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REVIEW

Current trends in medical image registration and fusion

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Abstract Recently, medical image registration and fusion processes are considered as a valuable assistant for the medical experts. The role of these processes arises from their ability to help the experts in the diagnosis, following up the diseases' evolution, and deciding the necessary therapies regarding the patient's condition. Therefore, the aim of this paper is to focus on medical image registration as well as medical image fusion. In addition, the paper presents a description of the common diagnostic images along with the main characteristics of each of them. The paper also illustrates most well-known toolkits that have been developed to help the working with the registration and fusion processes. Finally, the paper presents the current challenges associated with working with medical image registration and fusion through illustrating the recent diseases/disorders that were addressed through such an analyzing process.

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1. Introduction

The ultimate goal accompanied by image analysis is to extract useful underlying information contained in the processed images. Therefore, numerous processes can take place such as image registration and image fusion. The intent of image registration is to align images with respect to each other. The input for this process is two images: the original image is known as the reference image while the image that will be aligned with the reference image is known as the sensed image.

The result for this step can help in further analysis processes including image fusion. Image fusion is in turn the process of producing more informative and better descriptive images based on the input ones. Practically, image fusions, as well as image registration, are perceived as an important assistant that produces a valuable help in many application areas. Medical images in biomedical engineering, weather forecasting in remote sensing and geographical information systems (GIS) in machine vision domains are some examples of these application areas [1].

Nowadays, acquiring high resolution and more informative description of humans' anatomies and functions becomes possible due to the rapid advances in medical imaging technology. Such development encourages the research in the medical image analysis field. Furthermore, the growing importance of medical images in clinical applications provided a direct impact on this research field [2]. In the last two decades, the number of the published scientific papers in medical image fusion has frequently been increased. The increment in this context is mainly influenced by the extended utilization of medical diagnostic devices, growing trust in medical diagnostics based technologies, and rapid development of low-cost computing and imaging technologies. Moreover, the usability, as well as the simplification of these technologies, leads them to be friendlier for medical personnel [3].

The aim of this review is to focus on medical image registration and fusion procedures due to their significance in the medical field. Therefore, the paper is organized as follows. In the beginning, Section 2 describes the common image fusion procedure including the registration process as an essential step when performing the fusion process. Sections 3 and 4 focus on medical imaging registration as well as fusion processes and present the classes of methods under each of these processes. In Section 5, the common medical imaging modalities along with the main characteristics, advantages, and disadvantages associated with each of these modalities are presented. Section 6 illustrates some of the well-known toolkits that were developed to assist the developers as well as the researchers of medical image registration and/or fusion fields. Section 7 presents current medical image registration and fusion work. It is grouped based on body organs related diseases/disorders to show the impact of such medical analysis processes in diverse medical areas. Section 8 discusses the current medical image registration and fusion challenges that in turn represent research areas for the researchers who are interested in these research fields. Finally, Section 9 concludes the paper with a summary of the main ideas that were introduced in this review.

2. The general image fusion procedure

As mentioned previously, the aim of image fusion procedure is to construct a more detailed and representative output image. In general, image fusion procedure consists of some steps that help in achieving such goal. Fig. 1 shows the main steps involved in image fusion procedure [4]. For medical image fusion, there are some considerations when such steps are implemented. The aim of this section is to illustrate the main steps of image fusion procedure in general. The following sections are then focusing on the registration as well as fusion steps along with the considerations of applying such steps in the medical field.

2.1. Image registration

The first step in image fusion procedure is to register the input images. Image registration is defined as the process of mapping the input images with the help of reference image. The goal of such mapping is to match the corresponding images based on certain features to assist in the image fusion process.

In general, the registration framework is considered as an optimization problem whose aim is to maximize the similarity or minimize the cost. On other words, in the registration process, a parametric transformation $T_g(.)$ is applied on the input (target) images I_t in order to maximize their similarity with the reference image I_r. It is important to note that the targeted similarity depends on the defined similarity (cost) function, $P(.)$. The optimization target can be represented as in Eq. (1) [5]:

$$T_g(.) = \arg\max_{T_g(.)} \rho(I_r, T_g(I_t)) \tag{1}$$

In Fig. 2 [5], an example of the registration process is presented through registering Computerized Tomography (CT) kidney images that in turn represent a type of radiology medical modalities as described in Section 5. To register the input images, they have to pass through some substages that are illustrated in Fig. 3.

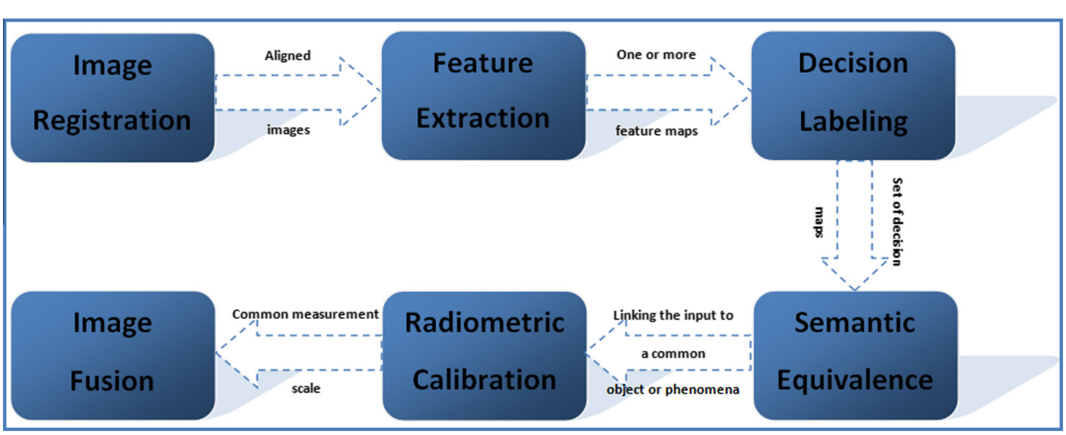


Fig. 1 The main steps of image fusion procedure.

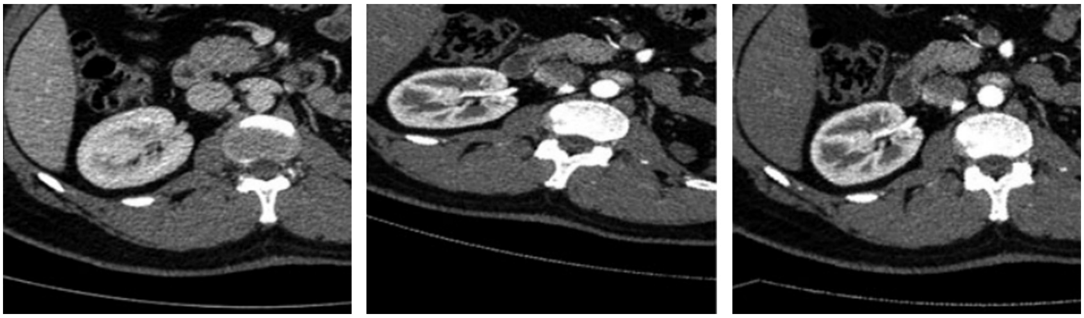


Fig. 2 Example of image registration: from left to right – the reference, target, and the registered CT kidney images.

Fig. 3 The image registration steps.

Similarity/Dissimilarity Measure is the first step where the input images are compared with respect to each other to measure the similarity between them. The effective measurement must resist the noise and background changes. It provides efficient computation results as well as efficiently dealing with semantic images meanings [6].

Then, point detectors are applied to describe the control/key points that carry critical information about the scene structure [7,8]. The detected points should be independent of any alteration including noise, blurring, contrast, and geometric changes.

After detecting the control points, the next step is to obtain these points that represent the critical information in the processed images. Extracting these points can be accomplished either manually or automatically [9]. The extracted points could be simple points, such as the statistical points including mean and variance. In addition, it could be sophisticated, such as texture points [10]. Regardless the type of the extracted points, they must guarantee some characteristics. These characteristics are a distinction to the spatial neighbors, invariance to the original image variations, robustness against noise, computational efficiency, and comparability to facilitate the detection of corresponding points in other images [11].

Image Descriptors are then used to represent the extracted critical points to help in estimating the similarity between the images. Therefore, all critical information as well as any other content information, should also be included in the image description. The aim is to facilitate the accessibility of the visual queries in addition to the content of the image [12].

Decreasing the number of the extracted points for further recognition or matching procedures is the aim of the points selection step. The selected points must have two characteristics [7]. First, they must be independent of each other to avoid redundant information. Second, they must provide complete information about the recognized objects to ensure least ambiguous in distinguishing between different objects.

Then, point pattern matching methods are applied that aim to establish a correspondence between the control points of the images. The purpose is to determine the correct and incorrect correspondences. Some control points can be outliers where others can be slightly displaced from their true positions due to noise or other factors [7].

In the following step, robust parameter estimation and transformation functions are applied. The aim of such functions is to use the determined correspondences of the control points for estimating the transformation functions' parameters used in the image registration. Many estimators can be used to perform the required parameters, such as ordinary least-squares (OLS) estimator, weighted least-squares (WLS) estimator, scale (S) estimator, and many others [7].

After defining the coordinates of the corresponding control points, the transformation function estimates the geometric relation between the images. The transformation functions can be classified based on the geometry of the images that are needed to be registered, although, it is hard to find a single transformation function that is better for all types of images due to the strengths and weaknesses associated with each function. There are a lot of desirable properties in the transformation function like [7]:

- Monotonicity: ensures that the transformation function does not produce high fluctuations and overshoots away from the control points.
- Adaptive to the density and point's organization: deal with the fact that the control points are rarely uniformly spaced.

A detailed description of the transformation categories is presented next in the medical registration section. In image resampling step, the reference image is scanned and for each point in this image, the corresponding point in the sensed image is determined. Diverse methods have been evolved to estimate the required coordinates. In general, the speed and the accuracy are the main key factors to evaluate the performance of these methods [7]. Finally, image composition step combines the registered images into a larger image called a composite or a mosaic image. The overlapping area of the registered images may have different coordinate's intensities due to the environmental and sensor parameters during the acquisition process [7].

2.2. Feature extraction

In this step, the characteristic features of the registered images are extracting and producing one or more feature maps for each of the input images [4].

2.3. Decision labeling

Based on a given criteria, a set of decision maps are produced through applying decision operator that aims to label the registered images' pixels or the feature maps [4].

