49]. Initially, it was shown how the complete spatial transformation can be represented in the log-domain. Subsequently, a symmetric extension was provided by averaging the forward and backward forces that were computed separately.

Recently, efforts have been undertaken that seek a mathematical justification of the smoothing step to allow for deformations bearing different physical properties [50, 51, 52].

Cahil *et al.* [50] 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 [51], 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 [53] where a non-stationary diffusion filter was used to exploit

available knowledge regarding the elasticity 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.

In another example, Mansi *et al.* [52] introduced a physical constraint in the registration process to estimate the myocardium strain from Cine-MRI. The logDemons algorithm [49] 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 to extend Demons for multi-modal registration. Guimond *et al.* [54] 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 [55, 56].

The application of the Demons algorithm is not limited to scalar images and has been extended to diffusion tensor images [57], multi-channel ones [58] as well as different geometries [59]. In [57], Demons forces were derived from 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 used to register 4D time-series of cardiac images by enforcing trajectory constraints in [58]. Each time instance was considered as a different channel while the estimated transformation between successive channels was considered as constraint. Finally, the Demons framework was employed to register cortical surfaces parametrized as spheres in [57]. To generalize Demons on the sphere, a method was introduced to measure the distance between two transformations and to regularize the transformation.

2.1.4 Curvature Registration

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

$$\Delta^2 \mathbf{u} + \mathbf{F} = 0. \quad (5)$$

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

Fischer and Modersitzki were the first to introduce this constraint in [60, 61]. To solve equation (5), the Gâteaux derivatives with respect to the data and regularization terms were calculated and a finite difference scheme was employed to solve the resulting PDE. Neumann boundary conditions were used since they result in a highly structured matrix problem that can be solved efficiently. Despite this fact, the resulting underlying function space penalizes the affine linear displacements as pointed out by Henn in [62]. 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.

Beuthien *et al.* [63] proposed another way to solve the curvature based registration problem. Instead of devising a numerical scheme to solve the PDE that results from the equilibrium equation (5), recursive convolutions with an appropriate Green's function were used following [37]. In [64], a curvature penalty was approximated in the case of parametric grid-based deformation models. The approximation was derived by simultaneously examining the displacements of two neighboring grid nodes while the third was assumed to be fixed.

2.1.5 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 [35, 65, 66]. The regularization term constrains the velocity field to be smooth:

$$\mathcal{R} = \int_0^1 \|\mathbf{v}_t\|_V^2 dt. \quad (6)$$

$\|\cdot\|_V$ 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 an appropriate kernel 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 at different scales [67, 68]. Lastly, the fact that the velocity field varies over time allows for the estimation of large deformations [69].

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 [70, 71]. The distance is defined as a geodesic according to a metric and can be used for studies of anatomical variability [72]. A number of theoretical aspects of this framework and especially the ones related with computational analysis were further developed in [73, 74, 75, 76, 77]. The interested reader is referred to [78] for an overview of its evolution 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 [69, 79, 80, 81, 82, 83], point-matching [70], point-matching on spheres [84], matching sets of unlabeled points [85, 86, 87], shape-matching [88, 67], curve-mapping [89, 90, 91, 92] and hybrid registration [93, 94].

Even though the LDDMM framework provides diffeomorphic transformations, it is not symmetric. To encode the symmetric property a number of approaches have been proposed [95, 79, 80]. Beg and Khan [79] focused on providing symmetric data terms. Younes [95] also discussed ways to render the alignment process symmetric while Avants *et al.* [80] presented a symmetric LDDMM registration process driven by cross-correlation.

The mathematical rigor 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 [96, 97, 81].

Marsland and McLachlan [96] formulated the problem in a PDE framework and used a particle method to solve for the diffeomorphism. A similar approach that involves a particle mesh method was presented in [97]. More recently, a Gauss-Newton implementation of the previous algorithm was given in [81]. These approaches were based on the fact that the initial velocity field is sufficient to calculate the intermediate and final deformations.

Instead of devising more sophisticated optimization schemes to efficiently calculate diffeomorphisms, one could simplify the problem by decreasing its degrees of freedom. Stationary velocity fields [98] 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 [34, 99, 100, 101]. Hernandez *et al.* followed this approach and used stationary Ordinary Differential Equations (ODEs) in the LDDMM framework [102].

2.2 Geometric Transformations Inspired by Interpolation Theory

Rather than being motivated by a physical model, the models of this class are derived from either interpolation theory or approximation theory. In interpolation theory, displacements, considered known in 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 smoothly approximates 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 that are present in image registration problems while having low degrees of freedom, facilitating the inference of the parameters. Among the most important families of interpolation strategies, one may cite (see Fig. 1): i) Radial Basis Functions, ii) Elastic Body Splines, iii) Free-Form Deformations, iv) basis functions from signal processing, and v) piecewise affine models.

2.2.1 Radial Basis Functions

One of the most important families of interpolation strategies is that of 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

$$\mathbf{u}(\mathbf{x}) = \sum_{i=1}^N \omega_i \phi(\|\mathbf{x} - \mathbf{p}_i\|). \quad (7)$$

An evaluation study comparing RBFs used as transformation functions in non-rigid image registration was first given in [103]. A more thorough presentation and an analysis with respect to their ability to preserve topology was given more recently in [104]. The advantage of 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 of points in the whole image domain. This behavior is undesirable when seeking local transformations.

One of the first and most important RBFs to be used in the field is Thin-Plate Splines (TPS) [105,106]. TPS minimize the bending energy assuming infinite boundary conditions. The solution is given in a closed-form and its uniqueness is guaranteed in most cases. Nonetheless, TPS are known to exhibit certain shortcomings. The transformation from one image domain to another is not inverse consistent. Moreover, their support is global, which does not allow for recovering local image warpings. 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 to lessen the importance of these drawbacks [107,108,109,110,111,112].

In [107], Johnson and Christensen tackled the inverse inconsistency problem. They considered the minimization of the bending energy 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 [109]. TPS were constructed in such a way that their support is restricted locally. In a subsequent work, Yang *et al.* [110] defined the support of each point in an adaptive way by taking into consideration the distribution of the points in the image domain. These approaches are based on heuristics and a truncation of the original basis, to limit the influence of the control points. Rohr and Wörz [112] introduced a variant of TPS that assumes Gaussian forces. The locality of the transformation can be influenced by controlling the spatial impact of the forces.

Rohr *et al.* [108] proposed to take into consideration the landmark localization error when estimating the dense deformation field through the use of approximating Thin-Plate Splines. The authors proposed to weaken the interpolation constraint and estimate the transformation by minimizing a functional that weights the approximation error according to the (isotropic or anisotropic) landmark position estimation error. The approximation problem admits an analytical solution that consists of the same basis functions as the interpolation problem.

Three ways to address the computational problems related with the presence of a great number of landmarks were studied by Donato and Belongie [111]. The straightforward approach of sub-sampling the points was compared to two more elaborated ones that use either a subset of the basis functions or a matrix approximation technique based on the Nystrom method. The more sophisticated methods were shown to outperform the naive approach in terms of mean squared error. The matrix approximation method was also shown to be useful when principal warp analysis was taken into account.

Clamped-Plate Splines [71, 113] minimize the same energy as TPS though under specific boundary conditions. Following the LDDMM framework, the energy is minimized so that the resulting dense deformation field is diffeomorphic and thus this type of splines are referred to as Geodesic Interpolating Splines [114]. An extension to combine them with affine transformations was given in [115] while two ways to calculate them were presented by Mills *et al.* [116].

Another family of RBFs that has global support is that of multi-quadratics [117]. They are defined as $\phi(r) = (r^2 + d^2)^{\frac{\mu}{2}}$, where 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, and μ is a nonnegative scalar. This approach has been extended to treat the presence of a rigid object, by Little *et al.* [118].

Gaussian functions ($\phi(r) = e^{-\frac{r^2}{\sigma^2}}$) is another class of RBFs that can be used to parametrize the deformation [119]. Their advantage is that their spatial influence may be controlled by choosing an appropriate Gaussian kernel σ . By choosing a small size for the Gaussian kernel, their influence can be greatly restricted and thus local displacements may be recovered. A recent example of the use of this deformation model in brain registration can be found in [120].

Dense deformation fields can be created by considering the normalized weighted average of sparse displacements [103]. Despite the global support of the control points, the locality of the transformation can be adapted by choosing an appropriate weighting function.

In medical imaging, the presence of different anatomical structures characterized by different properties and the subsequent need to recover local deformations render the previous models not well suited. To cope successfully with such cases, interpolation methods where control points have spatially limited influence are appropriate.

