A Practical Review on Medical Image Registration: from Rigid to Deep Learning based Approaches

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***Abstract*—The large variety of medical image modalities (e.g. Computed Tomography, Magnetic Resonance Imaging, and Positron Emission Tomography) acquired from the same body region of a patient together with recent advances in computer architectures with faster and larger CPUs and GPUs allows a new, exciting, and unexplored world for image registration area. A precise and accurate registration of images makes possible understanding the etiology of diseases, improving surgery planning and execution, detecting otherwise unnoticed health problem signals, and mapping functionalities of the brain. The goal of this paper is to present a review of the state-of-the-art in medical image registration starting from the preprocessing steps, covering the most popular methodologies of the literature and finish with the more recent advances and perspectives from the application of Deep Learning architectures.**

Keywords: Image Registration, Medical Imaging, Deep Learning.

I. Introduction

Medical image registration is an optimization process of applying a variety of geometric transformations over one or more moving images in order to match their spatial pose with the one of a target image, establishing a correspondence among them [1] (see Figure 1). For that purpose, moving and target images must contain some common anatomical structures which are expected to lay at similar location and orientation after the registration process [2]. The series of geometrical transformations may be rigid, preserving the Euclidean distance between structures in moving image or deformable [3] which allows deformations of the moving image domain up to a well-defined extent.

Registration is a crucial procedure for several analytical studies including researches which aim at understanding population tendencies of phenotypes, measuring longitudinal changes (e.g. monitoring the size of tumor tissues), executing guided surgeries, relating individual anatomy with a standard space system (i.e. atlas), among other applications [4] [5]. Due to the wide range of applications around more than 320 papers with some 7,500 citations are published each year regarding medical image registration [6].

There are many challenges faced while registering images and also a lot of different ways to perform it. Medical images are prune to signal corruption by inhomogeneity field effects and high-frequency noise [7]. Also, during image acquisition blur artifacts may be inserted into the image due to body motion and ring artifacts are generated because of imperfect or defect detector elements [8]. Other difficulties arise from specific applications. Some anatomies such as the brain cortex sulci and gyri are composed of structures with very similar shape, leading to misregistration. Finally, multi-modality image registration coming from distinct types of equipment (e.g. Magnetic Resonance Imaging (MRI) and Computed tomography (CT) scanners or combined scanning like Positron Emission Tomography (PET)/MRI), important for several medical health treatments [5], do not have effective methods for comparing tissues with a great variability of intensities [9]–[11].

The goal of this paper is to present a review of the state-of-the-art in medical image registration. It was designed to be a practical guideline for using or implementing high quality rigid or deformable registration of single- or multi-modality images, instructing readers to select the most appropriated software or methods in the literature, depending on the target application. The content was also carefully reviewed to include the most important classical and modern Deep Learning based methodologies.

The remainder of this paper is organized as follows: In Section II we present medical imaging fundamentals, medical data formats, preprocessing steps, and evaluation metrics. Section III follows with classical image registration methods and Section IV contains Deep Learning-based approaches. Section V shows some preprocessing pipelines and registration software. Finally, in Section VI we state the conclusions and future perspectives of the area.

II. Fundamentals, Preprocessing, and Evaluation

Medical image registration applies to a huge variety of applications which is not possible to enumerate in this paper. We may cite for instance myocardial single-modality single photon emission computed tomography (SPECT) image registration in rest and stress conditions for diagnosis purposes [12]. Other application consists of verifying anatomical dysfunction or tumor identification based on multi-modal positron emission tomography (PET) vs MRI registration [13]. During radiotherapy, rigid registration between computed tomography (CT) and cone beam computed tomography (CBCT) is required to irradiate the tumor volume with precision [14]. Finally, in a population study of degenerate diseases of the brain or addiction behavior multiple functional MRI (fMRI) are registered with very flexible deformable methods, mapping all of them over a probabilistic atlas [15]. Therefore, depending on the specific application, there are distinct requirements with respect to image acquisition protocols, pre-processing steps, and registration methods with their parameter.

