Long-range medical image registration through generalized mutual information (GMI): towards a fully automatic volumetric alignment

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Abstract

Objective. Mutual information (MI) is consolidated as a robust similarity metric often used for medical image registration. Although MI provides a robust registration, it usually fails when the transform needed to register an image is too large due to MI local minima traps. This paper proposes and evaluates Generalized MI (GMI), using Tsallis entropy, to improve affine registration. Approach. We assessed the GMI metric output space using separable affine transforms to seek a better gradient space. The range used was 150 mm for translations, 360° for rotations, [0.5, 2] for scaling, and [−1, 1] for skewness. The data were evaluated using 3D visualization of gradient and contour curves. A simulated gradient descent algorithm was also used to calculate the registration capability. The improvements detected were then tested through Monte Carlo simulation of actual registrations with brain T1 and T2 MRI from the HCP dataset. Main results. Results show significantly prolonged registration ranges, without local minima in the metric space, with a registration capability of 100% for translations, 88.2% for rotations, 100% for scaling and 100% for skewness. Tsallis entropy obtained 99.75% success in the Monte Carlo simulation of 2000 translation registrations with 1113 double randomized subjects T1 and T2 brain MRI against 56.5% success for the Shannon entropy. Significance. Tsallis entropy can improve brain MRI MI affine registration with long-range translation registration, lower-cost interpolation, and faster registrations through a better gradient space.

1. Introduction

Mutual information (MI) is a widely used and robust statistical metric function that drives image registration. Although MI has derived many improved techniques, it still has the drawback of local extrema, i.e. minima or maxima, that challenges image registration, especially long-range automated registration and inter-subject with inter-modality. Several medical applications require long-range or automated image registration, e.g. medical atlas creation from numerous images (Lancaster et al 2000) and image-guided therapies (Pouliot et al 2005, Markelj et al 2012).

1.1. History

MI was transposed to the image registration domain by Viola and Wells (1997) with the proposal of an algorithm named EMMA, evaluated using 2D MRI slices. EMMA registration was successful in 50 randomly generated translations up to 32 pixels, rotations of 28°, and scalings up to 20%. Wells et al (1996) obtained a success rate varying from 100% for 10 mm translations and 10° rotations, dropping to 90% for 20 mm and 20°, 68% for 20 mm and 68° and finally 41% for 100 mm and 20°, concerning MR-CT registration. Maes et al (1997) reported registrations for up to 10° rotations and 40 mm translations by tuning the parameter optimization order.
1.2. Derived metrics

Studholme et al (1999) introduced the normalized MI (NMI) with success up to 30 mm and 30° when using smaller fields of view. Russakoff et al (2004) introduced the regional MI (RMI) in 2004 and compared results to (Pluim et al 2000, Rueckert et al 2000), and classical MI. RMI is more robust with a success rate above 85% in target registration errors (TRE) with transforms up to 15 mm. The study approached RMI as a translation cost function, showing good results in a range up to 60 mm, but with an abnormal asymmetrical shape. Loeckx et al (2010) introduced conditional MI (cMI), which improves the MI results for nonrigid B-spline registration. However, the algorithm demands up to 37 times more computational time than conventional MI.

The MI function was also modified to use generalized entropy, where the parameter $q$ modifies the entropy around the classical Boltzmann–Gibbs–Shannon entropy, where $q \to 1$. Wachowiak et al (2003) used 2D and 3D images with transforms up to 10 mm and 30° rotations, with 0.25 $\leq q \leq 2$, and noted that the ‘problem of entrapment in local minima was not completely avoided’. Martin et al (2004) used 2D images with transforms up to 10 mm and 15° and 0.5 $\leq q \leq 0.9$. Khader and Hamza (2011) used 3D images with transforms up to 40 mm and 40° and $q = 2$. Amaral-Silva et al (2014) used 3D images with transforms up to 12 mm and 15°, and 0.1 $\leq q \leq 3$.

Over the past two decades, existing published investigations assessing MI corroborate it as a valid and robust image registration technique. However, the local extrema problem still restricts the capture range, challenging MI automatic and long-range registration. To overcome this long-range challenge human intervention is often used to manually pre-align and post-process the images checking for failed registrations.

1.3. Mutual information origin

Shannon and Weaver (1963) defined MI originally as $R = H(x) + H(y) - H(x, y)$, where $R$ is the bit rate of a communications channel, $H(x)$ and $H(y)$ are the entropies of the two sources, $x$ and $y$, and $H(x, y)$ is the sources’ joint entropy. Shannon also defines a source $x$ entropy as $H(x) = - \sum_i p_i \log p_i$ and the joint entropy as $H(x, y) = - \sum_{ij} p_{ij} \log p_{ij}$ where $i$ and $j$ are events from the sources $x$ and $y$ and $p_{ij}$ are the occurrence probability of the event $i$.