2.4. Semantic equivalence

In some cases, the obtained feature/decision maps might not refer to the same object/phenomena. In these cases, semantic equivalence is applied to link these maps to common object/phenomena to facilitate the fusing procedure [13]. It is important to note that such procedure is unnecessary for the inputs obtained from the same type of sensors.

2.5. Radiometric calibration

In this step, the spatially aligned input images and feature maps are transformed to a common scale to result in a common representation format to act as an input to the upcoming fusion step [13].

2.6. Image fusion

The final step is to combine the resulting images into a single output image containing a better description of the scene than any of the inputs images. The ultimate benefit of image fusion is the quality of the information contained in the output image. Other benefits involve [4]: extending the range of operations, extending spatial and temporal coverage, reducing uncertainty, increasing reliability, achieving robust system performance, and representing the information more compactly.

3. Medical image registration

As previously mentioned, the ultimate goal of the registration process is to align the corresponding features in some sensed images with respect to a reference. Such a process is essential to achieving the fusion process. Its importance is due to merging/fusing the images that is primarily performed based on the corresponding features of these images. Throughout the time, various methods were presented to perform image alignment registration task. These methods can be classified depending on the number of criteria as illustrated in Fig. 4 [15]. The

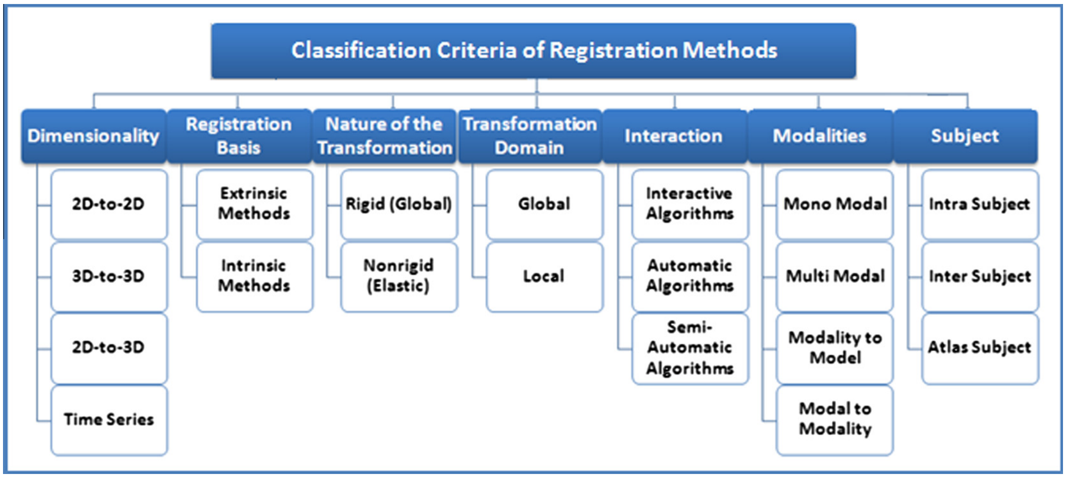


Fig. 4 The classification criteria of the registration methods.

aim of this section is to present a description of these registration classes in much more detail.

3.1. Dimensionality

The dimensionality criterion is classified into spatial as well as time-series dimensions. For spatial dimensions, image dimensionality refers to the number of geometrical dimensions of the image space. In medical applications, these dimensions are typically three-dimensions but sometimes they can also be of two-dimensions [14]. In the registration process, computing the required transformation can be done by either the images' coordinate systems or the physical space and the input image [15]. In other words, the registration might be accomplished based on a set of corresponding point pairs or a set of corresponding surface pairs [14–16].

I. 2D-to-2D:
If the image acquisition tightly controls the images' geometry, the images can simply be registered via a rotation and two orthogonal translations. In addition, differences in scaling from the real object to each of the images may need to be corrected. In practice, controlling the geometry of the image acquisition is usually a very difficult task.

II. 3D-to-3D:
Here, the registration process is based on assuming that the internal anatomy of the patient is not distorted or changed in spatial relationships between organs. In general, 3D-to-3D registration is used to align tomography datasets, or a single tomography image to any spatially defined information. It is important to note that determining the scale of the scanned images requires careful calibration of each scanning device.

III. 2D-to-3D:
The registration process takes place when it is required to establish the concurrence between 3D volumes and projection images such as X-ray or optical images. Furthermore, they are needed when the position of one or more slices from tracked B-mode ultrasound, interventional CT, or interventional MR images is to be constructed regarding 3D volume. It is important to note that with respect to 3D-to-3D registration, 2D-to-2D registration is considered to be less in complexity, easier in the implementation, and faster. Moreover, accurate registration of multiple 3D volumes of MR and CT images is considered the most common and fully developed method. In addition, 3D-to-3D registration produces accurate registration results with tomography datasets or when single tomography image is registered to any spatial information source. Finally, the computational complexity and the speed of applying 2D-to-3D registration in offline situations away from the operations and radiotherapy are not considered as an issue.

IV. Time series:
Registration based on time series deals with aligning medical images of the same or different modalities over different time instances. It helps in monitoring disease progress and assessing treatment response. Consequently, this can provide an opportunity to increase the precision as well as the treatments' accuracy. In other words, registering images that are acquired during different time intervals assists in various studies including tissue perfusion, blood flow and metabolic or physiological processes and other dynamic processes. For instance, applying this type of registration during the radiotherapy helps in quantifying particular physiological motion in addition to estimating treatment response of the patient under the therapy.

3.2. Registration basis

The methods under this group are classified based on the nature of the registration basis into Extrinsic and Intrinsic methods [16].

(a) Extrinsic registration methods: Here, clearly visible artificial objects are attached to the patient with the necessity to be accurately detectable in all the acquired modalities. Examples of the commonly used attached external objects in the medical imaging are [13]:
- Stereotactic frame reinforces strictly to the patient's outer skull table.
- Markers of Screw-mounting.
- Markers stuck on the patient skin.

Computation efficiency and automation simplicity are the main features of these registration methods. Moreover, these methods do not require complex optimization algorithms because of the easily computed transformation parameters [16].

Extrinsic methods do not include image information about the patient. In addition, the registration transformation nature is in many times limited to rigid ones (only translations and rotations are applied). On the other hand, applying these methods to images with low (spatial) information content requires additional spatial information. Due to the rigid transformation limitations and various practical considerations, these types of methods are highly restricted to brain and orthopedic imaging [16].

(b) Intrinsic registration methods: The methods of this class are based on information provided by the patient, such as apparent prominent landmarks, binary divided structures or voxel image intensities [16].

I. Landmarks based registration methods

Here, any identifiable and prominent elements such as the surfaces, curves, and point landmarks [17] in one image, are matched with their corresponding elements in the other image. It helps in defining the transformation that occurs on the images [16]. Subsequently, when pairs of point landmarks are explicitly corresponded, an interpolation is applied to infer the correspondences of the remaining image volume along with the matched landmarks [18].

The used landmarks can be identified geometrically or anatomically through analyzing how the voxel intensity changes throughout the image. Also, the landmarks can be defined manually. In the manual identification of the landmarks, it is important to incorporate the locations' accuracy measures in the registration process [15].

The benefits of such registration bases are that these elements ensure the biological validity of the mapping. It allows the transformation interpretation based on the underlying anatomy or physiology [15].

II. Segmentation based registration methods

In these methods, rigid or deformable models are the basis for the registration process. In rigid models, the surfaces are extracted from the both images, source and target images, which are used as an input to the registration process. In contrast, in the deformable models, the surfaces or curves are extracted from one image to be used in fitting the other image through elastically deforming them [16].

It is important to know that rigidly based methods are simpler than the deformable based ones. The complexity of deformable methods resulted from the existence of some regularization terms in the cost function. Hence, the rigidly based methods were the most popular methods in clinical applications for a long time. In addition, since performing the segmentation process is quite easy and the computational complexity is relatively low, the method is popular. Consequently, many follow-up papers present an automatic segmentation step to enhance the optimization performance or to extend the method [16].

III. Voxel property based registration methods

In these methods, the intensity patterns in each image are matched using mathematical or statistical criteria. These methods are based on the assumption that the images at the correct registration will be the most similar. Based on this assumption, the intensity similarity of the input images is measured to guide transformation adjustment until finally reaching the maximum similarity. Common voxel-based similarity measures are Mean Squared Difference (MSD), Normalized Correlation (NC), Mutual Information (MI), and Normalized Mutual Information (NMI). The Sum of Squared Gray value differences (SSD) can be utilized between the input images in the mono-modal registration when they have the same gray level structure. When the same gray level structure not exists but a linear dependency among the gray level is at least supposed, Cross Correlation (CC) can be applied.

In the multimodal registration, entropy-based measures as MI have to be used since the linear dependency is not given. MI and NMI are the most commonly used similarity measures due to the advantage of producing satisfactory accurate, robust, and reliable results. However, the MI-based methods are considered to have a high sensitivity to the implementation decisions. Particularly, the probability distributions' estimation and the interpreter selection highly impact the accuracy as well as the robustness of the registration process. It is important to note that the intensity-based similarity measures take place among the corresponding pixels without regarding the spatial pixels' dependency due to assuming spatial stationary intensity relationship. It leads to the measures' failure against the distortion corruption of spatially varying intensity when two images need to be registered [15].

IV. Hybrid based registration methods

These methods combine geometric, and intensity features with the aim of producing more robust methods that establish more accurate correspondences in difficult registration issues.