A. Image Formats

Medical images, in special CT and MRI, are acquired, transmitted and stored according to Digital Imaging and Communications in Medicine (DICOM) standard [16]. DICOM is not just a file format but a series of specifications to enable communication of therapeutic and diagnostic information. Each file may contain distinct information according to the body region, image modality, and desired application. Because of that, it is no sense in writing a simple program for general DICOM file visualization. For each kind of image, for each distinct scanner, DICOM files may contain distinct headers and data organization.

Some image file formats have been proposed to eliminate header and data inhomogeneity concerns. In the beginning, each software developer designed their own format and several of them are still in use. More recently, Neuroimaging Informatics Technology Initiative (NIfTI) 1 and 2 were proposed by a group composed of some of the prominent neuroimaging software developers [17], in special for registration purposes. Even though the format is specific for neuroimaging, it has been used as well for other applications. Several medical image registration software support NIfTI file format such as FMRIB Software Library (FSL) [18], Advanced Normalization Tools (ANTs) [19], FreeSurfer [20], [21], and 3D Slicer [22].

B. Preprocessing

There is no pattern or sequence of operations which should be applied to the input images before image registration. Some of the most commonly used operations are intensity standardization and noise or artifact filtering [24].

1) Intensity Standardization: Image intensity standardization is an important step for population studies [25]. It is a procedure to match the intensity range and distribution of all images using one of them as the reference. One may standardize images based solely on their full intensity range, or standardize by parts using the median intensity and possibly the quartiles as landmarks. It is important to note that intensity standardization is not always applicable prior to a registration procedures. In CT and CBCT for radiotherapy, the intensities indicate the Hassium number or the density of the tissues and should not be modified for registration. Multi-modal image standardization only makes sense in population studies, standardizing images of the same modality among themselves. For images with the same radiation source but distinct features (e.g. 1.5, 3.0, and 7.0 Tesla T1-weighted MRI) and even for images acquired by the same scanner with distinct input parameters, standardization is not recommended, since it may change their intensity distribution [26].

2) Noise and Artifact Filtering: Noise and artifacts present in medical images may have several distinct causes. For instance, metal implants generate artifacts in radiography based images [27]. For MRI images, most of the public available software (e.g.FSL, FreeSurfer, 3D Slicer) offer tools to remove a high-frequency noise and to correct a bias field inhomogeneity effect. The bias field is proportional and the high-frequency noise is inversely proportional to the magnetic field strength which may affect their optimal execution order [28]. In the specific case of MRI brain images, skull-stripping – segmentation of the brain tissues – is commonly used prior to or after inhomogeneity correction [29].

C. Evaluation

Evaluation of medical image registration methods is not trivial. Special care must be taken to design the preprocessing pipeline during experiments. If possible, they should be executed in exact same order and in the same way, unless it would configure a disadvantage to a method. For instance, skull-stripping significantly affects the results of image registration [19].

Of the same importance is to validate experiments with more than just one dataset [6]. Bellow follows three frequently used datasets.

- Internet Brain Segmentation Repository (IBSR): two datasets with 18 and 20 MRI T1-weighted images;
- POPI: Six 4D CT data sets of the lungs.
- TCIA: Collections of medical images of patients with cancer. There are images of several body parts and modalities.

III. Classical Medical Image Registration Approaches

Medical image registration may be divided in three basic components: deformation model, solution criteria, and optimization method [1], [30] (see Figure 2).

A. Deformation Model

The deformation model controls the compromise between a more computationally efficient method and the ability to perform more sophisticated deformations to the image. Some examples are rigid: composed of translations, rotations, and scaling operations; affine which encompasses the rigid and includes shear; linear elasticity model; and fluid model which contains the major number of deformation parameters.

Rigid registration is the fastest registration method. It is appropriated for tasks in which there must be no deformations such as radiotherapy and for quick and global procedures (e.g. bone matching). Deformable registration methods, on the other hand, are necessary for population studies and for soft tissue registration applications with no deformation restrictions [5].