Fornefett *et al.* [121] investigated the use of Wendland functions [122, 123] that exhibit the desired locality property, for elastic registration. Other local support radial basis functions include the C^2 smooth Wu functions [124] and the functions proposed by Buhmann [125]. Rohde *et al.* [126] 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, Siddiqui *et al.* [127] defined a new model based on the cosine function. Contrary to what is claimed in the paper, the new model is not positive definite [128]. Lastly, Lowitzsch [129] introduced a special class of matrix valued RBFs that are divergence free.

In [104], 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.

2.2.2 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), which were introduced by Davis *et al.* [130]. As the name implies, they are solutions of the Navier-Cauchy equilibrium equation for a homogeneous isotropic elastic body subjected to forces. When the applied forces are polynomial or rational, one can solve the equation analytically.

The previous work was extended in [131] by considering Gaussian forces. 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 for the equilibrium equation.

Wörz and Rohr further extended Gaussian Elastic Body Splines in [132]. 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.

2.2.3 Free Form Deformations

Free-Form Deformations (FFDs) is one of the most common types of transformation models in medical imaging. A rectangular grid $G = K \times L$ is superimposed on 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 [133, 134] but gained wide acceptance in the medical imaging community when coupled with cubic- B splines [135, 136, 137, 138].

The deformation in $2D$ is given as

$$\mathbf{u}(\mathbf{x}) = \sum_{k=1}^K \sum_{l=1}^L B_k(\mu) B_l(\nu) \mathbf{d}_{kl}, \quad (8)$$

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 l th basis function of the B -spline and $\delta_x = \frac{M}{K-1}$ and $\delta_y = \frac{N}{L-1}$ denote the control point spacing. The advantage of the transformation model lies in its simplicity, smoothness, efficiency and ability to describe local deformations with few degrees of freedom.

While in general the transformations that result from cubic B -spline FFDs are smooth, the preservation of topology is not guaranteed. Rueckert *et al.* [139] imposed the hard constraints proven in [140] to produce diffeomorphic deformation fields. The required condition is that the maximum displacement should not be greater than four tenths of the grid spacing.

Many extensions of FFDs have been proposed in the literature. For example in [141], an inverse consistent method based on FFDs was 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 [142].

Noblet *et al.* [143] presented a symmetric extension of FFDs. They assumed that both images deform toward a common domain, that is in an equal distance from the source and the target, under the influence of two isomorphic grids. Given the parametric nature of the transformation, this results in constraining the displacements of the corresponding nodes in the two grids to

sum to zero. Moreover, in order to calculate the mapping from one image domain to the other, the respective estimated mappings toward the common domain should be invertible. A similar model was employed by [144] with the difference that the registration problem was formulated as a discrete labeling one.

FFDs have been extended to treat multiple-image registration where hard constraints are employed to define a reference domain [145, 146, 147]. Last but not least, the transformation model has been extended to the spatio-temporal domain where B -splines are also used for the temporal axis [148, 149, 150].

2.2.4 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 transformations. An important reason to use them is the fact that they can naturally provide a multi-resolution decomposition of the displacement field. This is 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.

The consistent registration framework introduced by Christensen and Johnson [30] is probably the most well known registration algorithm that employs a Fourier-based transformation scheme. The Fourier series representation of the transformation has the advantage of simplifying the linear elasticity constraint and allowing 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 efficiently model local deformations.

Wu *et al.* [151] 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.* [152] modeled the deformation field with a finite-supported, semi-orthogonal wavelet toward tackling the problem of aligning rat brain histological images. In order to ease the optimization burden, the authors exploited the natural multi-resolution and multi-band decomposition of the wavelet coefficients. The transformation parameters were first inferred for low resolution levels, separately for each subband before proceeding to finer resolution levels.

Musse *et al.* [153] presented a topology-preserving multi-resolution approach that uses non-orthogonal Riesz basis of polynomial splines 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 [154] and was further validated in [155]. In the 3D case, the same multi-resolution framework was used, though the topology could not be preserved by satisfying linear constraints. This was made possible by solving a constrained optimization problem where the Jacobian was enclosed between two user specified bounds. Cathier [156] used the same wavelet basis as in [151] 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 led to sparse transformations with respect to the wavelet basis and thus facilitated their storage in memory.

2.2.5 Piecewise Affine

One of the simplest ways to deform an image is to use a piecewise linear deformation model. The image is mosaicked by a set of triangles or tetrahedra, the nodes of which parametrize the

deformation, while 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 using a piecewise affine model include, but are not limited to, the following. Hellier *et al.* [157] proposed a multi-resolution and multi-grid approach. The image was partitioned adaptively into cubes and an affine transformation was inferred for each one. A regularization energy term encouraged neighboring pairs to deform similarly. In a similar fashion, Zhang *et al.* [158] tackled 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.* [159] 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 calculating the affine transformation for each region and applying a non-linear interpolation in between the regions. A similar approach was presented in [160] 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 applications of piecewise affine models were presented in [161, 162]. Cootes *et al.* [161] favored the use of piecewise affine transformations as they can be easily inverted. Buerger *et al.* [162] proposed a hierarchical framework to adaptively separate the images into regions. Splitting was formulated as an energy minimization problem and three criteria were used. The first criterion tried to group regions with rich structural information. The second criterion treated regions with significant residual error in large blocks while the last criterion encouraged regions with similar motion to be considered together. The second was found to perform best.

Most 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 this 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 [163]. This 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.* [164] 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 a distance-weighted sum of infinitesimal velocities at the known points, integrated over time.. No closed form exists and a computationally expensive integration of ODEs is necessary. [165] 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 Knowledge-based Geometric Transformations

Devising a deformation model that may be applied successfully to a great variety of registration tasks seems not only too optimistic but also aiming in the wrong direction. The challenges entailed by different registration settings cannot be easily addressed in total by one method. Moreover, it is a waste of resources not to exploit our knowledge of the problem at hand to condition its solution. Creating knowledge-based geometric transformations should facilitate finding solutions while increasing their reliability.

Introducing knowledge about the deformation may be achieved in two ways. The most

straightforward is through training a high dimensional statistical model of deformations, which is subsequently used to penalize configurations that diverge from it. The second method of exploiting our knowledge about the deformability of the tissues and constructing biomechanical/biophysical deformation models that mimic their properties.

2.3.1 Statistically-Constrained Geometric Transformations

Statistical deformation models (SDMs) capture statistical information about deformation fields across a population of subjects. The advantage of such methods is that they are able to reduce the number of degrees of freedom, and thus the problem's computational complexity, while achieving more robust performance. Nonetheless, the use of SDMs implies important assumptions. First, one should be able to train the high dimensional statistical model from an often limited number of subjects. Second, it is assumed that the set of images used during the learning step is representative of the population that will be analyzed. Hence, a statistically-constrained registration framework is limited by previously-observed deformations; often subsequent refinement by conventional registration is required.

Statistical models of variability have been applied successfully to many problems in medical imaging. One of the most successful examples concerns statistical models of shape variability applied to segmentation [?] where shape variability was studied by performing Principal Component Analysis (PCA) on point correspondences. Wang and Staib [41] combined a statistical shape model over boundary points and a physics-based regularization term in a Bayesian approach to solve the atlas-based registration problem.

PCA has also been applied in the case of dense deformation fields to derive priors that can be used to constrain registration. In [28] the authors described a recursive way to update the model given new observations while accounting for the limited number of samples. In [?] PCA was used to model the deformation and registration was performed by adjusting the coefficients of the principal components while maximizing Mutual Information (MI).

Tang *et al.* [?] also used PCA to train an SDM to accelerate image alignment. Once the model was trained, the authors created a set of intermediate templates by sampling along each dimension of the estimated multidimensional Gaussian distribution. The registration of a new image was performed by projecting it to the intermediate template closest in intensity similarity, and by refining the result with a conventional registration method. In [?, ?] the intermediate template was predicted by support vector regression models that had learned the correlations between deformations and image appearances.

Rueckert *et al.* [166] performed statistical analysis on the displacement of the control points of the FFD grid that deforms the image. Most recently, it was demonstrated that this model can encode landmark position information [?]. Moreover, because the optimization was performed over the modes of the model, the number of degrees of freedom was greatly reduced lessening the computational cost. Loeckx *et al.* [?] used a similar model to tackle lung radiograph registration. The statistical model was augmented by incorporating translation and scaling, to account for the fact that the training set was created by manual alignment of image pairs without prior global spatial normalization.

Glocker *et al.* [167] also proposed a model that captures variations in the displacements of the control points of the FFD grid. In the first place, a clustering step was performed to reveal the co-dependencies between node displacements. Then, Gaussian mixture models were used to represent the probability density function (PDF) of the relative displacement of two cluster centers and thus capture information about the global nature of the desired deformations. Similarly, PDFs were learned over the relative displacements of the cluster and its cluster members capturing the local information of the desired deformations. The learned priors were introduced as soft

constraints in a discrete Markov Random Field registration framework through the consideration of appropriate pairwise interactions.