3.3. Nature of the transformation

All the mapping methods belong to one of the basic two categories: rigid (global) and non-rigid (elastic/local) transformations. In the rigid transformation methods, the entire 2D or 3D images are transformed e.g. translating, rotating, scaling and/or sharing every depicted object in the same way that in turn preserves distances, lines and angles [5,19]. Mathematically, these transformations can be represented as in Eq. (2) with up to four parameters w_{ij} [19]. Fig. 5 presents the practical cases of each of these global transformations with T_g.

$$\begin{pmatrix} x' \\ y' \\ 1 \end{pmatrix} = \begin{pmatrix} w_{11} & w_{12} & 0 \\ w_{21} & w_{22} & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} x \\ y \\ 1 \end{pmatrix} \tag{2}$$

Additionally, rigid methods include affine transformation, similarity transformation, and perspective projections [5]. Fig. 6 illustrates an example of such registration methods. An affine transformation can be defined as an independent translation, rotation, scaling, and sharing. It preserves the parallelization and intersection properties of the lines but not the angle nor the length of these lines [5,19]. Eqs. (3) and (4)

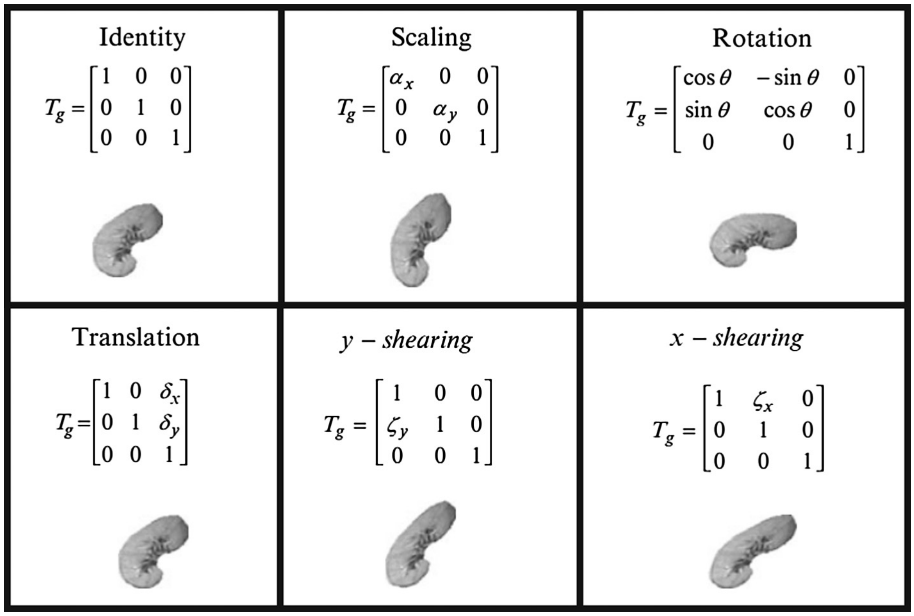


Fig. 5 Common Rigid transformation methods with coordinate-wise translation steps: δ_x and δ_y, rotation angle: θ, scaling factors: α_x and α_y and shearing factors: ζ_x and ζ_y [5].

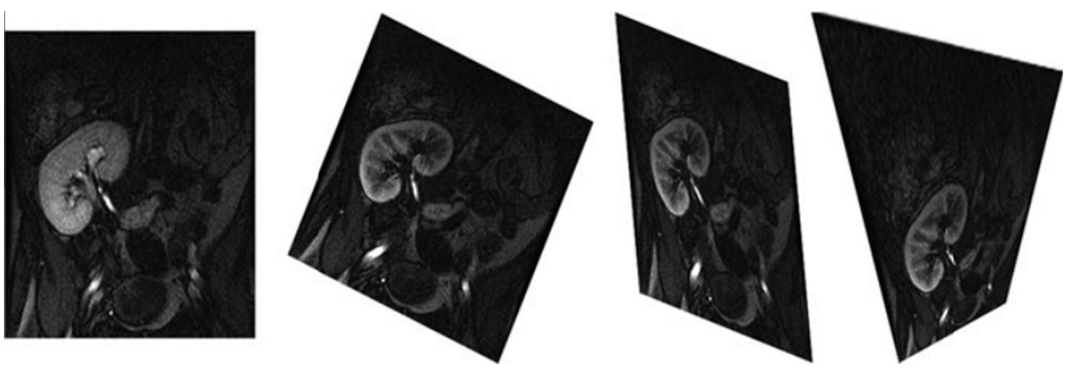


Fig. 6 Types of Rigid transformations: from left to right – the reference image and similarity, affine, and projective transformations of the target image [5].

represent the affine transformation in 2D and 3D respectively [5]. The similarity transformation is special case of affine transformation that preserves the angle but not the lengths between the lines nor the position of the points due to applying only translation, rotation, and uniform scaling $\alpha_x = \alpha_y$. Finally, perspective projection is the type of transformation that does not preserve the lines properties when mapping lines to lines. Further details regarding these methods can be found in [5].

$$\begin{pmatrix} x' \\ y' \\ 1 \end{pmatrix} = \begin{pmatrix} w_{11} & w_{12} & w_{13} \\ w_{21} & w_{22} & w_{23} \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} x \\ y \\ 1 \end{pmatrix}$$
$$\equiv \begin{pmatrix} 1 & 0 & \delta_x \\ 0 & 1 & \delta_y \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} \alpha_x & 0 & 0 \\ 0 & \alpha_y & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} \cos\theta & -\sin\theta & 0 \\ \sin\theta & \cos\theta & 0 \\ 0 & 0 & 1 \end{pmatrix}$$
$$\times \begin{pmatrix} 1 & 0 & 0 \\ \zeta_y & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} 1 & \zeta_x & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} x \\ y \\ 1 \end{pmatrix} \tag{3}$$

$$\begin{pmatrix} x' \\ y' \\ z' \\ 1 \end{pmatrix} = \begin{pmatrix} w_{11} & w_{12} & w_{13} & w_{14} \\ w_{21} & w_{22} & w_{23} & w_{24} \\ w_{31} & w_{32} & w_{33} & w_{34} \\ 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} x \\ y \\ z \\ 1 \end{pmatrix} \tag{4}$$

In medical image registration, the examples of rigid transformation type include bone or brain registration when the skull or dura has not been opened. In addition, it can be applied approximately to align the images that contain small changes in the object shape. The rigid methods are popular in medical image registrations due to the rigid body constraints in many medical images that lead to a good approximation. Furthermore, this class of methods includes few parameters to be determined, and finally many registration techniques are not prepared to apply more complex transformations [15].

Although rigid methods are useful for the registration in the presence of rigid bodies, various body organs have spatially variant geometric differences that in turn require more flexible methods to accomplish the registration task. The elastic methods are the methods that provide such flexibility through registering the input images by spatially variant local warping [5]. Fig. 7 presents an example of the elastic (local) deformation. The figure shows how this class of methods is more flexible than the rigid (global) ones but at the same time it shows the complexity of such methods. Producing such flexible image transformations can be finished through applying Radial Basis Functions (RBF), continuum methods of physical modeling or large deformation based models. Further description of the above methods is provided through Khalifa et al. [5].

Nowadays, most of the registration works comprise the proposition of non-rigid registration techniques in many applications ranging from modeling, tissue deformations to anatomical structures' variability. It is important to note that dealing with non-rigid registration is still considered as an open research area. The reason for this is due to the need of the smoothness and the high degree of freedom in the deformation process. A broad range of algorithms have been emerged to perform nonlinear medical image registration. Nevertheless, further researches are needed to focus on how to improve the precision, increase the speed and examine the results obtained from the registration process [15].

3.4. Transformation domain

The images' coordinate transformation can be either global or local. In the global case, the transformation is performed with mapping parameters valid for the entire image. In the local case, a small part of the image is transformed where the local mapping function parameters are exclusively valid for a small patch around the position of the selected control point [15].

3.5. Interaction

There are three levels of interaction exists in image registration methods based on the relation between the user and the registration process. Interactive algorithms are ones where the user uses certain software to accomplish the registration task through feeding it with the initial transformation parameters estimation. In contrast, automatic algorithms are the algorithms that are working without any interaction at all. Finally, in semi-automatic algorithms the user performs the algorithm initialization through segmenting the data or steering the algorithm to the desired solution [15].

Recently, there is a trade-off between achieving minimum interaction and speed, accuracy, and robustness. The interaction of the users in some methods will narrow the search space, refuse the mismatch and accelerate the optimization process. On the opposite direction and due to the absence of quantification or control of the interaction level, further human interaction will complicate the validation process [15].

In the extrinsic methods, since the markers are characterized by the visibility and easy detection, these methods often fall under the automatic types. Despite that, the user still can provide seed point or determine the initial location. Methods based on voxel or geometrical landmark are treated as automatic methods, while the intrinsically based anatomical landmark and the methods based on segmentation are considered semi-automatic since the user has to initialize the process [15].

3.6. Modalities

There are four types of registration tasks based on the different types of modalities applied to the registration. In mono-modal tasks, the registration process takes place between the images of the same medical modality, while in multi-modal tasks, the images involved in the registration process belong to different modalities [20]. There are also modality-to-model and model-to-modality registration tasks. In these types, only one image is included while a model or even the patient represents the other registration input. The model-to-modality task is frequently applied in intraoperative registration techniques [21] while modality to the model task can aid in tissue morphology through gathering statistics [22].

Mono-modal and multimodal tasks are the most famous types compared with the other types. Mono-modal tasks assist in applications that deal with monitoring growth, verifying intervention, comparing rest-stress, subtraction imaging, and much more applications [23,24], while multi-modal tasks assist in an enormous number of applications that in general fall under the concept of diagnosis. Anatomical–anatomical and functional anatomical registrations represent the major categories where the multimodal task can take place. The difference between these categories is that the anatomical–anatomical

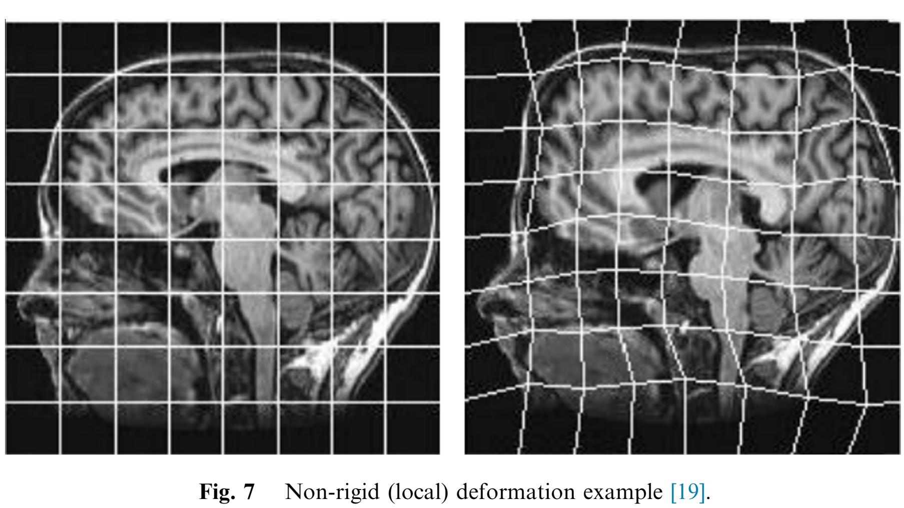


Fig. 7 Non-rigid (local) deformation example [19].

registration aimed to combine images that showed different sides of tissue morphology, while functional–anatomical registration aimed to relate together the tissue metabolism along with its associated spatial location with respect to the anatomical structures.