1.4. Generalized entropy

Tsallis (1988) proposed a generalization of the Boltzmann–Gibbs entropy applicable to the Shannon entropy and the MI concept (Borland et al 1998). Tsallis’ entropy is defined as $H_q(x) \equiv k (1 - \sum_i p_i^q) / (q - 1)$, where $k$ is a conventional constant, and $q \in \mathbb{R}$ is the entropic index. Using the assumption of $k = 1$ from Shannon, we finally get $H_q(x) = (1 - \sum_i p_i^q) / (1 - q)$, noting that $\lim_{q \to 1} H_q(x) = H(x) = - \sum_i p_i \log p_i$. Tsallis (1994) also defines the joint entropy for two independent systems, due to the pseudo-additivity, as:

$$H_q(x, y) = H_q(x) + H_q(y) + (1 - q) H_q(x) H_q(y).$$

1.5. Registration process

The figure 1 block diagram represents the basic registration process. The Metric block analyzes both image inputs, the fixed, $u(x)$, and the transformed moving, $T(v(x))$, providing a scalar output measuring how similar the images are. The optimizer essentially evaluates, on each iteration, how the metric signal changes, depending on the parameters $T$.

In an ideal scenario, the optimizer produces a sequence $T_i$ that progresses towards the best metric signal $F_{\text{mi}}(\cdot)$, i.e. supposedly, the best image registration. This final set of parameters $T$, at registration end, is called $\widehat{T}$.

In this way, the registration, i.e. optimization of the parameter set $T$, is driven by the similarity metric signal. Thus, the registration fails with poor similarity metrics even when one uses a good optimizer.

The metric signal changes concerning each $T$ input provided, i.e. $\partial F_{\text{mi}}(\cdot) / \partial T$, should be analyzed to improve the registration scheme. The block diagram in figure 1 shows the registration process with the Metric block comparing the Fixed and transformed Moving images. The Optimizer maximizes the Metric signal by changing...
the $T$ parameters and, consequently, the transformed Moving images, creating a loop iteration. Our investigation focuses on the $F_m(\cdot)$ output, the red-shaded region, and not the $\hat{T}$ output. The reason is that a better $F_m(\cdot)$ space leads to a better $\hat{T}$ solution.

### 1.6. Paper proposal

In this paper, we comparatively analyzed the MI metrics using our implementation of both Shannon MI and Tsallis GMI, and the ITK software (McCormick et al. 2014) implementation of Shannon MI, based on (Mattes et al. 2001). The evaluated transformation ranges were $[-150, 150]$ mm for translations, $[-180^\circ, 180^\circ]$ for rotations, $[0.5, 2.0]$ for scaling, and $[-1, 1]$ for skewness, all four transformations evaluated in a three-dimensional space, in order to exhaustively understand the entire transformation space, in the context of brain MRI affine registration. The Tsallis $q$ entropic index was evaluated in the $0 \leq q \leq 3$ range.

Our focus is not to solve a single medical need in the registration field but to investigate GMI functions, with a broader and more precise understanding of them, to understand how they can improve image registration.

### 2. Methods

#### 2.1. Images

Images from two databases were used, i.e. the WU-Minn Human Connectome Project (HCP 1200) young adults (Van Essen et al. 2011, Glasser et al. 2013) and the NAMIC Registration Library. One can find the detailed description and the acquisition protocols at the HCP website (see https://humanconnectome.org/hcp-protocols-ya-3t-imaging). Only the MRI 3T pre-processed structural images were selected from the HCP data. The acquired T1w images have the following parameters: TR = 2400 ms, TE = 2.14 ms, flip angle = 8 degrees, and bandwidth = 210 Hz Px$^{-1}$. On the other hand, T2w images have the following parameters: TR = 3200 ms, TE = 565 ms, variable flip angle, and bandwidth = 744 Hz px$^{-1}$. Both T1w and T2w have a size of [256, 320, 320], FOV of $224 \times 224$ mm, and isotropic voxel spacing of 0.7 mm. Initially using only the randomly chosen patients, 172 635 and 211 821, and later used the entire dataset for the Monte Carlo experiment (section 2.7).

Images N2_T1, N2_T2, and N4_T1, from the NAMIC Registration Library Case 19 (see https://na-mic.org/wiki/Projects:RegistrationLibrary:RegLib_C19), provided by the UNCMidas Database of healthy volunteers, with a size of [176, 256, 176] and isotropic voxel spacing of 1 mm, were also used in the first stages of Mattes MI analysis reducing from 3 days of computing time using HCP images to only one day of computing time.