B. Solution Criteria

The solution criteria or objective function dictates how similarity or dissimilarity the target and the registered images are after the deformation. Among the most used criteria is the mutual information since it allows comparison between multi-modality images. For a single-modality registration the Sum of Squared Differences (SSD) and the Sum of Absolute Differences (SAD) are usual choices [31].

The objective function may be classified as a geometric, iconic, or hybrid model. Geometric or feature-based methods

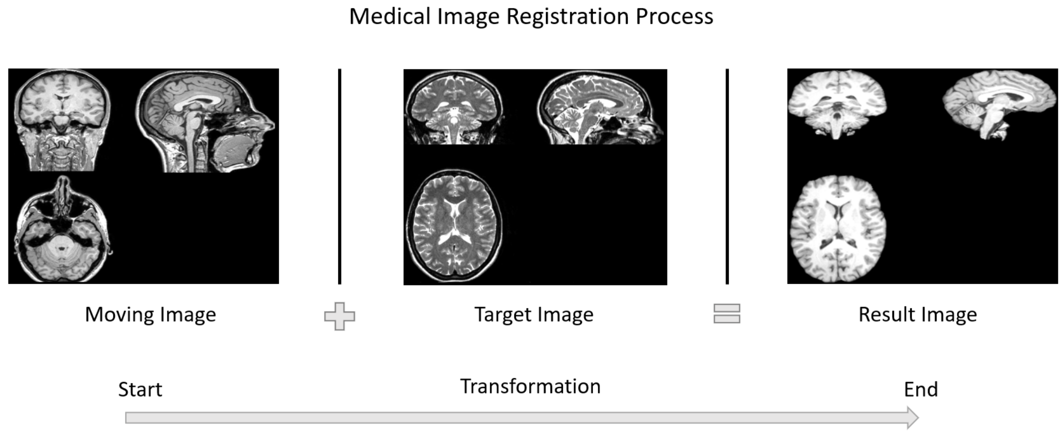

Figure 1: Illustration of registration process. Left: moving image; Middle: target image; Right: registration result. The arrow indicates the registration process direction.

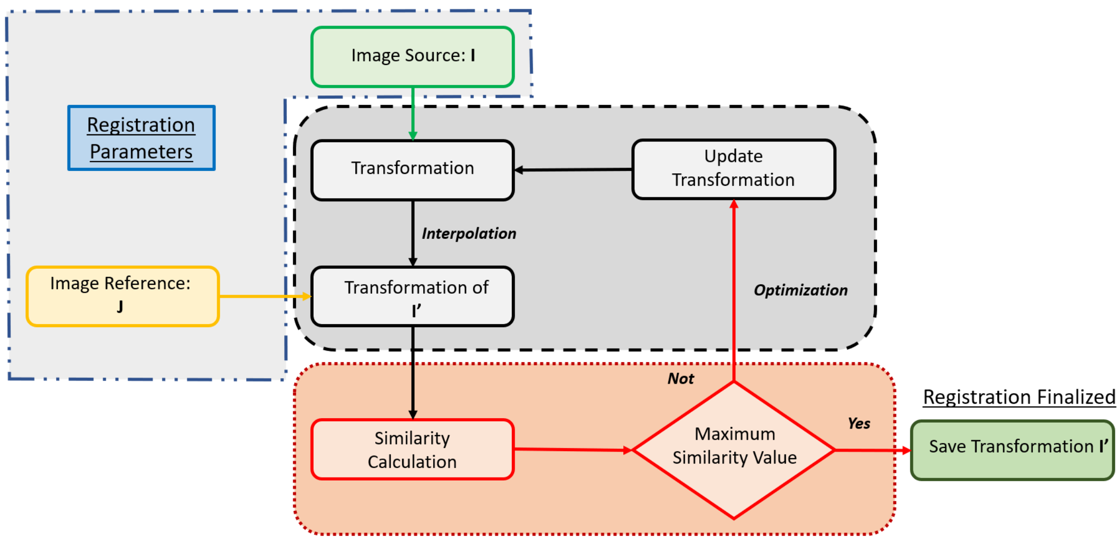

Figure 2: Image registration diagram inspired in Reel et al. [23].

measure the quality of the registration based on the pose of an anatomical or well-behaved landmark set. Iconic or voxel-wise methods qualify the registration utilizing pixel or voxel intensities. Hybrid methods combine both geometric and iconic elements [4], [5].