In addition, multimodal registration tasks provide an important role in medical applications along with the image fusion that will be described in much more detail in the preceding sections of this review. These applications include reconstruction of the 3D images, object recognition, and medical image analysis. Although multimodal registration task is difficult since the images obtained from different modalities can have extreme intensity mapping dissimilarity, this type of registration produces images that show physiological and anatomical information. In turn, this can assist in the clinical diagnosis and therapy [25–27].

3.7. Subject

The subject provides another criterion for dividing image registration methods. It refers to the patient whose images are to be registered. Therefore, the registration methods might be grouped into intra, inter and, atlas subject registration. Such division is based on whether the involved images belong to the same patient, to different patients, or one of the images belongs to the patient and the other obtained from an information database [15].

(a) Intra subject based registration methods: They help in achieving considerable clinical benefits through accurate alignment of the images gathered from the same subject using the same modality at a different time. They can simplify the detection of any intensity or shape changes of the structure [16]. Methods of this class are most frequently used in the diagnosis, surgery, and intervention procedures [16]. They are mostly used in the alignment of serial MRIs of the brain [28].
(b) Inter-subject based registration methods: Here, the images involved in the registration process belong to different patients. Accordingly, this type of registration is usually used in determining the shape and size changes in addition to the grosser topology changes [16].
(c) Atlas based registration methods: in these methods, one of the input images is gathered from a single patient while the other is constructed through a database of image information acquired via many subjects imaging. Consequently, this class of registration shows help in obtaining statistics about the size and the shape of a particular structure. Accordingly, these statistics assist in finding anomalous structures that can then help in transferring the segmentations from one image to another [29].

4. Medical image fusion

As described in Section 2, image fusion is the process that aims to produce a more representative image through merging the input images with each other. Various methods were proposed to perform the required fusion goal. Fig. 8 illustrates major classes of such methods while the upcoming subsections present a brief overview of each one.

4.1. Pixel fusion methods

In these methods, simple pixel-by-pixel operations are used to perform the fusion task. These operations include simple arithmetic operators, such as addition, subtraction, division and

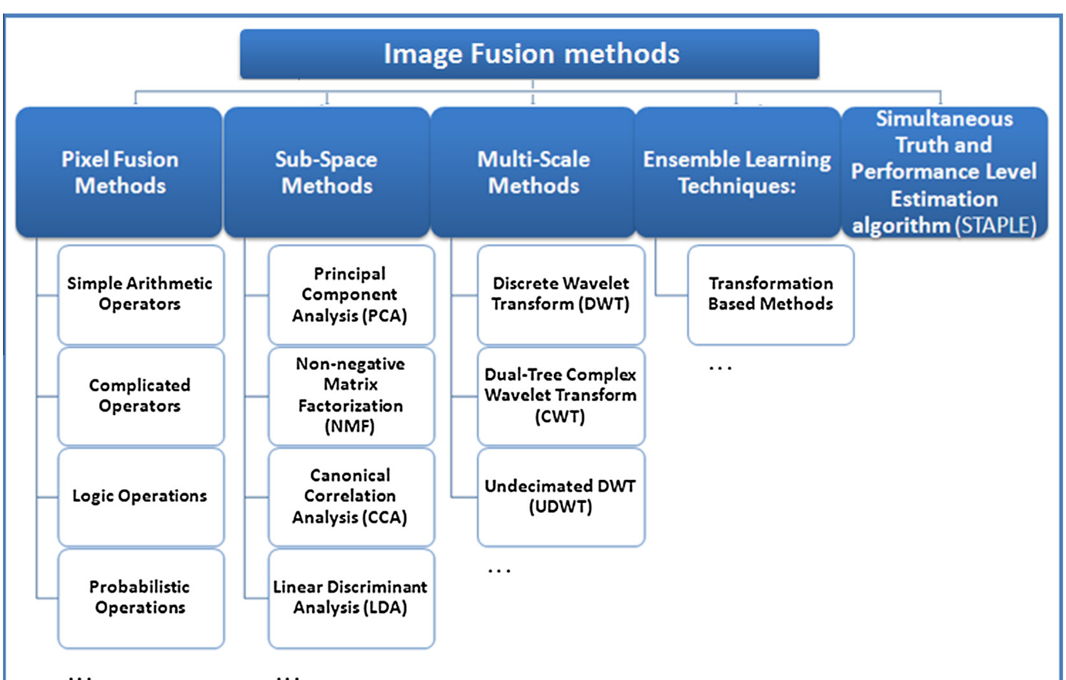


Fig. 8 The classes of image fusion methods.

multiplication as well as a minimum, maximum, median, and rank [4]. In addition, it includes sophisticated operators, such as the Markov Random Field (MRF) considered as a probabilistic model in which the local conditional probabilities are used to define such model. Li [30] introduced a detailed mathematical description of applying MRF in image analysis.

Although this class of fusion methods is simple, it often faces certain limitations including contrast reduction of the image. Despite their limitations, these methods provide good results in some cases, such as whenever the input images have an overall high brightness and contrast [31].

4.2. Subspace methods

These methods are a collection of statistical techniques that remove the correlation between the input images. On other words, a high-dimensional input image is projected onto a lower dimensional space or subspace for the following reasons [4]:

- Visualization: the reduction of the images' dimensions helps in understanding the intrinsic structure of the input data.
- Generalization: projecting the images in the lower dimensions allows for better generalization.
- Computation: dealing with images in lower-dimensional spaces is faster and requires less memory than dealing with them in higher-dimensional spaces.
- Model: representing the data in the lower dimensions can be used as a model in its right.

Principal component analysis (PCA), independent component analysis (ICA), non-negative matrix factorization (NMF), canonical correlation analysis (CCA), and linear discriminant analysis (LDA) are examples of the well-known subspace methods [4].

4.3. Multi-scale methods

Multi-scale also known as Multi-Resolution Analysis (MRA) of images consists of a collection of techniques that transform each input image $I^{(k)}$ so that it can be represented in a multi-scale manner $\left(y_0^{(k)}, y_1^{(k)}, \ldots, y_L^{(k)}\right)$. To imagine that graphically, the decomposed sequences of the images I_l can be arranged in a pyramid where the bottom contains image I_0 that is identical to the input image I. Then, at the following l levels, the I_l images are reconstructed by applying low pass filtering along with sub-sampling the image I_{l-1} [4].

Discrete Wavelet Transform (DWT), dual-tree complex wavelet transform (CWT), and undecimated DWT (UDWT) represent examples of the methods that fall under this class of methods [4].

4.4. Ensemble learning techniques

Ensemble learning aims to construct an accurate predictors or classifiers through assembling weak predictors or classifiers. In the context of image fusion, ensemble learning represents the fusion of K images I_k, $k \in \{1, 2, \ldots, K\}$ that are all derived from the same base image I^*. The aim here is to obtain substantially improved quality fused image. The simplest way to generate I_k images is to apply K different transformations to the base image I^*. For the ensemble learning to be effective, the I_k images must be independent and should highlight different characteristics in I^*. Mitchell [4] illustrated detail description about common image transformations that can be applied to achieve this purpose.

After demonstrating, spatially and temporally aligning the I_k images, feature images or decision maps from the base image I^*, the pixel-based fusion operators, such as arithmetic mean or trimmed mean, can be applied on the I_k and the feature images. For the decision maps, majority-vote or a weighted majority-vote rule can be used.

4.5. Simultaneous Truth and Performance Level Estimation

Simultaneous Truth and Performance Level Estimation (STAPLE) algorithm is the category where the Expectation–Maximization (EM) algorithm is used as a basis for fusing a large number of segmented images together [4]. The main idea behind EM algorithm is to assess the maximum-likelihood of an underlying distribution of a given set of incomplete data on a powerful iterative basis. On the STAPLE algorithm, the EM algorithm helps in iteratively estimating the quality of the individual segmentations. These individual segmentations' qualities are then taken into account to compute the final segmentation by weighing the decisions made by a higher reliable segmentation algorithm than ones made by a less reliable algorithm.

It is important to note that despite different image fusion algorithms, some major requirements have to exist in these algorithms including [32]:

- Pattern conservation has to ensure that all relevant information in the input image is maintained in the fused version.
- Artifact free: should not produce any artifacts or inconsistencies that could confuse the human observer or subsequent image processing stages.
- Invariance: should be invariant to the rotational and shift changes.
- Temporal stability: The output of the fusion process should be temporally stable.
- Temporal consistency: The output has to include gray levels existed in the input sequences.

5. Medical imaging modalities and image fusion

Various medical imaging modalities exist with each having its unique characteristics. They can add a useful source of information for further processing procedures, including fusion process. Fig. 9 illustrates the classification of the medical imaging modalities based on ImageCLEF 2015 [33].

As shown in Fig. 9, the diagnostic images are classified into five categories. Each of these categories uses different medical technologies and consequently produces different output images. Despite sharing the overall category structure, each image has its characteristics that help in producing different types of information. This section is meant to describe the resulting information of these image modalities to deal with registration and/or fusion processes. Therefore, this section is

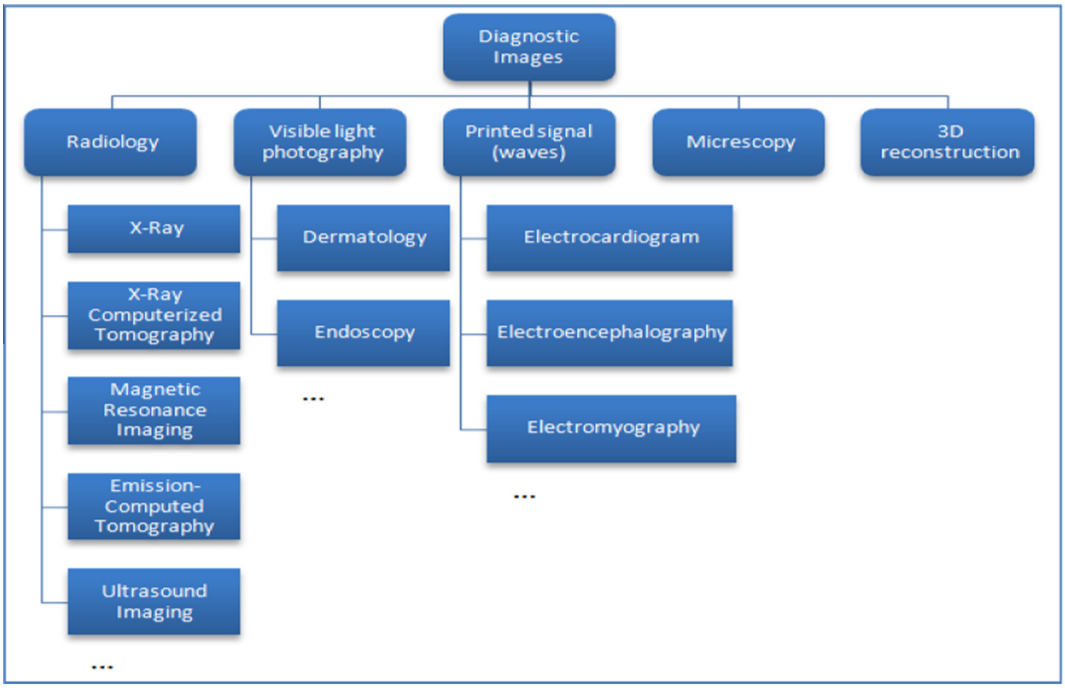


Fig. 9 The medical imaging modalities classification.

divided into five subsections based on the nature of the output images. These subsections are radiology, visible light photography, printed signals (waves), microscopy, and 3D remonstration.