#### 2.2. GMI additivity

We evaluate the following two GMI expressions in this investigation:

\[
I_q(x, y) = H_q(x) + H_q(y) - H_q(x, y),
\]

\[
I_q(x, y) = H_q(x) + H_q(y) - H_q(x, y) + (1 - q)H_q(x)H_q(y)
\]

equation (2) is the original Shannon formulation for additive entropies, here transposed to Tsallis entropy as is and referred as the ‘additive’ GMI, while equation (3) is the ‘nonadditive’ GMI, used in the previous Tsallis registration studies mentioned in section 1. To the best of our knowledge, Tsallis additive GMI, i.e. (2), was not used for image registration in the literature.

However, (1), from where (3) derives, is only defined for independent systems, where $I_q(x, y) = 0$. In order to register images with MI, we need to have mutual information, i.e. $I_q(x, y) > 0$, making our system dependent.

Furthermore, Tsallis (2009) explains that, ‘the non-additive entropy $S_q (q > 1)$ can be extensive for a special value of $q$’, with the notation $S_q$ used in physics for entropy. Equation (2) can be used with Tsallis entropy, as long as it is used with this special value of $q$ that changes a normally nonextensive, or nonadditive, system into an extensive, or additive, system, in the context of entropy, and consequently MI.

#### 2.3. Histogram binning

The algorithm used in this paper for Tsallis and Shannon registration does not use by default histogram binning. Since the histogram is a sparse vector, or matrix in the case of joint entropy, modern data structures that benefit from sparsity were used to better manage computer memory. However, as further analyzes of transformations shown, histogram binning can improve the metric signal on some cases, e.g. rotation, shown in section 3.2.

Histogram binning is implemented by disabling the least significant bits (LSB) of the images, in a similar way done by Collignon et al. (1995). The images voxels were converted to 16 bits unsigned integers (uint16_t), normalizing the gray levels to spread them over this 16 bits space, and then applied a simple bitwise AND operator between the voxels values and the binning bitmask. The notation used in this paper is for the number of
bits left in the image, so when we use 6 bits binning histogram, we left 6 bits on both images, using a bitmask of 1111.1100.0000.0000, and the joint histogram will have $6 \times 6 = 12$ bits, with 4096 bins.

2.4. Metric image visualization

We mapped transform parameters into a 3D output space to understand the metrics regarding geometric transforms, e.g. a cube of $[-150, 150]$ mm in all three axes, except for the scaling that was mapped to a cube with $[-1, 1]$ range in the three axes, with the mapping function:

$$s = (1 + x)^{-1} \text{ if } x < 0; \quad s = 1 \text{ if } x = 0; \quad s = (1 + x) \text{ if } x > 0,$$

where $s$ is the real scaling factor and $x$ is the cube coordinate.

This cube space was discretized using 51 points in each direction, giving a dimension of $51 \times 51 \times 51$. Each voxel of this cube represents a single unique transformation parameter $T$, e.g. a translation of $[6, 12, 24]$ mm in the axes $x, y, z$, respectively, would be mapped to point $[26, 27, 29]$, and the point $[25, 25, 25]$ would be the center, i.e. a $[0, 0, 0]$ mm translation.

After defining the cube dimensions, and all the $T$ parameters associated with each cube’s voxel, this cube is populated with the metric signal, $F_m(\cdot)$, for each of the $T$ parameters, allowing a later inspection of the cube information and a comparison of multiple metrics signals, i.e. a comparison of ITK Mattes, Shannon and Tsallis MI functions.

2.5. 3D visualization using isosurfaces

Figure 2 introduces the 3D-isosurface visualization, in figure 2(a), representing the data collected in section 2.4, with an opacity effect to highlight the local minima. The MI profiles, in 2D plots, as is usual in the literature, are shown in figure 2(b), and a zoom of the 2D plots in figure 2(c). Each tube in the isosurface 3D plot (figure 2(a)) represents a pathway used to plot the MI function in figures 2(b), (c). We used pathways centered on the image axes, one pathway in a diagonal over plane $z = 0$, and one pathway in a diagonal from the axes minimum to their maximum. The dashed lines on the 2D plots are the usual pathways used in literature, centered on the image axes, without any local minima on them. Only the solid lines, which are profiles taken along the diagonals, show local minima.