Xue *et al.* [?] tackled the problem of training a high dimensional SDM from a limited number of samples by employing wavelet-based decompositions and estimating the PDF of each band by applying PCA to each one. Two SDMs were trained, one captured variations about the deformation fields while the second encoded information about the Jacobian determinant of the deformation fields. The registration result was constrained by these models as well as a nested Markov random field (MRF) regularization scheme. In a subsequent work [?] conventional registration followed the statistically-constrained registration to refine the result.

Pennec *et al.* [33] presented a statistical framework for nonlinear registration that takes into account the means and the covariances of the deformation tensors by computing their Mahalanobis distance. This framework was further developed in [?] by computing statistical priors on both the deformation tensors and the displacement vector fields in a nonconservative Lagrangian fluid registration algorithm. In both approaches, statistical priors were used to guide registration, instead of constraining it to follow the learned distribution.

Lester *et al.* [?] presented a modified version of the viscous fluid registration algorithm that incorporated tissue information by letting the viscosity vary according to the tissue. In a similar context, Commowick *et al.* [?] proposed to introduce prior knowledge regarding the stiffness of the deformability of different structures by weighting an elastic-type regularization term by a space-varying scalar or tensor field. The computation of the scalar map of deformability was based on the mean of the absolute value of the logarithm of the determinant of the Jacobian while the stiffness tensor map was based on the mean of the absolute value of the logarithm of the deformation tensor.

Last but not least, a conceptually complementary approach was presented in [168]. Instead of learning the set of admissible deformations, the weights for a weighted SSD similarity criterion were inferred by optimizing the cross-validation error of a specific task. One could state that estimating these weights is implicitly equivalent to estimating a stiffness map.

2.3.2 Geometric Transformations Inspired by Biomechanical/Biophysical Models

Biomechanical/Biophysical models are also inspired by physical properties. Their difference with respect to the models presented in Sec. ?? is that they relate closely to anatomy and physiology. Usually, Finite Element Methods (FEMs) are employed to model the biomechanical/biophysical properties of the tissues under consideration.

The main advantage of this category is that their use of more informed priors about biomechanical properties allows for the faithful estimation of complex deformation fields parametrized by few degrees of freedom. Moreover, the plausibility as well as the robustness of registration are improved. On the downside, the use of FEMs requires the definition of material properties, geometry and boundary conditions, which is often challenging. Our limited understanding of the material properties results in a choice of parameters that is most often based on crude estimations or a limited number of experiments, while at the same time being general and not case-specific. The definition of the geometry calls for an accurate segmentation of anatomical structures as well as appropriately meshing the image domain, both of which are demanding and influence the simulation quality. Specifying suitable boundary conditions is often equivalent to providing displacement constraints for the segmented organ surfaces. Uncertainty in the specification of these parameters may lead to undesirable bias. Last but not least, such models are not really suitable for inter-individual registration since the biophysical model is no longer valid in these cases.

Typical examples of biomechanical/biophysical models taken into account in medical image

registration are tumor growth evolution effects; cardiac function models; breast, prostate and brain tissue elastic properties as well as respiratory motion models.

Registration between normal atlas and pathological brain images in the presence of tumors is a problem that may profit greatly from the existence of brain-tumor interaction models [?, ?, ?, ?, ?]. One basic approach to tackle such cases is to correct for the topological difference between the pair of images by accounting for the tumor and its effects in neighboring structures in the normal subject.

In one of the first attempts to tackle the problem Kyriacou *et al.* [169] used a simple uniform expansion model for the tumor. First, the authors simulated a tumor-free anatomy that was used subsequently in a normal-to-normal atlas registration. Last, the tumor influence was taken into account in order to produce the final deformation field. In [?] Talairach landmark registration was used along with a simple radial mass-effect tumor model. A radial expansion model of the lesion was used in [?,?]. In the first case [?], it was combined with a Demons deformation model, while in the second case [?], with a mutual information flow [170]. A simple radial growth model was also employed in [?] where registration was performed between the Talairach atlas and a subject based on point correspondences and radial basis function interpolation.

Richer models have also been considered. In [?], after an initial affine registration between a normal atlas and the patient's image, a coupled model that predicts the anisotropic evolution of the tumor as well as its mass-effect was applied. Nonetheless, important differences between the images were still present at the end due to the fact that no deformable registration step was applied. Methods that combine sophisticated brain-tumor interaction with deformable registration have been proposed in [171, ?, ?, ?]. Mohamed *et al.* [171] trained a statistical model of the tumor-induced deformation based on a great number of tumor model simulations. This model was used to estimate the mass-effect in the atlas domain before applying deformable registration. Zacharaki *et al.* [?, ?] also trained a statistical model based on simulations of the tumor effect [?]. The parameters of the learned model were inferred through optimization that considered both deformation field information and image similarity. Gooya *et al.* [?] addressed the case of Glioblastoma multiforme brain tumors modeled previously [?]. The parameters of the tumor growth model were estimated jointly with the warping in an expectation-maximization setting. No statistical model was used in this case.

Another fertile field for application of biomechanical models is breast imaging. Our understanding of breast composition, the elasticity properties of the component tissues as well as the different conditions under which the breast is imaged allows for successful application of finite element models. Biomechanical modeling is important in tackling large deformations which are typical in breast imaging applications such as cancer diagnosis [?], surgical planning [?] and image-guided interventions [?]. Moreover, the ability of FEMs to faithfully simulate breast deformations has led to their use for the validation of deformable registration methods [?, ?, ?].

There are two main causes of breast deformation, gravity and plate compression. When patients are imaged under different positions (typically prone-supine), the breast is deformed greatly under the influence of gravity. FEMs have been used either to register the images [?, ?] or to provide a more appropriate initialization for standard intensity-based nonrigid registration methods [?, ?, ?].

The breast is typically compressed in mammography under the pressure of two plates in order to flatten and spread the tissue. As a consequence, alignment between 2D mammograms and images from other (typically 3D) modalities, is a challenging problem. Finite element methods have been proven successful in tackling this problem [?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?].

It is important to note that while these methods aim to align different images, most of them do not opt to optimize an image-similarity criterion. Instead, alignment is determined by the modeling boundary conditions and assumptions, which is exactly what differentiates these

methods. Breast may be modeled as a homogeneous material [?, ?, ?, ?] or as heterogeneous consisting of different homogeneous tissues (fat, fibroglandular, skin and/or tumor) [?, ?, ?, ?, ?, ?, ?]. The properties of these tissues may be defined based on experience or optimized with respect to image similarity or surface distance [?, ?, ?]. Other modeling choices include the inclusion of friction between breast and plates in the contact model [?, ?, ?] or do not (frictionless) [?, ?, ?, ?]. Lastly, maybe the most important choice regards the boundary conditions and whether it is the interaction of compression plates and the breast [?, ?, ?, ?, ?, ?, ?, ?], displacement loading [?, ?] or both [?, ?].

Biomechanical models have also been used to model the prostate and its surrounding organs with applications mainly in preoperative-intraoperative image registration problems. [?, ?] used biomechanical models to simulate prostate deformations due to transrectal ultrasound probe insertion for different material properties and insertion angles. The simulations were used for the statistical learning of the induced deformations, while the statistical model was subsequently used to constrain the registration. Alterovitz *et al.* [?] presented a 2D biomechanical model whose material properties and external forces were optimized by maximizing the overlap between the segmented prostate in both images. Bharatha *et al.* [?] presented a finite element model to register preoperative 1.5T MR to intraoperative 0.5T MR images. The central gland and the peripheral zone were considered separately as linear isotropic elastic materials and boundary conditions were provided by surface matching. In a similar approach, Crouch *et al.* [?] used medial shape models to facilitate meshing and boundary condition calculation. Hensel *et al.* [?] considered prostate, bladder, rectum, pubic bone and the tissue between them, isotropic linear elastic materials. Boundary conditions were given by calculating the difference between the centers of gravity and mass of the prostate in the two images as well as surface displacements.

Biomechanical models span a great range of applications. Detailing them all here is both out of scope and impossible. Nonetheless, let us note some applications in the estimation of cardiac movement [?, ?, ?, ?, ?, ?], of the brain shift during surgical operations [?] and of the lung movement [?, ?].