5.1. Radiology

The term radiology refers to the branch of medicine where the imaging technology is applied for the purposes of diagnosis and treatments. Two categories lie beneath the concept of radiology: diagnostic radiology and interventional radiology [34].

Diagnostic radiology, as its name implies, is the category where the internal structure of the body is imaged for different diagnosing purposes including symptoms interpretation, treatment progression, or illnesses monitoring. On the other hand, interventional radiology is the radiology category where the professionals use the imaging modalities to help with subsequent medicine procedures including inserting catheters [34].

Various imaging modalities can assist the radiologists in their diagnosis or intervention procedures. X-rays, Computed Tomography (CT) Scan, Magnetic Resonance Imaging (MRI), Ultrasound (US), Single Photon Emission Computed Tomography (SPECT), and Positron Emission Tomography (PET) are examples of the most frequent assistant imaging modalities. Additionally, Table 1 shows a comparison of these medical imaging modalities while a brief introduction of these imaging modalities along with the main application areas associated with each of them is presented in the following subsections [35–42].

5.1.1. X-ray Computerized Tomography

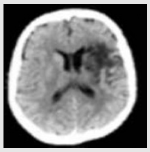
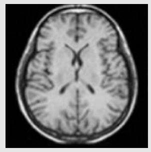
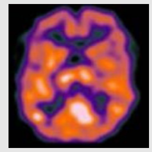
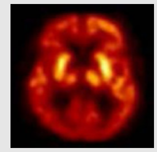
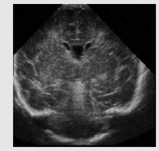
X-ray Computerized Tomography (CT) or Computed Axial Tomography (CAT) is a medical imaging modality that acquires cross-sectional images of the internal anatomical structure of the body [42]. As its name implies, the CT images fall under the X-ray imaging umbrella. Therefore, before going into the CT images, it is important to describe the X-ray medical modality.

X-ray imaging modality is considered as the oldest medical imaging modality that emerged in 1895. The formation of X-ray imaging is performed by positioning the patient between an X-ray tube and X-ray detector. The goal of X-ray tube is to produce a set of electromagnetic waves (X-rays) that represent high-energy photons. The subject of these X-rays is the patient who will absorb such rays to reconstruct on the other side the measured rays through X-ray detector. The measurements on the X-ray detector simply represent the degree of attenuation at each scanned point of the patient body [34,43]. The most common applications of X-rays imaging are bone broken detection. In addition, this class of medical imaging can also be used on pneumonia detection using chest X-ray [34].

The difference between X-rays images and CT scan is that the produced X-ray waves in X-ray images are emitted in one direction while in CT images the X-rays are emitted in all possible angles and distances [34]. The result of CT scan is a series of 2D axial slices that in turn accumulated to form a 3D representation of a patient [42]. CT medical imaging modality is frequently used in colon health estimation (CT colonography, pulmonary embolism, and vascular condition/blood flow (CT angiography)). It is also used in bone injuries and cardiac tissues and in detecting the presence, size, and location of tumors [44].

In medical image fusion, CT images assist in diverse applications including 3D tumor simulations, brain diagnosis/treatment, surgical planning, cancer diagnosis/treatment, tumor detection, 3D Voxel fusion, deep brain stimulation, telemedicine, and classification fusion.

Table 1 A comparison of major diagnostic radiology images.

	CT	MRI	PET	SPECT	Ultrasound
Example					
Main characteristic	Scan body organs using X-rays and produce a series of cross-sectional based images via the computer	Produce "slices" that represents the human body through applying magnetic signals	Nuclear imaging technique example where the tracers are used in diseases diagnosis	A non-invasive based technique where cross-sectional images of radiotracer within the human body are structured	Sound waves based technique that possesses a high temporal frequency and which is capable of producing quantitative and qualitative diagnostic information through a set of comprised methodologies
Advantages	– Wide field of view	– Higher resolution	– Effectively used to distinguish between benign and malignant tumors in single imaging	– Images free of background	– High spatial resolution
	– Detection of even subtle differences between body tissues	– Capable of showing anatomical details	– Can image biochemical and physiological phenomena	– Confirm neurodegenerative diseases (Alzheimer's, Parkinson's)	– Low cost
	– Tomographic acquisition eliminates superposition of images of the overlapping structure	– Does not use any ionizing radiation	– High sensitivity	– High sensitivity (but lower than PET)	– Safety profile
	– High spatial resolution	– No short term effects are observed	– High penetration depth	– High penetration depth	– Clinical translation
	– High penetration depth	– Clinical translation	– Clinical translation	– Clinical translation	– Noninvasive (no noodles or injections)
	– Clinical translation				– Widely available
					– Easy to use
					– No radiation
Disadvantages	– Limited sensitivity	– Strong magnetic field disturb	– Limited spatial resolution	– Blurring effects is produced	– Operator dependent
	– Radiation	– Cannot be used in patients with metallic devices, such as pacemakers	– Radiation	– Attenuation compensation is not possible due to multiple scattering of electrons	– Imaging limited to vascular compartment
	– High dose per examination	– Low throughput	– High costs	– Fails to predict neuropsychological deficits	– Difficult image of bone & lungs
	– Cost	– Cost	– Most expensive technique	– Limited spatial resolution	– Limited resolution
	– Tissue non-specificity		– Motion artifacts are the serious problems	– Radiation	– Attenuation can reduce the images' resolution
	– Poor soft tissue contrast		– Lower resolution compared to CT and MRI		– Reflected very strongly on passing from tissue to gas or vice versa
			– Interpretation is very challenging		
			– The radioactive components used in PET allow only a limited amount of times a patient undergoes procedure		

(*continued on next page*)

Table 1 (*continued*)

	CT	MRI	PET	SPECT	Ultrasound
Contrast	– High	– High	–	–	–
Application	– Anatomical – Functional	– Anatomical – Functional – Molecular	– Functional – Metabolism – Molecular	– Functional	– Anatomical – Functional
Cost	– Intermediate cost	– Intermediate cost	– High cost	– High cost	– Low cost
Radiation Source & type	– X-rays (ionizing)	– Electric & Magnetic Fields (Non-ionizing)	– Positron (ionizing)	– Photons (ionizing)	– Sound waves (Non-ionizing)

5.1.2. Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a major fabrication in the field of medical imaging technology [42]. Rather than depending on the X-rays and their high-energy photon properties, MR imaging technology relied on the orientation of protons inside a strong magnetic field where resonant radio-frequency waves can be used to manipulate the oriented protons. Then, the returning of the protons to their equilibrium state is measured [43]. The resulting output images show a detailed description of the human body in addition to contrasting unparalleled soft tissue on a non-invasive basis. Although MR imaging technology is a more adequate in contrasting soft tissues than CT, it requires more acquisition time unless special high-speed protocols are often used that suffer from poor image quality [43].

It is important to note that the CT and MR images are used to acquire the structural information of the body. Such characteristic is due to the nature of the radiation that they are based on and their way of working. For CT images, this is the case all the time, but for MR images this is the case with the standard class of MR imaging modality. On the other hand, MR imaging modality has another class of imaging known as functional MRI aims to extract the internal functional information of the scanned body. The extracted functional information represents the levels of blood oxygenation and, therefore, the metabolic activity of the body [43].

MR imaging modality is considered as the primary clinical medical modality that assists in many diagnosing areas including blood vessels, abnormal tissue, breasts, pelvis, bones, and joints. The diagnosing areas also include spinal/tendon injuries, ligament tears chest, and abdomen (heart, liver, kidney, and spleen) [44].

For medical image fusion, there are intensive applications on different human organs where the impact of MRI takes place. These applications include prostate studies, image regeneration, lung/liver diagnosis, tissue classification, cancer assessment and diagnosis, surgical planning and training, visualization, MRI-guided treatment, and 3D tumor simulation [3].

5.1.3. Emission-Computed Tomography

Instead of dealing with the anatomical structure like many other modalities, Emission-Computed Tomography (ECT) is a medical imaging modality that focuses on physiological functions and the mapping associated with such functions. The main objective of ECT is to determine the isotope compound distribution within the patients' body [42].

Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) are the applications of ECT imaging modality. The SPECT technology applies radioisotopes that decay emitting a single gamma photon, while the PET technology employs isotopes where a couple of photons are produced in each annihilation [42].

The major application where SPECT technology is widely used is the study of the blood flow to tissues and organs. The applications also include [3]: brain and cancer diagnosis and treatment, liver diagnosis, multi-modal images fusion, visualization, pattern recognition, and biopsy.

For the PET, the major application where this technology is primarily used is in the radiology studies for brain diagnosis and treatment [3]. Other applications contain [3]: cancer treatments, image segmentation and integration, the 3D tumor simulation, tumor detection and treatment, telemedicine and pancreatic tumors characterization.

5.1.4. Ultrasound imaging

Ultrasound (US) is sound waves based technique that possesses high temporal frequency. It is capable of producing both quantitative and qualitative diagnostic information based on a set of comprised methodologies. The US technology can be used in many applications, such as a cancer diagnosis, detection and treatment, conformal radiation therapy, image fusion, liver tumor diagnosis, and prostate biopsy [3,42].