This comparison of line plots and isosurfaces illustrates the problem of analyzing only a fraction of the space, as is done in the literature. Even with the difficulties imposed by the isosurface’s complexity, it provides way more information to the researcher, and after some familiarity with it, one can perceive in a glance, in the convoluted contours, the local extrema points. Furthermore, the gradient lines are normal, i.e. perpendicular, to the isosurfaces, and the most common MI optimization method is the gradient descent, making this 3D plot analysis an intuitive way to understand how and why a gradient descent optimizer succeeds or fails image registration.
2.6. Registration simulation

The registration capability of the metrics was determined using a naive algorithm that simulates a gradient descent registration, using the cube images generated in section 2.4. The algorithm starts using the center of the parameter $T$ space, i.e. the gold standard, as a seed. Then it grows the registration space around the seed if their neighbors are lesser since that would give a gradient pointing to the seed. Each incorporated voxel will act as a seed in the next iteration, with the algorithm stopping when there is no more growth.

This algorithm does not guarantee the same results as in the real scenario since the gradient descent’s learning rate is not simulated, i.e. it is equivalent to using a constant learning rate equal to the image spacing. However, despite those algorithm limitations, it can estimate, quantitatively, each metric’s capability of registration in the transformation scenario studied, e.g. a scenario with only the translation transforms.

Table 1. Registration scenarios using Monte Carlo simulation.

| Name            | Fixed | Moving | Subject   |
|-----------------|-------|--------|-----------|
| T1              | T1    | T1     | Same      |
| T2              | T1    | T2     | Same      |
| Randomized T1   | T1    | T1     | Randomized|
| Randomized T2   | T1    | T2     | Randomized|

![Figure 3. Isosurfaces of the MI function using translation parameters. Jet colorbar used, minimum values as blue and maximum as red.](image)
Furthermore, this provides more quantitative value from the metric images generated from section 2.4 and is very fast to calculate since the algorithm is simple.

2.7. Monte Carlo
Monte Carlo simulations were carried out by probing translation parameters using a normal distribution with a standard deviation of 50 mm, giving a three-sigma region (99.7% of the transforms) within $[-150, 150]$ mm, in each one of the translation axes. Four scenarios were simulated for the image registrations, enumerated in table 1. The first two scenarios used a single random subject image, and the last two scenarios using a set of double randomized subjects from the HCP dataset for each registration trial.

These simulations provide more reliable assessments than the ones from section 2.6, and the randomized scenarios simulate inter-subject and inter-modality clinical registrations. An essay consists of at least 1,000 registration trials for each metric tested, counting different entropic indexes as different metrics. In addition, we logged each essay’s start and end parameters, fixed and moving images used, time spent to register, and a flag if the registration is within 5 mm of the center to allow further analysis.

3. Results
All results presented used the nearest neighbor’s interpolation unless noted otherwise since it abbreviates the computational needs without losing too much registration quality. In our Shannon and Tsallis implementation, results for other interpolations were provided for the Monte Carlo in section 3.6. An exhaustive list of results can be found in the supplementary material available online at stacks.iop.org/PMB/67/055006/mmedia.

The entropic parameters $q$ shown are the most interesting cases, i.e. best and worst. The supplementary material also has an exhaustive list of $q$ values tested. Although there is some work to determine the best $q$ value for a transformation. Once we have this $q$ value defined, other similar images can be registered using it.

The registration of an image using MI is the search for the maximum mutual information. However, most optimizers in computer science are programmed to search for the minimum value in a function. In this way, some metric functions have their sign inverted, i.e. $F_q(x) = -F_q(x)$, to work with those optimizers.

3.1. Translation
Figure 3 shows the MI isosurface’s contours for the translation transformation on the HPC dataset. Mattes (figure 3(a)) have several local minima that prevent long-range registration, i.e. the local minimum traps the optimization algorithm. Shannon MI does not have local minima except for the solution, although it is challenging for the optimizer to work on the nonsmooth surfaces. Tsallis has several local minima on the nonadditive version. However, the Tsallis additive metric has just the solution and smooth surfaces that provide an excellent registration gradient.
3.2. Rotation

Rotation isosurfaces are shown in figure 4, presenting a different result than the translation ones. Both (a) Mattes and (b) Shannon present similar results, with local minima on the corners and an acceptable registration range. Tsallis metric presents an unusual periodicity with no histogram binning (c)–(d) on the multiples of 90°. With histogram binning, this periodicity is reduced, as seen on (e) with 8 bits binning. Results show that the best binning on the HCP dataset is 4 bits, with stable results over a wide range of entropic indexes, as seen on (f)–(h).