2.4 Task-Specific Constraints

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

There are two possible ways to regularize the problem: explicitly and implicitly. Explicit regularization may be achieved through the addition of a smoothing term in the energy function that penalizes non-regular configurations. This is mostly used in the case of physically motivated models. Implicit regularization may be achieved by parameterizing the deformation field with smooth functions. It does not exclude the use of explicit regularization but may be used now to achieve complementary goals, usually tailored to the problem at hand. Such goals include (see Fig. 1): i) topology preservation, ii) volume preservation, and iii) rigidity constraints,

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 naturally delivers such results, the other deformation models do not exhibit these properties. In this 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 [35].

This technique is efficient but the method that guarantees the preservation of topology seems

rather awkward. More elegant methods incorporate an appropriate term acting upon the Jacobian in the objective function. In [30], 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 [172] used a regularization term that takes into account the length, area and volume deformations. 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 [153], 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 [154], the energy was optimized under the constraint that the Jacobian will stay 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 [173] who used a variant of a log-barrier method to solve the optimization problem. Instead of solving the initial constrained problem, a sequence of unconstrained ones was employed. 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 [138] also proposed a constrained optimization framework to ensure that the transformation, parametrized by cubic B -splines, is invertible. Two constraints were investigated. The first constrained the Jacobian of every pixel to be greater than a threshold. As this constraint did 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 was restricted to be within a range of values. Moreover, when approaching values close to the bounds, its derivatives were constrained to be close to zero. In [174], a simpler penalty was devised for the case of B -splines. The penalty takes into account the difference between two adjacent nodes and is memory efficient.

In many applications, volume preservation is also important. Such a constraint is of particular interest when we know that the imaged anatomical structure is not compressible and that all changes are due to either motion or intensity changes provoked by the action of a contrast agent. A simple example is a rigid part of the body such as a bone structure. More complicated cases include deformable structures that preserve their volume such as breast, myocardium and liver.

In [175], such a strategy was employed to register contrast-enhanced MR breast images. Along with the image matching term a second term that penalized volume changes was considered. The penalty integrated the absolute logarithm of the Jacobian determinant and was zero only when local volume was preserved. A sequential approach was proposed by Tanner *et al.* [176]. 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 influenced these areas were fixed to the mean of their previous ones and the registration was solved again for the rest of the variables. Haber and Modersitzki [177] presented a constrained optimization approach for volume preservation. An energy function comprising a matching and regularization term was minimized under the constraint that the determinant of the transformation is equal to one ($\det(\mathbf{J} + \nabla \mathbf{u}) - 1 = 0$).

Another category of problems that call for an incompressibility constraint are those involving the deformation of the myocardium, as it is known to be a nearly incompressible material. Bistoquet *et al.* [178] approximated the previous constraint with $\nabla \cdot \mathbf{u} = 0$. This constraint was enforced by the use of divergence-free radial basis functions as deformation model [129]. In addition, a hard constraint was introduced in the objective function to penalize deviations from incompressibility. In [179], the determinant of the Jacobian was constrained to be close

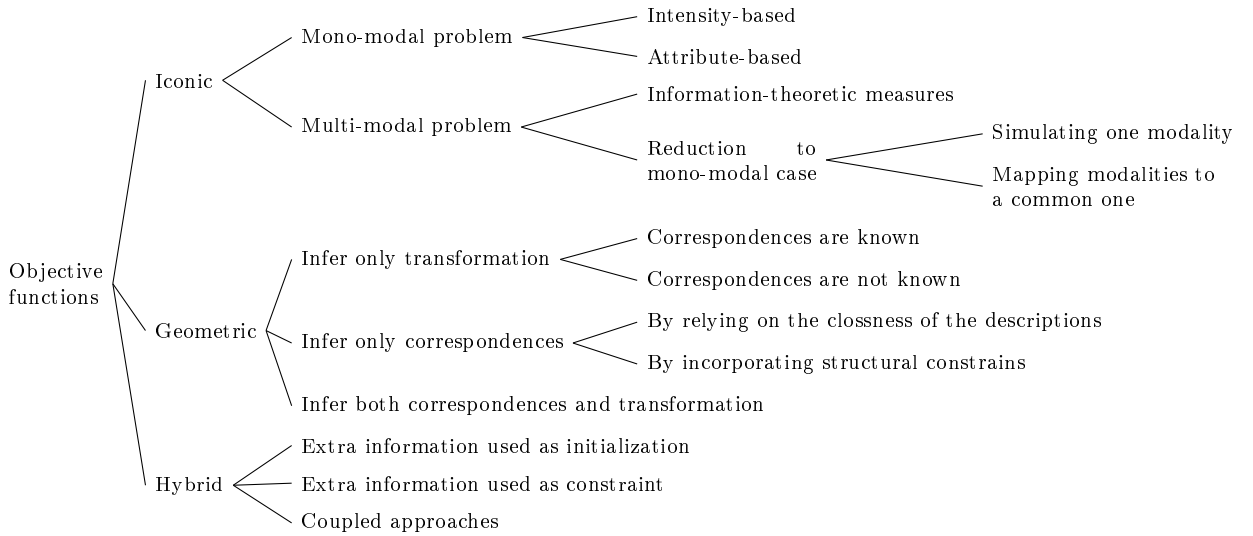


Figure 2: Classification of objective functions.

to one in a predefined region by using Lagrange multipliers. A different approach was taken by Mansi *et al.* [52] in which the velocity field \mathbf{v} was constrained to be divergence-free. This method was based on the fact that the integration over time of divergence-free velocities results in incompressible deformations.

Last but not least, the presence of rigid anatomical structures in medical images motivates the incorporation of rigidity constraints in image registration. Loeckx *et al.* [180] locally constrained a non-rigid FFD registration method by penalizing deviations of the Jacobian from orthogonality. In [181] rigidity was imposed by introducing three conditions. The first condition required the second derivatives of the transformation to be zero. The second condition forced the orthonormality of the rotation matrix while the third condition required the determinant of the Jacobian to be equal to one. Local rigidity has also been considered in a variational setting by Modersitzki [182]. Along with the matching and the regularization term, a third one was introduced in the objective function to control the rigidity of the transformation by forcing its Jacobian to be linear, orthogonal and orientation preserving.

3 Objective Functions

We can distinguish three groups of registration methods according to how they exploit the available information to drive the matching process (see Fig. 2). On one hand, iconic methods quantify the alignment of the images by evaluating an intensity-based criterion over the whole image domain. On the other hand, geometric methods opt for the establishment of sparse point correspondences that capture salient geometric information. Last but not least, hybrid methods combine 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 considerable computational expense. Due to the fact that all image

points are considered as equal, salient points might fail to get the importance they deserve. In addition, initial conditions greatly influence the quality of the obtained result. In the presence of large deformations, which are 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. Devising an appropriate criterion is an important and difficult task as the criterion should be able to account for the 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 examined and high 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 distinguished (see also Fig. 2): i) the mono-modal case, involving images from one modality, and ii) the multi-modal one, involving images from multiple modalities.

3.1.1 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 reasonable to assume that the 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 assumptions made about 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) [21, 183, 80].

Intensity information by itself is considered a poor feature often leading 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 ones.

In their seminal work, Shen and Davatzikos [120] 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 was that a rich enough attribute vector would be able to differentiate voxels that otherwise would be considered the same based only on their intensity information. Thus, fewer local minima would be present and better accuracy may be achieved. To further reduce the effect of the local minima, they proposed a hierarchical scheme that successively approximated the objective function by progressively increasing the number of voxels where the matching criterion was evaluated.

The success and importance of the above method becomes evident in view of the number of approaches that have been proposed to improve its performance. One drawback is that it requires a pre-segmentation step in order to introduce local spatial information. To remove this requirement, the use of Daubechies wavelets to populate the attribute vector was proposed in [184]. The attribute vector was constructed in a multiscale fashion to be translation and rotation invariant. The wavelet-based attribute vector was shown to be more discriminative when compared to the geometric moments. Another approach to tackle the above shortcoming is to use local histograms and boundary information as attributes [185]. In [186], 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. Second, 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.

Local information may also be incorporated by exploiting the local frequency representations obtained as response to Gabor filters [187, 188]. 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.* [187] 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. However, Liao and Chung [189] argued that frequency spectra 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 a uniform spherical region descriptor, was proposed in [190]. It is invariant with respect to rotation as well as monotonic gray-level transformation and thus is able to account for the presence of a bias field. Last but not least, Residual Complexity (RC) is a method that can account for complex spatially-varying intensity distortions [?]. This method attempts to register two images by minimizing the number of basis functions that are required to code the residual image.