5.1.5. Other medical imaging modalities

Infrared, fluorescent, microwave, and microscopic medical modalities are considered as additional medical imaging modalities. Each one has a notable footprint in various applications including medical imaging fusion [3]. For example, Infrared imaging modality can be applied to breast cancer detection. Fluorescent imaging can help in oral cancer detection, prostate brachytherapy, and treatment. Microwave imaging can assist in breast cancer detection and tumor identification. Microscopic imaging can be implemented in mosaicing medical image, multi-feature based fusion, extracting distinctive features as well as assisting in medical systems of decision support. Trans-Rectal Ultrasound (TRUS) is an alternative to US imaging modality that is used in prostate brachytherapy dosimetry, biopsy planning, segmentation, and image-guided prostate intervention and prostate seed implants' quality evaluation. Mammography is an imaging modality that is based on X-ray and that has been widely used for breast cancer assessment and microcalcification diagnosis. Performing image fusion of mammogram with other modalities has the capability to significantly improve the detection accuracies of problems like abnormal tissue identification in case of calcification. Finally, molecular imaging is a modality that was applied and proved its help in improving the imaging interpretations in the application of brain diagnosis and treatment [3].

There are many combinations of different imaging modalities to produce medical fused images exist. Some of these applications include the following: MRI–CT fusion [44], MRI/CT–PET–SPECT fusion [45], PET–CT–US fusion [46], US–MRI fusion [47], US–X-rays fusion [48], US–CAD–mammograms–infrared fusion [49], and finally MRI–TRUS fusion [50]. It is important to note that MRI–CT is deemed to be the most famed combination because of the technology's maturity and clinical setting's usability [3].

5.2. Visible light photography

Rather than exposing the patient to invisible light through emitting different types of rays, visible light photography/optical tomography exposes the patient to visible light to produce color or grayscale images [51]. The formation of such images helps in capturing a sequence of images that represent a dynamic range of information that occurred over time [51]. The captured dynamic information in turn helps in producing patients' record that assists in following up the patients' condition at certain time points and recording the effect of the therapeutic approaches [52]. The following subsections show some medicine specialties that are benefitted from using visible light photography. Fig. 10 shows examples of the usage of this technology in different specialties [53].

5.2.1. Dermatology

Dermatology is the specialty of medicine that focuses on the skin, its structure, its function, and the skin related diseases and treatment [54].

5.2.2. Endoscopy

Endoscopy is also a specialty of medicine that lies beneath visible light photography. This spatiality focuses on the therapies and surgeries that are performed in the internal part of the body [55]. The name endoscopy was derived from the endoscopes or shortly named scopes that represent certain devices used by the doctors to look inside the body. In general, various endoscopes exist with variations in their lengths, shapes, and flexibility. In addition, some endoscopes are attached with a small video camera for computerizing the images of the internal body. According to the endoscopies variations, various organs of the body can be monitored using an appropriate endoscope. Further details of endoscopies and viewed body area can be found in [55].

5.2.3. Other organs/specialties

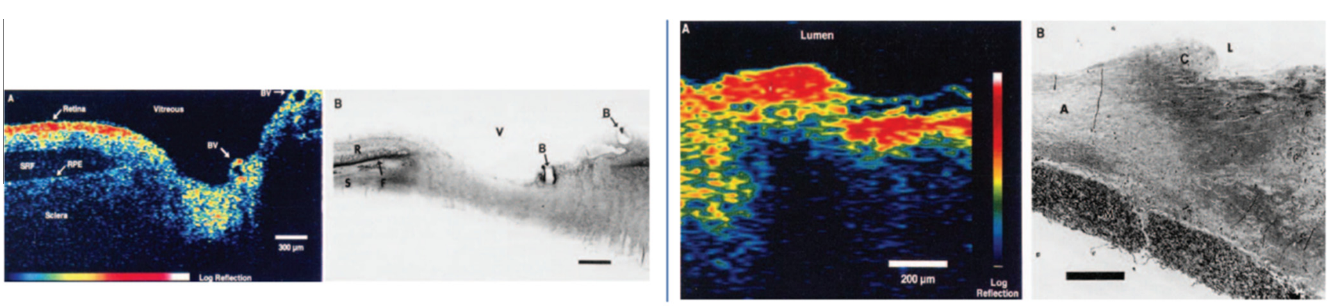
In addition to the previously described medical specialties, there are many other specialties in which the diagnostic images can take place to assist in the diagnosing as well as surgeries and different therapies monitoring. An example of these specialties of medicine is the Ophthalmology. Ophthalmology is the branch of medicine that focused on the eye, its structure, its functions and related diseases [56]. In addition, otorhinolaryngology is a medical branch that cares about the diseases of the ear, nose, throat, and related structures of the head and neck [57]. All of these medical branches and many other branches obtain many benefits of the visible light images.

5.3. Printed signals/waves

Printed signals, also known as electrograms, are electronic waves that aim to capture physical and cognitive functions of the body. Such waves can consequently aid in diagnosing the patient's conditions as well as monitoring their treatment progression. The term electrograms is composed of two Greek parts electro which means electricity and gram that means write or record. Therefore, the term reflects the goal of recording electrical signals from the body [58]. Different methods and procedures were developed with each help to produce a certain type of electrograms [58]. These electrograms methods are Electrocardiogram (ECG), Electroencephalography (EEG), and Electromyography (EMG). A brief description of the main well-known electronic waves is presented next, and an example of these waves is illustrated in Fig. 11 [59]. Any further related details can be found in [58].

5.3.1. Electrocardiogram (ECG)

ECG is considered as the most common method of electrograms where the term cardio is a Greek word that refers to



Human retina ex vivo and corresponding histology   Human artery ex vivo and corresponding histology

Fig. 10 Example of Visible light photography/optical tomography images in different medicine specialties.

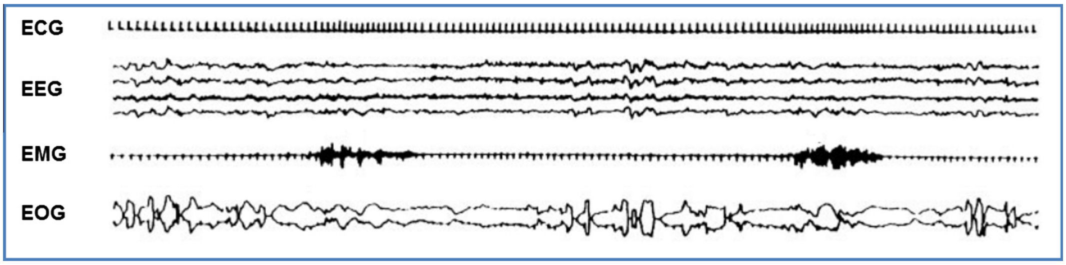


Fig. 11 Examples of the common electronic waves.

the heart [58]. The objective of the ECG is to record the electrical activity of the heart that represents the subject of this electrogram method [34]. Analyzing the ECG signal helps in obtaining substantial information about the heart, such as myocardial infarction, different cardiac arrhythmias, the effects of hypertension in addition to rehabilitation, and exercise information of the cardiac [58].

5.3.2. Electroencephalography (EEG)

EEG is the electrogram method whose target is the brain. Since brain cells are communicated through electrical signals, any abnormalities in the electrical activity of the brain can be discovered through performing EEG test [60]. In other words, EEG test aims to detect the functional status of the brain. Such detection in turn helps in diagnosing various

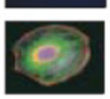
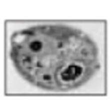
Type of Microscope	Typical Image	Description of Image	Special Features	Typical Uses
Light Microscopes		Useful magnification 1× to 2000×; resolution to 200 nm	Use visible light; shorter, blue wavelengths provide better resolution	
Bright-field		Colored or clear specimen against bright background	Simple to use; relatively inexpensive; stained specimens often required	Observation of killed stained specimens and naturally colored live ones; also used to count microorganisms
Dark-field		Bright specimen against dark background	Use a special filter in the condenser that prevents light from directly passing through a specimen; only light scattered by the specimen is visible	Observation of living, colorless, unstained organisms
Phase-contrast		Specimen has light and dark areas	Use a special condenser that splits a polarized light beam into two beams, one of which passes through the specimen, and one of which bypasses the specimen; the beams are then rejoined before entering the oculars; contrast in the image results from the interactions of the two beams	Observation of internal structures of living microbes
Differential interference contrast (Nomarski)		Image appears three-dimensional	Use two separate beams instead of a split beam; false color and a three-dimensional effect result from interactions of light beams and lenses; no staining required	Observation of internal structures of living microbes
Fluorescent		Brightly colored fluorescent structures against dark background	An ultraviolet light source causes fluorescent natural chemicals or dyes to emit visible light	Localization of specific chemicals or structures; used as an accurate and quick diagnostic tool for detection of pathogens
Confocal		Single plane of structures or cells that have been specifically stained with fluorescent dyes	Use a laser to fluoresce only one plane of the specimen at a time	Detailed observation of structures of cells within communities
Electron Microscopes		Typical magnification 1000× to 100,000×; resolution to 0.001 nm	Use electrons traveling as waves with short wavelengths; require specimens to be in a vacuum, so cannot be used to examine living microbes	
Transmission		Monotone, two-dimensional, highly magnified images; may be color-enhanced	Produce two-dimensional image of ultrastructure of cells	Observation of internal ultrastructural detail of cells and observation of viruses and small bacteria
Scanning		Monotone, three-dimensional, surface images; may be color-enhanced	Produce three-dimensional view of the surface of microbes and cellular structures	Observation of the surface details of structures

Fig. 12 A comparison of different microscopy images [63].