![Figure 5. Isosurfaces of the MI function using scaling parameters, Jet colorbar used, minimum values as blue and maximum as red.](image)

3.3. Scaling

Scaling transform (figure 5) performs well using Mattes. Tsallis, by itself, performs poorly (figure 5(c)) in both additive and nonadditive forms. However, using histogram binning with 10 bits, as in the rotation case, improves Tsallis and Shannon MI, allowing them to compete with Mattes. Still, nonadditive Tsallis with an entropic index near Shannon is needed. The range $0.9 \leq q \leq 1.1$ performs well, while values outside this range performed poorly in this scenario. Therefore, using Tsallis GMI, in additive or nonadditive form, with an entropic index away from $q \rightarrow 1$, yields poor performance and constrains the registration range. The Mattes outperforms Shannon, but both MI metrics can register all the space and do not present local minima other than the solution.

3.4. Skewness

Skewness transforms isosurfaces shown in figure 6 indicates good performance for both Mattes and Shannon. The nonadditive Tsallis only performed well using $0.8 \leq q \leq 1.1$, while additive Tsallis performed well for $q > 1$.

3.5. Registration simulation

The rates of successful registration for each metric and transform are presented in table 2, estimated using the naive algorithm presented in section 2.6. This estimation shows that all transformations, except rotation, could be registered over the entire evaluated range. Histogram binning is essential for rotation registration as it raises Shannon’s range from 81.4% to 87.4% when going from no binning to 2 bits binning. The maximum rotation range is 88.2% using Tsallis nonadditive with $q = 1.3$ and 4 bits binning. However, those results use the same image as fixed and moving, allowing comparisons between metrics but not necessarily those results reflect on actual clinical registration made with different images, subjects, and modalities.
3.6. Monte Carlo translation

Figure 7 shows the Monte Carlo translation registration results in a scatter plot representing the registration error, i.e. the distance between the solution and the gold standard. ITK Mattes performed poorly in all scenarios, with its registration's end parameters, $\hat{T}$, far from the gold standard. Local minima problems in the metric appear in the scatter plot as marks concentrated on the minimum regions. An example of this problem is the Mattes T2 scenario, where we have a local minimum of about the 75 mm mark, also appearing in the Mattes T1 scenario. These metrics' drawbacks can be observed on the scatter plot, also affect the statistical results in table 3, with means values far from the center, i.e. zero, and large standard deviations.

Tsallis outperforms ITK Mattes, and even Shannon, in all scenarios as Shannon produces more failed results than Tsallis in the Monte Carlo experiments made. The failure rates are even more significant in the

| Metric          | $q$ | Binning | Translation | Rotation | Scaling | Skewness |
|-----------------|-----|---------|-------------|----------|---------|----------|
| Mattes          | 1.0 | Yes     | 65.8%       | 86.3%    | 98.8%   | 100.0%   |
| Shannon         | 1.0 | No      | 100.0%      | 81.4%    | 99.4%   | 100.0%   |
| Shannon         | 1.0 | 2 bits  | 56.3%       | 87.4%    | 97.4%   | 99.8%    |
| Tsallis Additive| 0.5 | No      | 0.2%        | 28.3%    | 30.4%   | 6.9%     |
| Tsallis Additive| 1.05| No      | 100.0%      | 74.8%    | 100.0%  | 100.0%   |
| Tsallis Additive| 2.0 | No      | 100.0%      | 49.6%    | 70.7%   | 100.0%   |
| Tsallis Nonadditive| 0.5 | No      | 6.7%        | 74.0%    | 70.1%   | 89.4%    |
| Tsallis Nonadditive| 2.0 | No      | 10.1%       | 0.0%     | 17.4%   | 0.1%     |
| Tsallis Nonadditive| 1.3 | 4 bits  | 84.7%       | 88.2%    | 99.9%   | 100.0%   |
| Tsallis Additive| 1.3 | 4 bits  | 100.0%      | 86.0%    | 99.8%   | 100.0%   |

Figure 6. Isosurfaces of the MI function using skewness parameters: (a) Mattes, (b) Shannon, (c) Tsallis GMI nonadditive $q = 2$, (d) Tsallis GMI additive $q = 2$, and (e) Tsallis GMI nonadditive $q = 1.5$. 

Table 2. Comparison of different metrics with the registrable space, using the naive algorithm from section 2.6: $q$ is the entropic index, best results are shown in bold.
Figure 7. Monte Carlo registration essays for multiple metrics and scenarios. Each gray diamond represents a single registration result. (Close to the left is better in this graph).