3.1.2 Multi-Modal Registration

Multi-modal registration is more challenging as the choice of an appropriate objective function is a harder task. Two main approaches have been proposed to solve the problem (see also Fig. 2): i) use of information theoretic measures, and ii) reduction of the multi-modal problem to a mono-modal problem. The latter can be achieved by either 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 [191, 192, 193, 194] when both teams introduced the use of Mutual Information (MI) in multi-modal image registration. The difference between their approaches is the way entropy is estimated. In [191, 192] a non-parametric estimator was used while in [193, 194] 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 [195].

The widespread use and study of MI has revealed some of its shortcomings. Primarily, 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 [196]. 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 [197].

The success of MI paved the way for the introduction of an important number of statistical criteria in image registration. Roche *et al.* [198] 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 the appropriate similarity

measure when the assumption of functional dependence between the image intensities is valid.

Pluim *et al.* [199] compared the performance of a number of f -information measures (including MI) in medical image registration. In the context of registration, f -measures quantify the difference between the joint distribution of the intensities and the joint distribution that would arise if images were independent. The most important finding of the study was that there are f -measures that were able to perform better than MI at the cost of more difficult inference.

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 [200,201] to register multi-modal images. The joint intensity distribution was either learned from aligned pairs of images or by segmenting corresponding anatomical structures. Images got aligned by minimizing the divergence between the observed and estimated distributions. Jensen-Shannon Divergence (JSD) was used to compare learned distributions in [202]. The authors argued that JSD is better than KLD since it is a symmetric, bounded and true metric.

Another family of information theoretic approaches is built upon Renyi Entropy (RE) [203]. 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 [204,205]. In [206,207], 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 [208]. The latter demonstrated the superiority of the entropic graph estimator compared to standard estimators. A generalization of KLD was introduced in [209]. The new divergence measure was based on modified Bessel functions of the second kind and allowed for an efficient recursive computation. The generalization of KLD was shown to perform better than the standard measures of divergence.

Most of the aforementioned approaches share a common drawback; they are based on 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 [210]. To rectify this shortcoming, local context should be introduced in the used criterion.

One way to relax the way statistical criteria are globally taken into account consists of computing them locally, thus coping with the fact that the relation between the two image intensities is non stationary. This approach was investigated by Hermosillo *et al.* [170] and Karaçali [211]. Hermosillo *et al.* derived the Euler-Lagrange equations for MI, CR and CCoef based on locally estimated probability distribution functions. Karaçali followed a deterministic rationale to express the mutual information, joint entropy and the sum of marginal entropies over small spherical regions in closed form.

Local evaluation of mutual information has also been proposed by other researchers. For instance, [212] 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.* [213] proposed to condition the evaluation of MI upon the position. More recently, locally evaluated MI in combination with standard global MI was used in [214]. Under their approach, the local evaluation of the probability distribution function assesses pixels relatively to their distance from the FFD control points.

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

In one of the first attempts to exploit spatial information, Pluim *et al.* [215] used the 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.

At approximately the same time, Rueckert *et al.* [210] proposed to use second-order MI to encode 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 kept reasonably small. More robust and accurate registration with respect to standard MI was obtained.

Russakoff *et al.* [216] introduced Regional Mutual Information that pushed forward the previous idea by taking into account 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 [217], NMI between blocks of image elements was studied. The high-dimensional NMI was estimated using random lines and reducing the number of bins. Recently, a similar approach was presented by Yi and Soatto [218]. 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 explicitly taking into account neighboring voxels, a more compact way to consider local information would be to extract features that concisely describe regional characteristics. In [219], Gaussian scale space derivatives were employed and incorporated 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 [220] 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 [221], 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 [222] to tackle high dimensional α -MI registration of ultrasound images. Both approaches coped with global linear registration. Most recently, deformable registration of Cervical MRI using high-dimensional MI was presented in [223]. Features were used to describe local geometric information and a k -nearest neighbor graph was used 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 [224], regions were segmented by thresholding and labeling connected components. The

labels were used as an additional image and the objective function considered the difference between the entropies of each image and the joint entropy.

Knops *et al.* [225] performed a k -means clustering before registration. Based on this clustering, voxels that shared similar intensity profiles but belonged 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.* [226] 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. For the intensity-to-labeled 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 to reduce 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 available knowledge of 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, which is task specific, was first proposed by Roche *et al.* [227] towards rigidly registering ultrasound (US) images to MR ones. In [227], US intensities were predicted by exploiting MR intensities and MR gradient magnitude information. Complex phenomena such as US signal attenuation and speckle were neglected, leading to images that only roughly resembled actual US images. A more sophisticated model was proposed in [228] to tackle the problem of CT-to-US registration. Based on the physical principles of ultrasound, the authors were able to simulate a US image that was then used along with a locally evaluated statistical criterion to drive the registration.

In [229], the mixture of experts methods was 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 over 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.* [230] 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 a surface registration with the difference that instead of having binary values, real ones were used. Haber and Modersitzki [231] 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. The objective function was based on the difference in angles between the normalized gradient vectors. In [172], 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 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 and Thiran [232] also experimented with edge related information. They used an edginess operator that takes into account 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 [233], 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 [188, 187]. In [188], 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 the matching criterion. The responses of Gabor filters were used in [187] to construct a rich vector descriptor. The images were aligned by minimizing a weighted sum of the vector differences. In [234], the authors took a different direction to estimate the local frequency information. Instead of using Gabor filters, the Riesz transform was used. Recently, Heinrich *et al.* [235] presented a new descriptor for multi-modal registration. The driving idea behind the new descriptor is the use of similarities between neighboring patches as features. This idea is borrowed from the image denoising literature. Once the descriptor is constructed a vector-difference can be used as a matching criterion.

Andronache *et al.* attempted to tackle the problems related to the estimation of MI in small patches in [236]. Their strategy consisted of identifying the patches where the estimation of MI becomes unreliable and then mapping them to a common pseudo-modality. The pseudo-modality depicted only common structures in both images and was constructed by decreasing the variance of the mapped intensities. In the intermediate domain, simpler criteria may be used to drive registration. Recently, Wachinger *et al.* [237] proposed two techniques that derive from information theory and manifold learning to create the intermediate structural representation. The first one used 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 to learn the similarity measure for multi-modal image registration was presented in [238]. 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 [239, 240] 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 likely to have the same code while wrong ones are not. The embedding was constructed by using AdaBoost. The proposed method was experimentally proven 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 [241] or a divergence criterion [200, 201, 202, 208] is used to compare the estimated and learned distributions.

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 can overcome some of the limitations of iconic registration since it is robust with respect to the initial conditions and the existence of large deformations. The solution of the registration problem is obtained in a relatively straightforward way once landmarks have been extracted. However, locating reliable landmarks is an open problem and an active topic of research. Most importantly, the sparse set of directly obtained correspondences gives rise to the need for interpolation, which results in a decrease in accuracy as the distance from the landmarks increases. This, as well as the advance in technology that meets both the memory and computational demands of iconic registration have boosted research in that direction, stripping geometric methods of the interest they enjoyed during previous decades. Nevertheless, for some task specific applications geometric registration is the most reliable choice.

created by thresholding in the intensity domain, are tracked and selected based on their area's stability as the threshold value varies.

Before describing any methods, let us introduce the known and unknown variables of the problem. The set of known variables comprises two sets of points ($K = \{\kappa_1, \dots, \kappa_n\}$ and $\Lambda = \{\lambda_1, \dots, \lambda_m\}$, $m \geq n$) that can be created given a point detector strategy. The first set of points contains points belonging to the source domain Ω_S , while the second contains points that belong to the target one Ω_T . The set of unknown variables usually comprises: i) the correspondence, and ii) the transformation. Based on how these variables are treated, three classes of methods can be separated (see also Fig. 2): i) Methods that infer only the spatial transformation; ii) Methods that infer only the correspondence; and iii) Methods that infer both variables.

3.2.1 Methods that infer only the spatial transformation

Two categories of methods should be considered (see Fig. 2). 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 correspondences 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 [242, 243, 244, 161]. In Procrustes analysis, a least-squares distance is minimized. Given the correspondences, an analytical solution that consists of translating, rotating and scaling [243], exists. In the affine case, the solution is usually given by numerical optimization [245]. Recently, an algebraic method based on complex numbers, to solve for the affine registration of planar sets, was presented in [246].

During the last decade, it became possible to estimate non-rigid transformations based on point correspondences. As we saw in the previous section (Sec. ??), 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 [108, 132]. What is more, both the exact and inexact landmark matching problems have been solved for the case of diffeomorphic deformations [247]. This method has been extended to the case where the domain is a sphere [84]. This is of interest as surfaces are often mapped to spheres in order to facilitate their study.

The second subclass opts to estimate 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 [248]. The point sets were transformed into their canonical forms by using 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 and Kehtarnavaz [249] 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 employ robust ways to calculate the distance between the points [250].

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.* [86]. 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 [251] 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 [252].