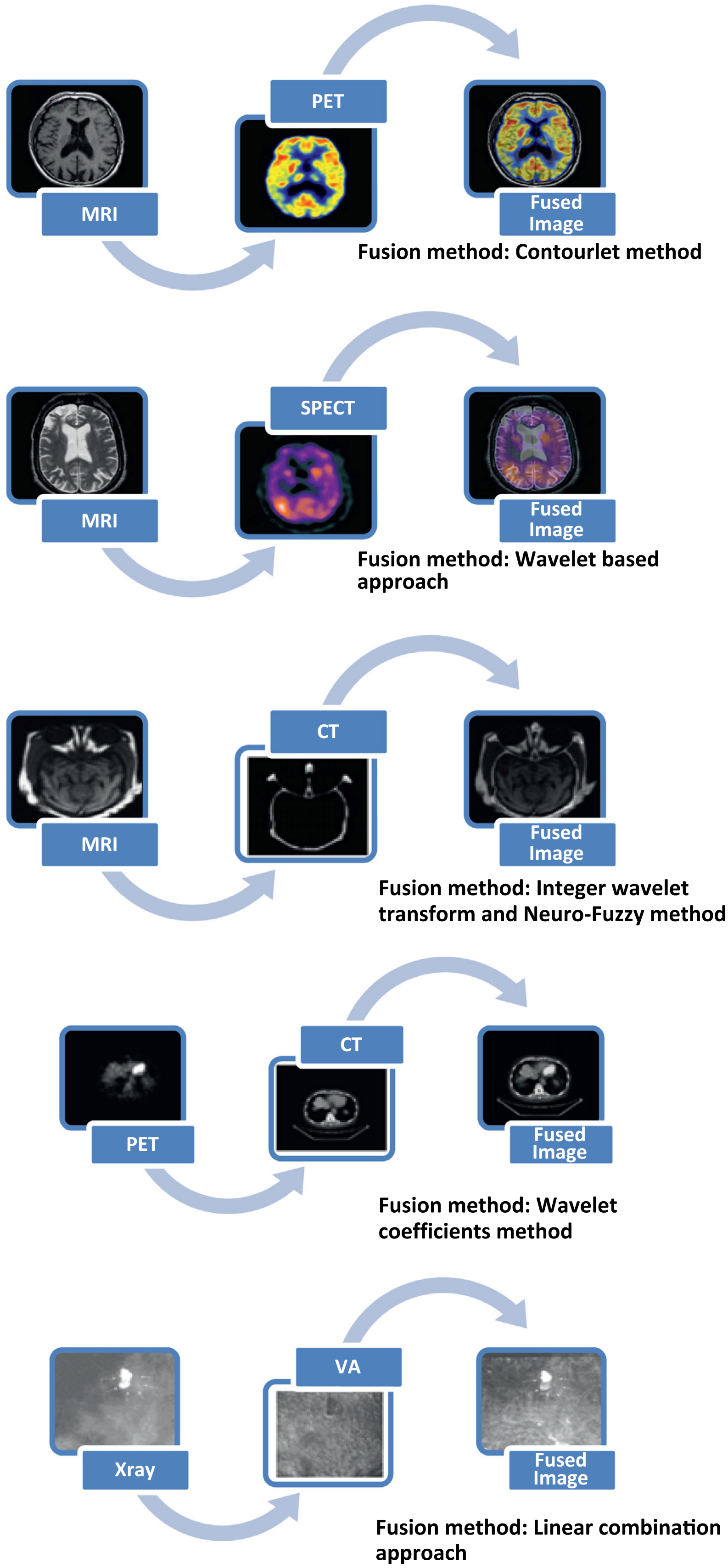


Fig. 13 Examples of medical imaging modalities under the fusion process.

neurological problems including common headaches, dizziness, stroke, brain tumors, epilepsy, multiple sclerosis, sleep, and movement disorders [61].

5.3.3. Electromyography (EMG)

EMG is the test that concerns with recording the response of the muscles when they are exposed to nervous stimulation. This test takes place by inserting needle electrode through the skin until achieving the muscles and then recording the presence, size, and the shape of these muscles responses to the nervous stimulation [34]. The two major applications where such signals can aid in are neuropathies and myopathies. In addition to these applications, EMG can assist in diagnosing nerve compression or injury and nerve root injury, and rarely assist in myasthenia gravis and muscular dystrophy [58].

5.3.4. Other methods

In addition to the previously stated methods, Electrooculography (EOG) test also represents a class of electrograms. The target of this test is the retina where the test helps in writing the steady and resting electric potentials of the eye. Obtaining such signal can mainly assist in diagnosing ophthalmological and recording eye movements [58].

5.4. Microscopy

Microscopic images are the class of diagnostic images that are captured through the microscope to help in enlarging small scanned objects and thus extracting fine details that cannot be obtained otherwise [61].

Different types of microscopic images can be captured depending on the microscopes' waves that are focused on the specimen. In general, there are two categories of microscopes: Light (optical) and electron microscopes [62]. Light microscopes are the category where optical lenses and light waves are applied. Bright light microscopy, dark field microscopy, fluorescence microscopy, and phase contrast microscopy are microscopes that lie under the umbrella of light waves system. In the other hand, in the electron microscopy's category, the diagnostic images are formulated through exposing the specimen electron beams rather than light waves [62]. Transmission and scanning electron microscopes represent the subcategory of microscopes that relied on applying the electron waves in their images formations [62].

It is important to mention that electron-based microscopes guarantee more magnification and higher resolution than light category [61]. Although these are main classes of microscopy, other types also exist with each having its characteristic and different resulting images. Fig. 12 shows a fine comparison of various microscopy images while any further description of such microscopes can be found in [63].

5.5. 3D reconstruction

3D reconstruction is the field of science concerned with constructing a 3D model of the scanned objects using a set of 2D images. In medical imaging, the source of these 2D images can obtain some diagnostic images, such as CT scans, electron microscopy, or Magnetic Resonance Imaging (MRI) [64]. Finally, different examples of performing medical image fusion process using various methods are illustrated in Fig. 13 [3].

6. Software tools

Diverse collections of toolkits have been emerged recently to assist the researchers in their work on the medical image registration and fusion. This section illustrates some image registration and fusion toolkits along with a description of each of them.

6.1. Insight segmentation and registration toolkit (ITK)

ITK [65] is the most popular toolkits that dealt with medical image processing with a particular concern for registration and segmentation processes. ITK toolkit is considered as an open source toolkit that helps in accomplishing the registration process through providing four groups of components: similarity metric, transform, optimize, and interpolation [66].

The toolkit presents various features for its users. The major feature of such toolkits is the assistance of creating an enormous repository of the fundamental algorithms that in turn facilitate these analysis processes. Various papers used ITK to evaluate their performance [67,68]. In addition, several examples related to the usage of the toolkit along with source code of such examples are available on the toolkit website through a free book named *The ITK Software Guide* [66].

6.2. Elastix

Elastix [69] is an open source toolkit that relies on ITK and provides a broad range of rigid and non-rigid registration algorithms. The toolkit focuses on medical images and helps in configuring, testing, and comparing different registration methods. In addition to these features, the Elastix toolkit also facilitates applying the presented registration methods on a broad range of datasets. Examples of scientific work that applied Elastix software include [70,71].

6.3. Advanced Normalization Tools (ANTs)

ANTs [72] is a registration toolkit that helps users through presenting various registration methods as well as similarity metrics (landmarks, cross-correlation, mutual information, etc.) to facilitate their work.

6.4. NiftyReg

NiftyReg [73] is an open source registration toolkit that provides various registration methods. The developers of NiftyReg are working on enabling Open-CL, central processing unit (CPU) or Compute Unified Device Architecture (CUDA) based implementations. Examples of scientific research that applied NiftyReg software include [74,75].

6.5. Medical Image Processing, Analysis, and Visualization (MIPAV)

MIPAV [76] is an application that provides wide processing services in the medical image processing field including

Table 2 The current diseases based registration works.

Disease/disorder/surgery	Registration classes	Diagnostic modality	Dataset availability
Head			
Arterial steno-occlusive disease of the head to study head motion scanning errors [81]	Rigid Monomodal	PET	Not Available
Pituitary adenoma [82]	Rigid Monomodal	MR	Not Available
Brain			
Huntington's disease [75]	Nonrigid Monomodal	MR	Not Available
Parkinson's Disease [83]	Nonrigid + Rigid Multimodal	MR SPECT	Not Available
Cerebral tumor deformations [84]	Nonrigid Multimodal	CT MRI	Not Available
Gliomas [85–87]	Rigid Multimodal Nonrigid Monomodal	US MRI MRI	Not Available Not Available
Elderly and frontotemporal dementia cortex [67]	Nonrigid Monomodal	MRI	Two datasets: 1. The first one is unavailable 2. The second one: BrainWeb atlas [88]
Mild to Mild Alzheimer's [89]	Nonrigid Monomodal	MRI	Open Access Series of Imaging Studies (OASIS) [90]
Eye			
Eye fundus (ocular pathologic conditions) [91]	Rigid Multimodal	Ophthalmological images	Not Available
Retinal diseases [92]	Rigid Multimodal	Ophthalmological images	Two datasets: 1. The first one was collected from [93,94] 2. The second one is unavailable
Oral			
Tongue disorders [95]	Nonrigid Multimodal	hMR Cine MR	Not Available
Lung			
Assist in detecting and diagnosing lung cancer [96]	Nonrigid Monomodal	Chest radiographs	Not Available
Chronic obstructive pulmonary (Lung) [97]	Nonrigid Monomodal	CT	Not Available
Breast			
Breast cancer [98]	Nonrigid Monomodal	MR	Not Available
Post-mastectomy regional radiation therapy [99]	Nonrigid Multimodal	PET CT	Not Available
Cardiac			
Coronary artery diseases [100,101]	Rigid Multimodal Nonrigid Monomodal	X-ray CT MR	Not Available Not Available
Ischemic heart disease [102]	Rigid + Nonrigid Monomodal	CT	Not Available
Trans-catheter Aortic Valve Implantation (TAVI) [103]	Rigid + Nonrigid Monomodal	CT	Not Available
Left ventricular regional wall motion abnormalities [104]	Nonrigid Monomodal	Echo-cardiographical image (Ultrasound of the cardiac)	Not Available

(*continued on next page*)

Table 2 (*continued*)

Disease/disorder/surgery	Registration classes	Diagnostic modality	Dataset availability
Cardiac arrhythmia [105]	Rigid Monomodal	MR	Not Available
Aortic atherosclerosis [106]	Rigid Monomodal	Transesophageal echocardiographic (TEE) images	Not Available
Myocardial Motion (assist in diagnosis and treatment of Cardiovascular diseases) [107]	Nonrigid Monomodal	MR	Not Available
Carotid arteries (to assist in analyzing atherosclerotic plaque) [108]	Rigid + (Nonrigid) Multimodal	US MRI	Not Available
Vascular diseases [109]	Nonrigid Monomodal	CT	SOVAmed GmbH [110]
Liver			
Hepatocellular carcinoma [111]	Nonrigid Monomodal	CT	Not Available
Liver Tumor Ablation [112]	Rigid Multimodal	CT US	Not Available
Prostate			
Prostate cancer [113,114]	Nonrigid Monomodal	MR	Not Available
	Nonrigid Multimodal	TRUS MR	Not Available
Bone			
Bone mineral density (bone health) [115]	Rigid + (Nonrigid) Monomodal	Quantitative computed tomography (QCT)	Not Available
Peripheral arterial occlusive disease [116]	Two alternative registration cores: 1. Rigid + (Nonrigid) 2. Nonrigid Monomodal	CT	Not Available

registration process. The provided services of MIPAV include the following: analyzing different medical modalities, supporting the developments of different tools (in both hardware and software) that facilitate analyzing and consequently discovering new biomedical related knowledge. Additionally, the application enables the researchers to share their analyzing results that in turn enhance the diagnosing as well as the treatment of the medical data. Examples of scientific research that applied MIPAV application include [77].