Table 3. Monte Carlo results, means and deviations, in mm. Registration capability is the percentage of registrations that ended within this distance in relation to the gold standard. Interpolation is nearest-neighbor, unless noted FL for FastLanczos.

| Scenario     | Method        | Mean  | Deviation | 1 mm   | 3 mm   | 5 mm   |
|--------------|---------------|-------|-----------|--------|--------|--------|
| T1           | Mattes        | 48.08 | 72.24     | 64.70  | 65.80  | 66.00  |
|              | Shannon       | 0.68  | 5.38      | 97.04  | 99.61  | 99.62  |
|              | Tsallis (1.7) | 0.48  | 3.31      | 99.33  | 99.97  | 99.97  |
|              | Tsallis FL (1.2) | 0.39  | 0.15      | 98.90  | 100.00 | 100.00 |
| T2           | Mattes        | 55.14 | 72.01     | 58.15  | 58.25  | 58.25  |
|              | Shannon       | 1.48  | 8.69      | 97.20  | 99.00  | 99.10  |
|              | Tsallis (1.3) | 0.45  | 0.10      | 99.90  | 100.00 | 100.00 |
| T1 random    | Shannon Nearest | 1.62  | 10.88     | 94.09  | 98.21  | 98.26  |
|              | Tsallis (1.3) | 0.63  | 6.04      | 98.87  | 99.91  | 99.91  |
| T2 random    | Mattes        | 45.23 | 56.94     | 0.10   | 1.10   | 5.05   |
|              | Shannon       | 7.46  | 16.81     | 2.10   | 37.15  | 56.50  |
|              | Tsallis (1.3) | 1.51  | 0.71      | 20.85  | 95.80  | 99.75  |

Figure 8. Monte Carlo registration essays as parallel coordinates, each line represents a registration essay. ‘Start’ is the starting distance from the gold standard and ‘End’ is the final distance achieved, an ideal registration will come from anywhere on the left and end on the right bottom where the gold standard is on this graph.
Figure 9. Monte Carlo rotation registration essays for multiple metrics and scenarios using rotation versors smaller than $\pm 0.2$ ($\approx \pm 23^\circ$). Each gray diamond represents a single registration result. (Close to the left is better in this graph).

Figure 10. Example of affine registration between HCP subject 172 635 T1 MRI and 901 038 T2 MRI, using ITK Mattes, Shannon and Tsallis. 3D renders of subjects (top) and checkboard axial views from moving and registered images (bottom).
Randomized T2 experiments, the most critical and challenging scenario for the similarity metrics, registering a T1 image with a T2 image from different random subjects.

Another result from figure 7 is in the usage of heavier computational interpolation algorithms. For example, the Tsallis 1.2 FL essay uses the Lanczos interpolation algorithm with fast trigonometric functions, with slightly better results than the nearest-neighbor interpolation, removing the few remaining outliers.

Table 3 shows the success rate of the similarity metrics depending on the acceptable final error, i.e. the threshold for a successful registration. Mattes have a poor performance in the randomized T2 scenario, even with an acceptable error of 5 mm. We obtained 5.05% success for Mattes, 56.50% for Shannon, and 99.75% for Tsallis, with $q = 1.3$, and within the 5 mm distance threshold. This 5 mm error is considered acceptable for a first and coarse registration stage, followed by a finer stage.

Figure 8 shows results from the experiments using a parallel coordinates plot with the starting distances of each random sample and the corresponding end distance, i.e. the final registration distances.

3.7. Monte Carlo rotation

Figure 9 shows the Monte Carlo rotation registration in a scatter plot representing the registration error as an Euclidean distance between the final registration parameters and an identity transformation, i.e. no rotation made using the image presented on the dataset. Table 4 shows the same data as above in a tabular format and some registration capacity considering some acceptable errors. All rotation results presented used initial random rotations with versors within the $[-0.2, 0.2]$ range.

3.8. Affine registration

Although our focus is an empirical and objective analysis of GMI, there is a need and interest in actual registration results. An example of affine registration can be seen in figure 10, where Tsallis provides a different registration result than ITK Mattes and Shannon. This difference can be helpful or not, depending on the medical application and later registration stages, e.g. a deformable spline registration.

4. Discussion

This study assessed Tsallis GMI as a similarity metric in medical image registration compared to Shannon and the ITK Mattes. We presented evaluations of the metrics’ signal for translation, rotation, scaling, and skewness with favorable GMI metric outcomes.

The studies discussed in section 1.1 compromised the MI metric due to a lack of computational power at their time. To compute all voxels would take too much computational time, so the most common solution was to compute a sample of the image voxels. Also, histogram binning was introduced to limit the memory structures needed to compute the probabilities and entropies associated with MI and registration.

The emerge of parallel computing allowed us, with high bandwidth GPUs, to sweep all the translation space, as explained in section 2.4, within one hour, making the experiments included in this study possible. To make it more precise, it is possible, by using GPU computing, to make $51^3 = 132,651$ image transformations, calculate gray levels probabilities from all voxels values of both images, and all the entropies necessary for the MI metrics and entropic indexes values of interest within an hour.