C. Optimization Method

The optimization method makes use of regularization terms, solution criteria, and strategies (e.g multiresolution) in order to find optimal parameters efficiently. The optimization method may be continuous (e.g. Powell, Levenberg-Marquardt), discrete (e.g. graph-based, message passing) or a mixture of both (e.g. Greed approaches and Evolutionary algorithms). [5], [32]. The performance of each method depends on its computational complexity and convergence rate.

D. Constraints

There are several important features desirable for an accurate registration. These features are achieved by constraints applied to the registration methods. The most desirable feature is the backward transformation which is the inverse of the forward transform. This property is implemented by the so called diffeomorphic registration methods [30]. In that case, both transformations are differentiable [33].

E. Description of Registration Methods

In this section, we describe some of the most important and consolidated registration methods that are publicly available and are free to download and to use. Table I presents information about the following methods: AIR [34], [35], SYN [33], DARTEL [36] , DRAMMS [37], Diffeomorphic DEMONS (DF) [38], [39], Mutual Information DEMONS (MU) [40], DROP [5], FLIRT and FNIRT [18], [32], [41], and S-HAMMER [42].

The Automatic Image Registration (AIR)[1] brought several novel contributions such as the usage of high order polynomi-

[1] AIR: http://air.bmap.ucla.edu/AIR5/index.html

Table I: Registration Methods

Algorithm	Deformation	Similarity	Regularization	Optimization	Applications
AIR (1992)	Third Order Polynomial	RIU, SSD, SLS	Increase of order	Continuos (Newton-Raphson with Muti-Resolution)	Brain MRI, PET
SYN (2008)	Diffeomorphic	CC, JHCT, MI, MSD, NCC, PSE	Gaussian filter	Discrete (Euler Lagrange with Muti-Resolution)	MRI, brain image, thorax CT
DARTEL (2007)	Diffeomorphic	Multinomial model	Linear-elasticity;	Continuous (Levenberg–Marquardt strategy with Muti-Resolution)	Brain
DRAMMS (2009)	Cubic B-splines	CC, SSD	Bending energy	Discrete (Gradient Descent with Muti-Resolution)	Prostate, brain MR, Cardiac
DEMONS DF (2009)	Diffeomorphic	SSD	Gaussian filter	Continuos (Gauss-Newton with Muti-Resolution)	Brain MRI
DEMONS MU (2009)	Non-parametric	MI	Gaussian filter	Continuos (Broyden-Fletcher-Goldfarb-Shanno*)	Brain MRI, CT
DROP (2011)	Free form deformation	SAD, SADG, SSD, NCC, NMI, CR, CCGIP, HD, JRD, MI, JE, GRAD	Pott's regularization	Discrete (FastPD)	Thorax CT; brain MRI
FLIRT (2001)	Linear, Rigid Body	NMI, MI, CR, NCC	-	Continuos (Powell based)	Brain
FNIRT (2007)	Cubic B-splines	SSD	Membrane energy	Continuos (Levenberg-Marquardt minimisation)	Brain MRI
S-HAMMER (2014)	Diffeomorphic	GMI	Bending energy	Miscellaenous	Brain MRI

RIU: Ratio Image Uniformity, SSD: Sum of Squared Differences, SLS: Scaled Least-Squared difference image, CC: Cross-Correlation, JHCT: Jensen-Havrda-Charvat-Tsallis divergence, MI: Mutual Information, MSD: Mean Squared Difference, NCC: Normalized Correlation, PSE: Point-Set Expectation, SAD: Sum of Absolute Differences, SADG: Sum of Absolute Differences plus Sum of Gradient Inner Products, NMI: Normalized Mutual Information, CR: Correlation Ratio, CCGIP: Normalized Correlation Coefficient plus Sum of Gradient Inner Products, HD: Hellinger Distance, JRD: Jensen-Renyi Divergence, JE: Joint Entropy, GRAD: Sum of Gradient Inner Products and GMI: Geometric Moment Invariants.
*Not described in the paper, but present in the software.

als. It is based on pixel intensity and may be applied to 2D and 3D images. The metrics used for implementation are ratio image uniformity (RIU), a Sum of Square Difference (SSD), and Scaled Least-Squared difference (SLS). Registration is performed in multiple resolutions from lowest to highest details using polynomials of increasing degree [34], [35].

Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra (DARTEL)[2] [36] employs small deformations simulating flow velocity fields which are easily invertible and Levenberg–Marquardt strategy is used for optimization.

Both Mutual Information Demons[3] [40] and Diffeomorphic Demons[4] [38] were grounded on the classical Demons paper [43] which models the registration problem as the demon of Maxwell which separated molecules of gases into two chambers. The diffeomorphic version constrained the high-deformation of the original method [38] and the mutual information version allowed multi-modality registration [40].

Symmetric image normalization method (SYN) found in ANTs plataform[5] employs Large Deformation Diffeomorphic Metric Mapping (LDDMM) in two symmetric components. Instead of having a target image, the transformation computation consists in applying the forward and backward transformation to each image until their contents match [33]. An implementation was designed with low computational cost [19].

DRAMMS[6] is a hybrid geometric and iconic objective function based on Gabor attributes. The implemented similarity metric suffers a minor impact from regions in which there is no correspondence [37].

DROP[7] is a deformable registration method with great contribution for discrete numerical optimization area. It also

[2]SPM: https://www.fil.ion.ucl.ac.uk/spm/
[3]DEMONS MU: https://www.mathworks.com/matlabcentral/fileexchange/21451-multimodality-non-rigid-demon-algorithm-image-registration
[4]DEMONS DF: https://med.inria.fr/
[5]ANTs: http://stnava.github.io/ANTs/
[6]DRAMMS: https://www.med.upenn.edu/sbia/dramms.html
[7]DROP: http://www.mrf-registration.net/

uses a hybrid objective function [5].

HAMMER [44] utilizes a feature-based similarity function over an attribute vector of landmarks. The attributes are based on the intensity and the type of tissue. This methodology contrasted with the Demons generating new feature-based techniques. S-Hammer[8] is a diffeomorphic method with a non-uniform selection of hierarchical points [42].

Finally, FLIRT e FNIRT are registration tools of the FSL[9]. FLIRT is a rigid and linear registration method which works on 2D to 3D images. It supports several similarity metrics and implements a very optimized gradient descent method [31], [45]. FNIRT is a deformable register method which uses the free-form deformation (FFD) metric.

IV. Deep Learning Approaches

Many works in different research areas adopted machine learning and recently, deep learning approaches for solving their real problems such as image registration, region segmentation, object detection, and image classification [46], [47].

Deep Learning (DL) is a sub-area of machine learning which aims at finding a representation from a set of unstructured data to solve an specific task. DL allows modeling layered processing units built from simple concepts, each of which dealing with a distinct level of abstraction of a given problem [26], [48].

In the literature, deep learning approaches are used in two different categories (See Table II): (1) Estimation of similarity or dissimilarity metrics; and (2) Prediction of transformation parameters through deep regression to direct the registration process [46]. Additionally, each category makes use of a learning technique (e.g., supervised, semi-supervised and unsupervised), a network architecture (e.g., convolutional networks, stacked autoencoders, restrict Boltzmann machines, and hybrid techniques), and a network optimization function (e.g., Batch Gradient Descent, Stochastic Gradient Descent, and Stochastic Gradient Descent Minibatch).

A. Estimation of Similarity or Dissimilarity Metrics

Several medical image registration publications proposed similarity metric learning approaches [26], [49]. The strategy is to find a well-suited similarity function for a target data distribution by means of a full scalar distance among samples, a ranking function, or a measurement of the proximity/separation of samples [50].