6.6. Medical imaging toolkit (MITO)

MITO [78] is open source software that focused on medical imaging analysis processes including 2D–3D visualization, ROI extraction, image segmentation, and image fusion. Moreover, MITO presents required techniques for touch less image and volume surgery' navigation.

6.7. OsiriX

OsiriX [79] is medical image processing software that is primarily focusing on 2D/3D visualization of multi-modal and multi-dimensional images, image registration, and image fusion processes [80]. Examples of scientific research that applied OsiriX application include [80].

7. Current diseases based registration/fusion work

As previously mentioned, different medical imaging modalities provide various information sources about the human body. Therefore, various medical registrations, as well as fusion research, have been proposed and relied on that fact. These researches can be classified based on the body organs that are addressed by each of these studies.

The aim of this study is to present some recent registration and fusion research. This presentation is classified mainly into two parts: medical image registration studies and medical image fusion studies. Therefore, each of these categories is divided into subcategories based on the Disease/Disorder/Surgery related to the organs that were targeted by each of the proposed studies.

7.1. Medical image registration studies

As previously stated, aligning series of images is a substantial step for further analysis procedures. Due to this fact, numerous medical image registration researches have been emerged to accomplish the alignment task. Table 2 illustrates some recent medical image registration researches that are grouped based on the targeted body organ. Under each organ category, different work that focused on different disease/disorder related to this organ is presented.

According to Table 2, numerous applications of image registration in the medicine field have emerged. The proposed research addressed various organs of the body in addition to addressing various diseases/disorders related to such organs. In general, the existence of such scientific works provides evidence to the impact of the registration process in the diagnosing as well as treatment processes. The illustrated research shows the role of the registration process in dealing with various diseases/disorders in addition to its help in the planning of different therapies with an aim of improving the treatment quality.

The brain and the cardiac represent the most interested organs that lie under the registration umbrella. The reason for that can be due to the number of factors. First, the diseases/disorders/surgeries related to such organs face a broad range of patients around the world regardless of the different cultures and environments. Also, the existing medical imaging technologies help in capturing different information sources that consequently can assist in the registration process. In addition, the complicated nature and the overlap of some brain and cardiac diseases/disorders encourage the scientific research to facilitate understanding such diseases/disorders. Such cases encourage the researchers to attempt to differentiate between such diseases/disorders to assist consequently in the diagnosing and decision-making procedures.

Although there is a broad range of medical image registration research, there are some limitations that still face such important process. The availability of the dataset is considered as one of the main problems that face the implementation of the registration process. As illustrated in the table, most proposed researches are dealt with a specific dataset acquired specially for the research goal without a standard dataset for the research to refer to when it is needed. Such a problem often restricts the possibility of comparing, generalizing and assessing presented methods.

Additionally, despite the existence of various medical imaging technologies that acquire various information sources, these technologies still suffer from limitations that face the implementation of the registration process. Finally, it is important to note that the overlapping/similarity between different diseases/disorders represents an issue that opens the door in front of the research for attempting to differentiate between such diseases/disorders.

Table 3 The current diseases based fusion works.

Disease/disorder/surgery	Fusion classes	Diagnostic modality	Dataset availability
Brain			
Various brain diseases [119,120]	Multi-Scale Methods	CT MRI	Two datasets [121,122]
	Two frameworks 1. Multi-Scale Methods (Anatomical imaging modalities) 2. (Color space): (Functional and Anatomical imaging modalities)	 1. CT + MRI 2. SPECT + MR	[122]
Brain Tumors (Sarcoma Astrocytoma) [123]	Ensemble Learning Techniques	CT MRI PET SPECT	[122]
Eye			
Optic Nerve Head vascular disorders (cynomolgus monkeys) [124]	Pixel level fusion SubSpace Methods	Ophthalmological images	Not available
Chest			
Tuberculosis bacteria [125]	Pixel level fusion + Multi-Scale Methods	Color microscopic image	Not available
Cardiac			
Cardiac deformation recovery [126]		MRI Electrocardiographic images	PhysioNet/computers in cardiology challenge 2007 [127]
Cardiac Resynchronization Therapy [128]		Echocardiography Electrocardiography CT	Not available
Abdomen			
Inflammatory bowel diseases (Crohn's disease) [129]	Pixel level fusion (optical flow field)	MRE (magnetic resonance enterography)	Not available

7.2. Medical image fusion studies

In addition to medical registrations research, various fusion studies have also been presented that also aimed to facilitate the professional diagnosing and treatment operations. Table 3 illustrates various recently proposed researches in the context of medical image fusion. As in Table 2, the medical fusion studies have been divided based on the addressed organs, and the illustrated research represents different diseases/disorders and treatment plannings related to such organs. In addition to the presented research, the fusion process of medical imaging modalities has been used to assess certain therapies and treatment planning for different diseases through analyzing the obtained fusion outputs by medical experts [117,118].

As presented in Table 3, the medical fusion process was applied in diverse disease/disorders to assist in producing more representative output images for further diagnosing procedures. Such a note indicates how the fusion process began to show an effective assistance to the experts in the medical fields.

Even though applying the fusion process has a useful impact in the medicine field, there are some limitations that restrict the research work in this area. As in the registration process and as indicated in Table 2, in the most proposed researches the applied datasets are not available for further developments. In addition, the computation efforts needed to perform the fusion process, especially the multimodal fusion, represent another source of challenges when dealing with medical fusion processes. The complexity of the organ nature and/or the complicated structure of the disease also introduce a challenge that faces the scientific research in this medical image analysis area.

8. Discussion

Despite the presence of many researches in the field of medical image registration and fusion, the way is still open for further development in this field especially with the existence of number of constraints that are faced by the researchers in these areas. These constraints can be classified into different categories due to the affecting factors. Medical imaging technologies, the applied methods/techniques, the medical datasets, and even human being himself are the major challenging categories in the context of registration and fusion advances. The aim of this section is to discuss each of these limitations in certain detail to clarify the current challenges arise in the context of registration and fusion processes.

8.1. Medical modality challenges

As mentioned previously, one of the major registration and/or fusion processes' challenges is the medical imaging modalities. In other words, despite producing valuable information, each medical modality has some disadvantages that may affect the outputs and subsequently the decision that has to be made by the experts. Therefore, the medical imaging modalities still need development to be able to acquire much more details and gain more access to the body organs.

Also, for some medical applications, certain types of medical modalities may be insufficient or incompetent to provide the required source of information that in turn reduces the efficiency of the necessary processes. This obstacle can be faced through other medical imaging modalities that can provide reasonable and sufficient information. The problems with these alternative modalities are as follows: the financial efforts in addition to exposing the patients to the radiations that are harmful to the human health by the time.

8.2. Methods/techniques challenges

The applied methods/techniques produce another source of challenges. Even if the modalities are suitable, the results may be constrained by the methods/techniques limitations.

The computation effort and the overall performance/quality are some of the limitations that prevent the implementation of various proposed works in the real world. Such limitations arise due to the sensitivity of time and the importance of obtaining high-quality results in medical applications.

The dependency to the initializations and the extracted features represents another source of limitations that affect the performance of some methods/techniques and consequently affect the results. Also, even though working with different modalities provides an opportunity to increase the sources of information, multimodal registration/fusion methods still face the difficulty of finding the suitable way for registering/fusing the different modalities.

It is also important to note that common registration methods perform the alignment procedure with respect to the reference image and so-called pair-wise registration methods. Although this is the standard case, such procedure is highly dependent on the chosen of the reference image that in turn affects the quality of the produced output. Therefore, a trend for performing the alignment procedure based on what is called group-wise procedure is developed to overcome such obstacle. The idea behind group-wise registration methods is to align a group of images at the simultaneous time to latent population center [130]. Although this procedure can face the drawback associated with applying pair-wise methods, the research in such area is still open. The reason for that is due to that most of the existing methods assume one center for a group of images and use such center as a reference for the subsequent registration process. The problem arises from the calculated center that prevents the implementation of such methods with broad and complex datasets of images because of the inter-subject variations that will certainly affect the performance of these methods.

8.3. Dataset challenges

The dataset and its availability also represent a constraint in the face of the researchers. The problem arises due to the sensitivity of the patients' medical data that prevents the accessibility of such data. Such obstacle consequently restricts the developments, improvements and the comparisons of the proposed works with the other researchers' works. To solve this problem, a broad range of researchers resorted to deal with specialized medical centers to obtain the required data. Although this can assist, the problem associated with such action is the financial effort that is high. Such problem forces the researchers to work with a small sample size of the patients' data. Such procedure in turn restricts assessing the proposed works performance and consequently reducing the chance of generalizing or even implementing these works in the reality.

8.4. Human being challenges

In addition to the previously mentioned limitations, the nature and complexity of certain organs, such as the brain and the cardiac, hinder the developments in the registration/fusion context. Also, the overlapping between certain diseases/disorders, such as the Neurodegenerative disorders, shows another source of challenge in this context.

Finally, it is important to note that the patient himself adds a source of limitation due to his motion during the acquisition time that leads to reducing the quality of the captured images. Certain researchers proposed attempts to face this problem through performing various preprocessing steps to minimize the effect of such constraint in the subsequent processing steps.

9. Conclusion

Among the last few years, image fusion especially medical image fusion has gained much concern due to the importance of such field as a powerful guide for the experts in the medicine area. A large number of medical modalities can act as an input to the fusion steps to produce a final informative output image.

The presented review introduced a description of image fusion steps with a special concern for the registration and fusion steps due to the importance of these steps in this context. Then, diverse medical imaging modalities are presented along with some of the common fields of them. A literature survey of different research of medical image fusion as well as medical image registration was introduced. Finally, a discussion of common challenges that faces the registration and/or fusion process was presented. The discussion of these challenges aims to uncover the weaknesses that still need further studies to help in eliminating their impact regarding the registration and/or fusion of medical images.

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