Speed comparison of GPU and CPU algorithms was not the focus of our research, but it is important to notice the performance gain in moving to parallel computing algorithms. In our case, we could evaluate 116.21 values per second using an NVIDIA GTX 1060 card, each value consisting of a nearest neighbor translation transform of the image and the MI calculation from both images, using the ITK platform on an Intel® XEON 6130 Gold CPU, we achieve 0.8388 values per second with only eight cores, and by using all 64 cores available in

| Scenario       | Method      | Mean   | Deviation | 0.01  | 0.05  | 0.1   |
|----------------|-------------|--------|-----------|-------|-------|-------|
| T1             | Shannon     | 0.0005 | 0.0017    | 99.10 | 100.00| 100.00|
| Randomized T1  | Shannon     | 0.0296 | 0.0396    | 42.70 | 81.10 | 96.10 |
| Randomized T2  | Shannon     | 0.0456 | 0.0548    | 34.20 | 67.40 | 87.50 |
| Randomized T2  | Tsallis     | 0.0016 | 0.0017    | 100.00| 100.00| 100.00|

Table 4. Monte Carlo rotation results using versors smaller than $\pm 0.2$ ($\pm 23^\circ$); means and deviations are represented as a euclidean distance to the identity transformation. Registration capability is the percentage of registrations that ended within this distance. Interpolation is nearest-neighbor.
our lab, we achieved only 2.3060 values per second. The comparison of a consumer-grade GPU against a high-end CPU gives a speed-up of 50.39, and if we compare it to an eight-core CPU, the speed-up is 138.54.

Although we achieved good results using Tsallis GMI metrics, the entropic index and additivity demand a sensible tuning and further study depending on the images used, as wrong choices can lead to local extrema. The 3D isosurfaces plots are an excellent tool for analyzing local extrema points that narrow the registration range. The typical approach on registration uses a unique $q$ entropic index and additivity set over the entire parameter space, i.e. for all the different geometric transformation parameters. However, this approach can show spurious results depending on the methodology used, as one Tsallis setting may be helpful for the translation but fails for the rotation.

Tsallis, in his work on discrimination between two hypotheses, noted the need for a good entropic index choice: "It is expected that, for every specific use, better discrimination will be achieved with appropriate ranges of values of $q$" (Tsallis 1998).

**4.1. Registration simulation**

Tsallis outperforms, on the translation scenario, other metrics, even without any histogram binning. As shown in figure 3 and table 2, Mattes has problems in the translation scenario while having good performance on the other scenarios. Shannon MI has a fair overall result, with only its rotation performing marginally worse than Mattes. Tsallis GMI metric outperforms on rotation when using $q = 1.3$, nonadditive form, and histogram binning with 4 bits. Scaling has shown a slight improvement by using Tsallis, and skewness performed well on all metrics.

**4.2. Monte Carlo**

The results from Monte Carlo were auspicious (table 3), reaching an ideal score if we consider results within 3 mm of acceptable distance on the scenarios of T1 and T2 from the same subjects. One can see a real problem with the current ITK Mattes implementation, especially on randomized T2, the most challenging scenario, with double randomized subjects, and Mattes has only 5.05% success within 5 mm. In comparison, Shannon has 56.5%, and Tsallis has a 99.75% success rate. The difference in registration quality is better shown in figure 7, where we can see the scatter plot showing all the Monte Carlo results. Mattes have several registration results above the 50 mm region and some local minima results for Mattes T2 around 75 mm. The Monte Carlo results for Tsallis GMI are close to 0 mm, i.e. the gold standard. Tsallis GMI results usually presented no outliers, i.e. failed registration, except for the few essays with Tsallis GMI 1.7 T1. Figure 8 compares the Randomized T2 results where Mattes has some problems, becoming farther to the gold standard than they started, as the metric pushes the registration optimizer the wrong way. One can also observe Shannon with a few problems, to a lesser degree than Mattes, while Tsallis GMI shows outstanding performance on this experiment.

Figure 8 indicates the superiority of Tsallis in this randomized T2 scenario since all starting distances converge to the center position at the registration end, i.e. the registered image is very near to the gold standard. In contrast, for Shannon, we have some registrations leading to worse distances than it started, and, on a different level, we have even worst results for Mattes.

Figure 9 also shows improvements to the rotation registration when using Tsallis entropy for small angles, i.e. versors smaller than 0.2 ($\approx 23^\circ$). There is a tiny improvement for the T1 scenario. However, for randomized T1 and T2 scenarios, there was a clear improvement in the final registration, noticeable in the mean values in table 4.