Gaussian Mixture Models (GMMs) are a common way to model distributions. In [253], each point set was modeled using GMMs and a L_2 distance was used to compare them. In [254], 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.* [255] 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 to tackle the problem of the simultaneous registration of multiple point sets [256]. Jensen-Shannon divergence was used as the similarity metric. The drawback of this approach was that the problem could not be solved in closed-form. Instead, a computationally and memory demanding estimation based on the law of large numbers was required. In a subsequent work, Wang *et al.* [257] alleviated this shortcoming by using the generalized L_2 -divergence that allows for a closed-form solution. Lastly, a GMM was also used in [258] with the difference that the Gaussians were 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 [85, 87, 259, 260].

3.2.2 Methods that infer only the correspondences

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 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 take into account 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 [261].

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

A popular way to introduce structural constraints is by formulating the problem as graph matching. Leordeanu and Hebert [262] proposed a spectral technique to solve the matching problem. Pairwise constraints were used to preserve pairwise geometry. Berg *et al.* [263] 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 [264] to model local spatial coherence. Moreover, the authors showed that it is possible to handle outliers during the optimization. In medical imaging, [265] recently presented 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 [262] was generalized to higher order constraints by Duchenne *et al.* [266]. A tensor power iteration method was employed to solve the matching problem. A similar formulation was also proposed by Zass and Shashua in [267] favoring the use of a different optimization method. Wang *et al.* [268] proposed a higher-order graph matching formulation that incorporates learned structural constraints in a segmentation framework. The inference was performed by a dual decomposition based method [269].

3.2.3 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.

One of the most well known approaches is the Iterative Closest Point (ICP) method [270]. The advantage of this algorithm lies in 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 until convergence.

ICP has drawn a lot of attention and a number of researchers have tried to improve the method over the years ([271] 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.* [272] investigated the use of invariant features in addition to the positional information in order to make the method more robust.

Penney *et al.* [273] 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. [274] 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. [271] improved on the robustness and accuracy of the algorithm for free form deformation shapes by using collinearity and closeness constraints.

One of the most important works in the domain was introduced by Chui *et al.* [275]. The proposed TPS-RPM algorithm iterates between estimating the correspondence with the softassign method and computing the transformation field with a TPS model. [276] further refined the latter approach by iteratively solving a clustering and matching problem. Stewart *et al.* [277] proposed a dual-bootstrap ICP method to register retinal images. The method operated initially on small regions where accurate correspondences could be obtained. Based on these correspondences low order transformations were estimated. In the subsequent steps, the size of the regions as well as the order of the transformation model were refined. The region refinement was 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 [278], 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 were considered. [279] aimed to render spectral methods for matching more robust to noise and outliers. Toward this end, the use of an extension of EM [280] along with a spectral method to compute the correspondence probabilities was investigated. Finally, an EM approach was presented in [281] where correspondences were found between scale-invariant salient region features. Based on the set of all pairs of correspondences, a global transformation was estimated. Then, the set of correspondences was refined by assessing the increase of global aligned-ness.

As previously seen, Procrustes analysis is a useful tool when the correspondences are known [242]. When that is not the case, iterative methods can be used to enhance the performance of the Procrustes method. In [282], the use of the Dual-Step EM algorithm was studied. Rangarajan *et al.* [283], treating the problem from an optimization point of view, proposed the softassign Procrustes method.

3.3 Hybrid Methods

Iconic and geometric registration methods each bear certain advantages while suffering from shortcomings. Hybrid methods try to capitalize on the advantages of each by using complementary information in an effort to get the best of both worlds. Among hybrid methods, the following subclasses may be distinguished based on the way the geometric information is exploited, that is (see also Fig. 2): i) as initialization, ii) as constraint, or iii) in a coupled fashion.

3.3.1 Geometric information as initialization

The first subclass processes 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, resulting in a rough alignment of the two images. Subsequently, iconic registration is performed to refine the result.

Johnson and Christensen initialized their consistent intensity algorithm with the result of a consistent landmark approach in [284]. The landmark and intensity registration were solved independently in an iterative way until a criterion was met. Landmark information was also

used in [285] to provide a coarse registration that was used as the initialization for a multi-scale deformable image registration. In [286], a hybrid algorithm that combined surface and volume information to register cortical structures was proposed. The algorithm was initialized with the result of a volumetric approach [120] and was subsequently refined using a surface warping method. Postelnicu *et al.* [287] on the contrary, started from the geometric registration, propagated the result to the whole volume using a biophysical model of the brain and refined it with a non-linear optical flow registration algorithm. Recently, a similar approach was presented in [288]. Moreover, Auzias *et al.* in [94] tested their diffeomorphic sulcal-based cortical registration (DISCO) in collaboration with an intensity method (DARTEL [34]) in a sequential manner to further improve their results. In [289], 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 were also proposed in the case of abdominal CT [290] and retinal [291] images.

3.3.2 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, recovered during a first step of geometric registration, to constrain the objective function that the iconic registration seeks to optimize. 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 [292]. In a first step, sulci were extracted and modeled as active ribbons. Then, a matching point algorithm was used to establish geometric correspondences, which were subsequently used in a robust function as constraints with local spatial support. In [293], 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 and minimized the normalized mutual information. Normalized mutual information combined with geometric cues was used to tackle brain registration in [294]. 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.* [295]. To register pairs of electrophoresis images, the local correlation coefficient was combined with landmarks, which were detected using a model fitting approach. The mean landmark distance was also incorporated in a multi-modal diffeomorphic demons approach to tackle the problem of diffusion weighted imaging distortion in [296]. Registration between preoperative and intra-operative images has also been attempted with hybrid approaches [297]. Avants *et al.* [93] 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 [298] by using both landmark correspondences and their localization uncertainties. The solution of the registration problem was a compromise between matching the image data, being regular and being close to the landmark-based deformation field. A similar approach was presented in [299]. 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 [300]. The transformation was given as an adaptive combination of intensity- and landmark-fitting. Point information was weighted more in the vicinity of landmarks. The advantage of this method was its ability to incorporate any intensity-based algorithm though it could not 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.* [301] 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 that, 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.

3.3.3 Coupled approach

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

Such a universal energy function for the problem of deformable registration was first proposed by Cachier *et al.* [302]. The coupling of the two problems 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 accomplish brain registration. The problem was solved by iterating between three steps: i) solving for the deformation that minimizes the iconic criterion, ii) solving the geometric problem by establishing correspondences between the closest points of the geometrical structures, iii) and finally opting for a smooth deformation that respects both iconic and geometric constraints.

More recently, a coupled approach formulated as a first-order Markov Random Field was presented in [303]. There, a graph was constructed for each problem and the consistency constraint was imposed by appropriately adding edges to connect the two graphs. This approach has the following advantages: it can encompass any iconic objective function due to the discrete nature of the formulation; it provides diffeomorphic deformation through the use of hard constraints; it takes into account in an adaptive and local way the landmark information; and the problem is solved 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 this work were addressed in subsequent attempts. In [304] for example, the exact L_2 distance was used to couple the geometric and iconic information. The inner product was developed to allow for its modeling by pairwise relations. In [305], learned higher-order relations were used for the graph that models the geometric problem, which alleviated the need for a global linear registration. Moreover, the landmarks were matched by using an optimized similarity metric.

In the same context, the method proposed by Joshi *et al.* [306] should also be mentioned. 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

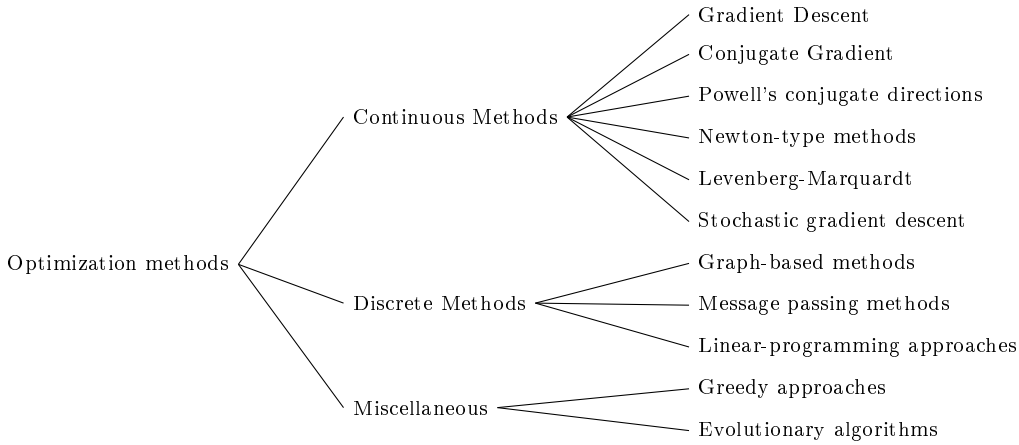


Figure 3: Classification of optimization methods.

could be established by involving the complete sphere domain or both the surface and iconic information at the same time.