Cheng et al. [49] proposed a multi-modal stacked denoising autoencoder network aiming at pre-training a standard neural network for classification. This approach learns a similarity function through two image patches (multi-modalities). However, it does not perform the medical image registration.

Simonovsky et al. [11] proposed a similar strategy to Cheng et al. [49] but using a Convolutional Neural Network (CNN) to compute similarity costs and to optimize the transformation parameters of the registration task. CNN was trained with patches of multi-modal image sets such as T1-MRI and T2-MRI.

In Grant Haskins et al. [51], a similar method to Simonovsky et al. was applied to distinct image modalities: T1-MRI and transrectal Ultrasound. A novel similarity measurement was specifically designed to deal with enormous differences in image pose and intensity, achieving better results than using mutual information.

Sedghi et al. [52] used IXI brain development dataset [10] composed of jointly acquired T1 and T2-weighted MRI with the data augmentation, to show that it is possible to create a similarity metric for the registration task through the use of a semi-supervised learning with misaligned images. This work uses CNN and exempts perfectly aligned training images (semi-supervised) during the metric learning step.

Wu et al. [26] utilized an extended version from the framework of [53] with a convolutional Stacked Auto-Encoder (SAE) with 8 layers, 4 auto-encoders, and max-pooling at the lowest layer by a factor of 3 to reduce image dimensions and achieve more a relevant feature set. From the lowest to the highest level, each SAE used 512, 512, 256, and 128 hidden nodes, respectively. This metric was also extended to a Multichannel Demons with Deep Feature Representation and to HAMMER with Deep Feature Representation.

B. Prediction of Transformation Parameters

Several works employed DL for predicting image registration transformation parameters.

In Miao et al. [54] several CNNs executed a rigid registration in synthetic images to assess the pose and location of an implanted object. Each CNN was trained in a separated region of the image in a hierarchical way, dividing the registration into subproblems with simpler learning solutions.

In Yang et al. [55], a deep encoder-decoder has been used to predict the deformation model through regression. It focused on a Large Deformation Diffeomorphic Metric Mapping (LDDMM) model. This approach is nonparametric and allows the learning of a voxel-wise metric at the same time as it predicts the transformation parameters from the image patches reducing the computational complexity of the registration process.

For deformable registration, Bob D. de Vos et al. [56] utilized a register structure with a CNN regression to compare input images and generate parameters for a local deformation. Then, a neural network estimated a spatial transformation and performed the resampling process. This approach differs from Yang et al. [55] by executing a single step registration with an only one neural network.

In recent work, Mahapatra et al. [3] proposed a fully end-to-end Deep Learning medical registration based on elastic deformation with generative adversarial networks (GAN) to perform efficiently similarity metric, registration process, and deformation field. According to the author, GANs have the ability to retrieve a greater amount of different types of deformations for multi-modal images.

[8] S-HAMMER: https://www.nitrc.org/projects/hammer_suite

[9] FSL: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/

[10] IXI: Information eXtraction from Images. http://brain-development.org/

Table II: Deep Learning Approaches in Registration Methods

	Algorithm	Neural Network	Type of Learning	Training Set	Optimization	Application	Dimension
Estimation of Similarity or Dissimilarity Metric	Cheng et al. [49]	AE and DNN	Supervised	4000 patches pairs	Gradient-Based	CT, MRI	2D
	Simonovsky et al. [11]	CNN	Supervised	Data augmentation and IXI	SGD	MRI	3D
	Sedgi et al. [52]	CNN	Semi-Supervised	1 million patches	Adam	Brain MRI	3D
	Grand Haskins et al. [51]	CNN	Supervised	670 images pairs	Adam	MR-TRUS	3D
	Wu et al. [26]	CAE	Unsupervised	7000 patches from 40 images	Gradient-Based	MRI	3D
Prediction of Transformation Parameters	Miao et al. [54]	CNN Regressors	Supervised	25000 pairs of synthetic images	SGD	CT	2D/3D
	Yang et al. [55]	CNN Regressors	Unsupervised	140000 patches from 373 images	SGD	Brain MRI	3D
	Bob D. de Vos et al. [56]	CNN using STN	Unsupervised	69540 pairs of images	Adam	Cardiac MRI	2D
	Mahapatra et al. [3]	GAN	Supervised	39000 pairs of images	Adam and Batch Normalization	Cardiac MRI, Retinal Image (FA)	2D
	Eppenhof et al. [57]	VGG based	Supervised	Synthetic, based on 7 pairs of images	SGD	Thoracic CT	3D
	Sheikhjafari et al. [58]	Fully Connected Generative NN	Unsupervised	30000 images from 100 cine MR sequences	Backpropagation using SGD	Cardiac MR	2D