Experiments using greater angles, with versors smaller than 0.5, were also made but with no improvement and some degradation of the registration when using Tsallis compared to Shannon. This registration degradation clearly shows that registration in the entire rotation parameters space is not possible with a gradient descent optimizer and Tsallis metrics as tried in this study. However, this does not discard the improvement in a small angle scenario relevant to clinical usage since the physical alignment made before the imaging process reduces the rotation needed to register the images.

Those Monte Carlo results put GMI as a competitive alternative to other techniques if we compare those results with other studies, as So and Chung (2017) registered 3D CT and MR images from RIRE (West et al 1996) with translations up to 150 mm, except in the $z$-axis with 70 mm, and rotations up to 30° with an 85.67% success rate within 4 mm. The statistical sample provided by the HCP dataset, with 1113 subjects, is way more significant than the RIRE subset used with only six subjects, supporting the argument of GMI fully automatic image registration with long-range transformations.

There are more recent research for better metrics, although the range of transformation investigated is much narrower than our proposal, as is the case of Hu et al (2021) that used reinforced learning to register 2D slices of MR and CT with translations up to 30 mm, rotations up to 45°, and scalings in the [0.75, 1.25] range, Guryanov and Krylov (2017) used a MI acceleration to register 2D slices of CT and MR from RIRE with translations up to
30 pixels, i.e. 38.4 mm, rotations up to 30°, and scalings in the [0.8, 1.2] range, Panda et al (2017) used an evolutionary algorithm to register 2D MR slices with translations up to 45px, i.e. 56.25 mm, and rotations up to 40°, Sedghi et al (2021) used deep learning to register 3D MR images with translations up to 25 mm and 0.2 radians (≈11.4°) rotations and Frysch et al (2021) used Grangeat’s relation to register 3D MR images with translations up to 30 mm and 30° rotations. Finally, Markiewicz et al (2021) compares 3D MR and PET image registration of multiple software packages, but with translations up to 10 mm and rotations up to 10°.

5. Conclusion

This paper analyzed different MI similarity metrics, the Mattes, Shannon, and Tsallis MI metrics, with 3D images from known datasets and 3D-isosurfaces contours to better view the local extrema points that challenge image registration. Moreover, we developed a technique for image registration using different Tsallis metrics, i.e. additive and nonadditive, and multiple entropic indexes. The analysis of Tsallis additive GMI equation (2), ignoring the formality of mutual information discussed in section 2.2, shows that using the classic Shannon MI equation with Tsallis entropy, called additive Tsallis in this paper, may benefit in some scenarios, e.g. in the translation. In contrast, we needed to use the Tsallis nonadditive equation with histogram binning to achieve good results in other scenarios, e.g. rotation.

Our results suggest that the best approach for image registration using GMI is to use a specific q entropic index for each of the parameters elements, or dimensions, and alternating between additive and nonadditive Tsallis, depending on the parameter being optimized. To better explain, each of the transforms groups, i.e. translation, rotation, scaling, and skewness, needs its value of q and its setting of additivity. From our experimental data, one wants q > 1 and additive for translation, q = 1.3, 4 bits binning and nonadditive for rotation, q = 1.04 and additive for scaling, and q > 1 and additive for skewness. Although we only assessed translation through Monte Carlo simulations, one can reason towards similar results from the remaining transformations, i.e. rotation, scaling, and skewness, as the Monte Carlo results (see section 3.6) corroborates the registration simulation results (see section 3.5) that should hold valid for those other transformations.

Our experiments’ immediate result is to rethink the computational approach since we do not need shortcuts, like voxel sampling or histogram binning. Instead, our current computational power allows complete scanning of all the available data in images, providing, with more data, a better overall registration assessment. Histogram binning still has its place on registration since it can, as the rotation results show, make the space quasi-convex and without local extrema points in some situations.

When we added double randomized subjects and inter-modality with the Monte Carlo experiments, we observed that Tsallis was significantly better than Shannon, not equal as registration capability alone shown, mainly because the image set used in Monte Carlo is broader than the set used for registration capability tests, reflecting on the quality of the results provided, which better reflects reality.

We hope further studies can benefit from the analysis tools developed in this paper, like the 3D isosurfaces, and better inspect the metric’s space under research to evolve it, looking for metrics with smoother surfaces and without local extrema, helping, in this way, the optimizer to achieve a better registration. Although, in some techniques, like deformable registration, we have a higher number of parameters that will challenge the visualization, having simulations of how the metric behavior changes concerning the parameters changes can help researchers to improve their metrics or even choose more suitable optimizers for their metrics’ signal.

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