4 Optimization Strategies

While most research efforts have 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. Despite the fact that 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 separated into two categories based on the nature of the variables that they try to infer (see Fig. 3): i) *continuous*, and ii) *discrete*. The first class of methods treats real valued variables while in the second class, the variables take values from a discrete set. Both 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 do not bear the previous limitations, though they also do not enjoy theoretical guarantees regarding the optimality of the solution. Next we present some typical exemplars of each class of methods that have found applications in image registration. 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 variables take real values and the objective function is differentiable. In medical image registration, it is often the case that both constraints are satisfied. Moreover, being rather intuitive and easy to implement, continuous optimization methods have been applied to numerous registration problems. Continuous optimization methods estimate the optimal parameters following an update rule of the following form:

$$\boldsymbol{\theta}_{t+1} = \boldsymbol{\theta}_t + \alpha_t \mathbf{g}_t(\boldsymbol{\theta}_t), \quad (9)$$

where $\boldsymbol{\theta}$ denotes the vector of parameters of the transformation, t indexes the number of iteration, α_t is the step size or gain factor, and \mathbf{g} defines the search direction.

There are various ways to define the previous parameters. For example, the step size may be constant, decrease with each iteration or such that it minimizes the objective function along the search direction (exact or inexact line search). The search direction can be specified by exploiting only first-order information or, for example, by also taking into consideration second-order information. It is the choice of these parameters that distinguishes different methods. The approaches most frequently used in medical image registration are (see also Fig. 3): i) Gradient Descent (GD), ii) Conjugate Gradient (CG), iii) Powell's conjugate directions; iv) Newton-type methods, v) Levenberg-Marquardt (LM), and vi) Stochastic gradient descent. A comparison study of some algorithms in the previous categories along with their descriptions was presented in [307].

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 $\mathbf{g} = -\nabla_{\boldsymbol{\theta}}(\boldsymbol{\theta})$. In [307], two variants of gradient descent were tested. The first employed a function of the step size that decayed with each iteration, while the second was based on the inexact line search algorithm of Moré and Thuente [308]. Other line strategies include keeping the step size fixed, monotone line search [309], line search and golden section search [310]. Gradient descent has been used by numerous researchers to solve registration problems. In the LDDMM framework, usually posed in a variational setting, gradient descent is often used to solve the problem [69, 77, 82]. Johnson and Christensen's consistent registration approach [284] as well as Rueckert *et al.*'s FFD registration algorithm [136] were also based on a gradient descent optimization scheme. Without trying to give a full account of all registration methods that employ gradient descent, a task that can be deemed impossible, let us also cite two more variational approaches [172, 259].

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 and propose a search direction that does not follow the new gradient but is conjugate to the previous direction. Thus, the direction now is given as $\mathbf{g}_t = f(\nabla_{\boldsymbol{\theta}}(\boldsymbol{\theta}_t), \mathbf{g}_{t-1})$, where f usually denotes a linear combination $\mathbf{g}_t = \nabla_{\boldsymbol{\theta}}(\boldsymbol{\theta}_t) + \beta_t \mathbf{g}_{t-1}$. 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 [73, 301, 84, 287]. An interesting approach tailored for FFD image registration using a pre-conditioned gradient scheme was presented in [311].

An optimization similar in spirit approach that has been used in an important number of registration problems is Powell's, or the Direction Set method [310]. 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 $\mathbf{g}^i = \mathbf{e}^i$, $i = 1, \dots, N$; 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 until convergence. Despite being less efficient than the previous method, by virtue of being gradient free, Powell's method has been applied in many registration tasks [194, 199, 200, 215, 220].

Another class of optimization methods that has been tested in an important number of registration applications is that of Quasi-Newton (QN) methods [310]. This class of methods, like the two previous two, 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 $\mathbf{g} = -\hat{H}^{-1}(\boldsymbol{\theta})\nabla_{\boldsymbol{\theta}}(\boldsymbol{\theta})$, where the $\hat{\cdot}$ denotes that an approximation is used

(the true Hessian is used in the case of Newton's or the 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 [307]. Other efforts where researchers have experimented with Quasi-Newton methods can be found in [256, 100, 213, 150]

An optimization method of the same family is the Gauss-Newton (GN) algorithm. It is devised to solve optimization problems involving sum of squared function values. This is of particular interest for image registration as this type of objective function is common when aligning images of 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 with $\hat{H} = 2J^T J$ where J denotes the Jacobian. The search direction is now given as $\mathbf{g} = -(J^T(\boldsymbol{\theta})J(\boldsymbol{\theta}))^{-1}\nabla_{\boldsymbol{\theta}}(\boldsymbol{\theta})$. The Gauss-Newton optimizer has been used in [81, 173, 182]. The Gauss-Newton algorithm is the optimizer that is most frequently used in the demons registration framework to tackle mono-modal registration [48, 45, 57, 99, 59]. In the demons registration setting, an extension of Gauss-Newton [47] was employed to derive the symmetric demons forces [49, 52]. 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.* [312] proposed a preconditioning scheme that improves the convergence speed of registration algorithms. The scheme is based on normalizing the length of the point force vectors.

A method related to the previous one 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: $\mathbf{g} = -\left(\hat{H}^{-1}(\boldsymbol{\theta}) + \zeta\mathbf{I}\right)\nabla_{\boldsymbol{\theta}}(\boldsymbol{\theta})$. \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 [34, 137, 151, 152]. Based on the LM algorithm, Thevanez and Unser [313] proposed an efficient optimizer for mutual information driven registration. [137] compared the LM algorithm with GD, GD with a quadratic step size estimation and CG to find that it performs the best for an FFD registration task.

The aforementioned 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 because of the great dimensionality of both the data and the search space. Thus, to alleviate the computational burden, many researchers have experimented with *stochastic* gradient approaches. Their update rule is based on an approximation of the gradient, or $\boldsymbol{\theta}_{t+1} = \boldsymbol{\theta}_t + \alpha_t \hat{\mathbf{g}}_t(\boldsymbol{\theta}_t)$, which is the only difference with respect to the deterministic approaches.

The variants of the stochastic gradient approach differ with respect to how the gradient is approximated. In [307], three approaches were discussed. The first one, referred to as Kiefer-Wolfowitz (KW) [314], approximates the gradient by a finite difference scheme. The second one, known as Simultaneous Perturbation (SP) [315], estimates the gradient by 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 was proposed by Robbins and Monro (RM) [316]. 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. [307] estimated the gradient by using a subset of the image voxels sampled uniformly. The conclusion of [307] is that the RM method performs best.

The RM method was extended in two subsequent works by employing adaptive image-driven strategies. In [317], an adaptive step mechanism was presented while in [318] an edge-driven

importance sampling was proposed to improve the gradient approximation. For some applications of stochastic gradient see [146, 192, 191, 223].

All the previous approaches aim to solve an *unconstrained* optimization problem. As we have seen in Sec. ??, *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, a log-barrier method was used in [173]. Most often, the transformation is achieved by augmenting the dimensionality of the problem using the method of Lagrange multipliers [177, 179].

4.2 Discrete Optimization

The main drawback of the continuous 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 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 than the continuous methods. Furthermore, their modularity permits their use in various settings. One 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. A second limitation regards the complexity of the constraints that can be encoded. Higher-order relations are more difficult to model since they require harder and more computationally demanding inference. 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 are 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 .

$$E_{MRF} = \sum_{p \in \mathcal{V}} \mathcal{U}_p(l_p) + \sum_{pq \in \mathcal{E}} \mathcal{P}_{pq}(l_p, l_q) \quad (10)$$

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

The first attempts to solve this difficult combinatorial problem were based on *heuristic* and *metaheuristic* strategies. In the first case, one may cite Iterated Conditional Modes (ICM) [319] and Highest Confidence First (HCF) [320, 321]. In the second case, a method inspired by

metallurgy, Simulated Annealing [322] should be referenced. These methods suffer from lack of optimality guarantees and slow convergence.

Interest in the field was revitalized during the nineties with the introduction of the graph-cut [323] and belief propagation methods [324]. If we would like to classify the methods according to the techniques they employ, three categories should be designated (see also Fig. 3): i) graph-based methods, ii) message passing methods, and iii) Linear-Programming (LP) approaches.