TPS: Thin-Plate Spline; SGD: Stochastic Gradient Descent; Adam: mini-batch stochastic gradient descent; DNN: Deep Neural Network; CNN: Convolutional Neural Network; CAE: Convolutional Stacked Autoencoders; STN: Spacial Transformer Network; Generative Adversarial Networks (GAN); FA: Fluorescein Angiography; TRUS: Transrectal Ultrasound.

Eppenhof et al. [57] showed that it is possible to perform 3D registration with high speed using the CNN approach. In this work, a smaller version of VGG architecture has been adapted to learn transformation parameters between pairs of three-dimensional images for deformable registration task.

Sheikhjafari et al. [58] proposed a deep network model using FCNet (fully connected network) to generate spatial deformation fields in the same resolution of the input fixed and moving images. In this work, an Auto-Encoder (AE) is applied to find the latent vector, i.e., to bring data from a high dimensional input to low dimensional output.

V. Software and Pipelines

The main platforms to perform medical image tasks such as processing, enhancement, segmentation and registration are: FSL [41], SPM[2], FreeSurfer[11] [59], AFNI[12] [60], ANTs [19], ITK[13] [61] e 3D Slicer[14] [22].

[11] FreeSurfer: https://surfer.nmr.mgh.harvard.edu
[12] AFNI: https://afni.nimh.nih.gov/
[13] ITK: https://itk.org/itkindex.html
[14] 3D Slicer: https://www.slicer.org/

The major of those software and medical image registration are implementation in C, C++, Matlab, and Java [62]. There is a Python platform, which joins FSL, SPM, and FreeSurfer under a single pipeline called Nipype [15] [63]. Neural network libraries are predominantly implemented and used in Python language. Some of the main libraries for Deep Learning are TensorFlow [16] [64], Theano [17] [65], Caffe [18] [66].

Due to a large number of libraries and possible applications, DL based medical imaging platforms were created for applications such as NiftyNet [19] [67] and DLTK[20] [68]. These platforms have some tools, but they do not have any specific network or tutorials for medical image registration. They integrate different languages and methods providing a fairer environment for comparing and developing applications in a standardized way.

[15] Nipype: https://nipype.readthedocs.io
[16] TensorFlow: https://www.tensorflow.org/
[17] Theano: http://deeplearning.net/software/theano/
[18] Caffe: http://caffe.berkeleyvision.org/
[19] NiftyNet: https://niftynet.readthedocs.io
[20] DLTK: https://dltk.github.io/

VI. Conclusion and Future Prospects

The goal of this survey consists in presenting a practical review of the state-of-the-art in medical image registration showing preprocessing algorithms and a variety of registration methods from rigid to Deep Learning-based approached.

Based on the survey we point out the following future research trends:

- Solutions based on hybrid similarity metrics using machine learning techniques (see [69]);
- Creation and free availability of large datasets with correctly segmented and evaluated images in order to support future solutions;
- Proposal of new protocols for image registration validation and quantitative evaluation. Another possibility is to optimize deformation parameters instead of using a similarity metric [58];
- Creation of new approaches based on Deep Learning to improve the quality of the registration itself. So far, current advances are more related to the increase of the speed and robustness of the methods;
- Development of novel proposals based on meta-registration procedure, in which different registration techniques work in a collaborative and complementary way to improve results;
- Generation of image-label or multi-scale-patch network registration methods to estimate larger deformations;
- Implementation of CNN ensembles to learn regression parameters for each released methodology.

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