The first class of methods is based on the max-flow min-cut principle [325] 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 cite the push-relabel [326] and the graph-cut method [323]. Of particular interest due to its application in medical image registration is α -expansion [327]. α -expansion is the extension to the multi-label case of the method presented in [323]. In [323], it was 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. [327] extended the previous technique in the multi-dimensional case by iteratively applying binary graph cuts. The algorithm started from an initial labeling and then checked 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 was 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 energy functions that they can solve [328]. Several variants of these methods, like fusion moves [329] or dynamic graph-cuts [330] were introduced to further improve convergence at the expense of becoming problem specific.

In medical image registration, α -expansion is the optimizer used in [331, 332, 333, 334, 190]. A graph the size of the image was constructed assuming a 6-connectivity scheme and the solution space was sampled densely resulting in a large set of candidate solutions. The size of the graph as well as the large label set resulted in computational times that almost prohibit the use of this method in any reasonable clinical setting. Moreover, the registration setting that was used can not 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 [324], is based on local message exchange between the nodes of the graph and then backtracking to recover 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 to its neighboring node, regarding each solution. 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 an 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 [335, 336] (in this case, normally they are referred to as Loopy Belief Propagation). Their main strength is their ability to cope with non-submodular pairwise interactions.

Possibly 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 [337]. The most interesting of the proposed techniques showed how to decrease the complexity of the message computation by reinterpreting the process as a distance transform calculation. The methods proposed in [337] 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 [338].

Another drawback related to the messages is the large storage requirement when a large set of solutions is involved. Yang *et al.* [339] proposed a constant space $O(1)$ BP method that does not depend on the number of labels. The basic idea of the method was to apply a coarse-to-fine strategy to the solution space. The numbers of labels decreased from coarser to finer levels keeping the overall complexity constant. To decide which labels should be taken into account in every level, all data costs were calculated but only the smallest ones were selected. Heinrich *et al.* [340] applied this technique in a discrete registration setting to recover respiratory motion.

The aforementioned methods are rather generic as they are appropriate for any MRF problem. On the contrary, Shekhovtsov *et al.* [341] 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 modeled the displacement along each axis. Nodes placed at corresponding positions in each layer were connected with an edge that modeled the data matching term. In each layer, nodes were connected with each other following a 4-connectivity scheme. These edges encoded the regularization term. For this model, the operations needed to update the messages were greatly reduced. This model was extended to the $3D$ case in [342]. Similarly to the previous model, the original graph was decomposed into three layers. Intra-layer edges modeled the smoothing term while ternary interactions between the nodes were necessary to model the data cost.

In [343], the $2D$ 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 [344].

More recently, techniques based on Linear Programming, endowed with better theoretical properties, have been proposed to solve discrete optimization problems. Instead of trying to solve the original problem, that is in general NP -hard, these techniques opt for a solution of its LP relaxation. We are going to briefly present two methods that have been used in registration tasks, Fast-PD [345, 346] and TRW-S [347].

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 until 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 to infer the displacements of a grid-based deformation model in [348, 349]. 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. This method was extended to tackle atlas-based registration in [350].

Thereafter, the optimizer has been applied to a number of registration problems. In [144] a

symmetric version of the previous algorithm was presented. The label space was augmented to take into account the transformations of both images to a common domain that is equidistant to the two image domains. In [167] FastPD was used in a deformable registration setting with priors encoded with the use of learned pairwise relations. Ou *et al.* [187] used it to solve feature-based registration while Sotiras *et al.* [351] to solve diffusion tensor registration. In [349, 303] it was used to tackle hybrid registration by utilizing a two-layer graphical model. Each layer modeled a different problem while the edges connecting the two layers imposed the necessary coupling constraints so that the two solutions were consistent with one another.

A decomposed model for group-wise registration of both single- and multi-channel images was presented in [352, 353]. The problem was modeled as a n -layer graph where intra-layer edges encoded a smoothing term and inter-layer edges encoded the data matching term. A similar model was used to tackle group-wise atlas segmentation in [354]. Zikic *et al.* [355] also used a decomposed model to tackle linear registration. Each node of the graph encoded a different parameter of the deformation while edges relating them modeled their interactions.

TRW-S has also been used in a number of registration tasks. For example, it was chosen to optimize the efficient decomposed MRF deformation model in [341]. Moreover, because of its ability to deliver good quality solutions in reasonable computational time for difficult optimization problems, it was used in [303]. Last, Lee *et al.* [356] 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 examined. 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 [357, 344].

4.3 Miscellaneous

The continuous and discrete methods are limited regarding what objective functions and structures they can optimize. *Heuristic* and *metaheuristic* methods, on the contrary, can 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 the locally optimal choice at each step. 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 was applied to tackle the problem of feature-driven image registration where the cost function was based on the comparison of feature vectors and thus was not differentiable. The candidate sets were 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 [120, 184, 186, 185, 286].

Evolutionary algorithms are a strategy that has been used quite often in medical image registration [358], though most of the time limited to linear registration. These algorithms derive from the theory of evolution and natural selection. They start from an initial set of solutions that 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 [307], the covariance matrix adaptation method was investigated [359] 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 [358].

5 Discussion

In this report we have made a modest effort to provide a comprehensive and complete survey of the recent developments in the field of deformable image registration/fusion in biomedical imaging. It seems that the development of a single, universal registration/fusion algorithm for use in different clinical settings is an infeasible objective, at least based on the current state of the art.

Our approach was structured around the three core registration components, i) deformation models, ii) similarity/dis-similarity criteria, and iii) optimization methods. Let us now try to draw some conclusions regarding the current state and the future of deformable registration.

A great number of deformation models have been developed to meet the needs of biomedical imaging. The use of grid-like representations (using regular or irregular grids) and appropriate interpolation strategies seem to be the most prominent direction since they offer a good compromise between complexity and expression power. Such models can be enhanced to account for the local uncertainties of the obtained solutions that are then propagated to the deformation model towards better inference and more precise deformation representation. On top of that, introducing more complex, organ-specific priors depending on the clinical application is also a very promising direction. The current state of the art, with few exceptions, employs simple smoothness priors that could be enhanced by taking into account organ specific allowable deformations. The last element to be taken into consideration is the bias introduced in the deformation model due to erroneous estimation of the linear transformation preceding the dense registration. Such a bias can be significant in, for example, population and drug development studies. We can imagine that methods that are able to jointly address linear and non-linear transformations, at least in an off-line or interpretation setting, could be valuable.

The definition of appropriate similarity metrics seems to be an important bottleneck of the registration methods, particularly when considering the multi-modal case. Due to the different physical properties behind the acquisition protocols, the imaging quality varies and is natural to assume that different metrics could be optimal in different parts of the image. Intelligent combination of metrics across the image domain, to better take into account the nature and quality of the information, could lead to better results. Such a concept could also address the automatic setting of the parameters of the registration objective function. The use of recent advances in machine learning could have a strong impact in deformable registration. This can be viewed from two angles, the first consists of efficient integration of geometric and iconic cues since now the robust automatic extraction of anatomical landmarks through learning becomes feasible. Such landmarks could have a beneficial impact in the case of severe deformations, incomplete data or highly challenging visual discrepancies between modalities. Machine learning can also enable metric learning from data. For example, a massive amount of co-registered data could be fed to learning methods that could directly produce the similarity matrix between the modalities based on the local observed content. This could enable the automatic selection of the optimal image feature space for registration. In the same context, recent advances in signal processing using dictionary representations should not be neglected.

Inference is another area where research should be focused. Most of the existing methods fail in the clinical setting due to sub-optimal solutions and excessive running times. Computational efficiency can be improved using modern computational architectures that take into account the nature of local processing within registration. Multiresolution approaches that combine discrete and continuous optimization methods could be a promising research direction, to address the sub-optimality of the obtained solution due to the non-convexity of the designed objective function. The view of the inference problems from a probabilistic viewpoint is another great perspective in deformable registration. Up to now, few efforts have been made to quantify the quality of the

obtained results and represent the inference outcome as a probability. Such a direction becomes a necessity since it can influence the deformation and the definition of the objective function. Moreover, it is an indispensable component for clinical interpretation since it would give non-expert physicians a confidence measure on the registration result. Last but not least, to certain extent it will help address the presence of local optima in the objective function.

In terms of clinical impact, it seems that image-based guidance and navigation using deformable registration will shape the future. This will most-likely happen with the development of 2D-to-3D registration methods that are able to deal with plane and in-plane deformation, *i.e.* find the appropriate plane in 3D and in the in-plane deformation from a 2D image. Such methods could be used in rather challenging settings, such as low resolution 2D echo to high resolution 3D CT, under the constraint of near real-time performance. Successful development of the above mentioned components will take biomedical imaging to the next level of importance in the clinical chain by opening the surgery room of the future to biomedical imaging as an indispensable tool to guide and optimize on the fly interventions.

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