Topologically Constrained Template Estimation via Morse–Smale Complexes Controls Its Statistical Consistency

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Abstract. In most neuroimaging studies, one builds a brain template that serves as a reference for normalizing the measurements of each individual subject into a common space. Such a template should be representative of the population under study, thus avoiding bias in subsequent statistical analyses. The template is often computed by iteratively registering all images to the current template and then averaging the intensities of the registered images. Geometrically, the procedure can be summarized as the computation of the template as the “Fréchet mean” of the images projected in a quotient space. It has been argued recently that this type of algorithm could actually be asymptotically biased and therefore inconsistent. In other words, even with an infinite number of brain images in the database, the template estimate may not converge to the brain anatomy it is meant to estimate. Our paper investigates this phenomenon. We present a methodology that spatially quantifies the brain template’s asymptotic bias. We identify the main variables that influence inconsistency. This leads us to investigate the topology of the template’s intensity level sets, represented by its Morse–Smale (MS) complex. We propose a topologically constrained adaptation of the template computation that constructs a hierarchical template with bounded bias. We apply our method to the analysis of a brain template of 136 T1 weighted MR images from the Open Access Series of Imaging Studies (OASIS) database.

Key words. differential geometry, bias, statistics, medical imaging, template

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Introduction. In neuroimaging, as well as in many other medical image analysis domains, a template is an image representing a reference anatomy. A template is computed from a database of brain images to serve as the brain image “prototype” for further analyses.

Computation of a brain template. Various methods exist for estimating a brain template from a given database [15]. One is to select one image from the database as the template. If the selected subject’s anatomy is far from the population mean anatomy, the template is necessarily biased toward this specific individual. Thus, the template fails as a representative of the population. This is why researchers prefer the creation of an “unbiased template” that represents the average anatomy better.

Such an “unbiased” template is often constructed by performing an iterative averaging of intensities and deformations [17, 20, 24]. One initializes with a template chosen among the subject images. Then, during each iteration, one registers the subjects to the current template

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and computes the mean deformation. The new template is computed as the mean intensity of the subject images, deformed with the mean deformation. This procedure does not favor any subject’s image as long as it does not fall into a local minimum. In this sense, the procedure is called “unbiased.”

The computed brain template may look blurred or sharp depending on the design chosen for the registration in the above iterative procedure. If the algorithm is designed using linear registration, the template may appear blurred. In contrast, if one uses diffeomorphic registration, the template is more likely to look sharp, and the sharpness depends on the amount of regularization used [15].

**Purpose and desirable properties of the computed template.** Computing a template is often the first step in medical image processing. In general, the template is used as a standardized 3D coordinate frame where the subject brains can be compared. The subjects are then characterized by their spatial diffeomorphic deformations from the template. These deformations may then serve in a statistical analysis of the subject shapes [6]. One studies the normal and pathological variations of the subjects with respect to the template. The deformations also facilitate automated segmentation by mapping the template’s already segmented regions into each subject space.

What are the desirable properties of the brain template, with respect to the applications mentioned above? First, the template should be representative of the population, removing any bias toward a specific subject during the analysis [5, 7, 10]. Second, the template should be sharply defined, so that subtle anatomical structures can be easily observed or segmented.

**The brain template, an inconsistent estimator of the unique brain anatomy.** However, the two desirable properties cannot be fulfilled simultaneously: there exists a trade-off akin to the standard bias-variance trade-off in statistical learning.

This trade-off can be understood intuitively. Consider a database of brain images divided into two groups that have different topologies. The first group has subjects with three sulci, i.e., depressions or grooves in the cerebral cortex, in a specified brain region. The second group has subjects with only two sulci in the same region. A sharply defined template has to decide on a specific topology in this brain region, i.e., whether it shows two or three sulci. Therefore, it might not correctly estimate the brain anatomy of this population, which might be problematic for the following applications in neuroimaging. For example, during a statistical analysis, registering the subjects with the three sulci topology to a template that has chosen a two sulci topology might not be reasonable [7]. A sharp template is only meaningful if the anatomical structures shown are representative of the whole population, i.e., if the population is homogeneous.

The trade-off has been emphasized in recent studies. In the classical approach [2], an initial assumption states that there is a unique (brain) anatomy shared by the population. The subjects are then modeled through a generative model as random deformations of the unique brain anatomy, observed with additional noise. The unique brain anatomy is a parameter of this model. The template computation is interpreted as its estimation. One can ask about its asymptotic bias: does the template converge to the unique brain anatomy for a database with an infinite number of images?

This question has been investigated for signals (i.e., 1D images). Some authors prove the asymptotic unbiasedness of the template under the simplifying assumption of no measurement
error on the observed signals [27]. Other authors have already provided examples of asymptotic bias, and therefore inconsistency, when there is measurement error [2]. Their experiments show that the template can converge to pure noise when the measurement error on simulated signals increases. Bias is shown to occur in [8] for curves estimated from a finite number of points in the presence of noise.

Recently, an asymptotic bias has been shown in the setting of Lie group actions [35, 34]. Our argument, shown in an abstract geometric context in [35, 34] but adapted here to brain images, is as follows. We look at the subspace defined by all brains with the same shape as the unique brain anatomy. We show that the curvature of this space, at the scale of the measurement noise, introduces a bias on the brain template.

Using topology to investigate the brain template’s asymptotic bias. We want to link (i) the fact that a population with two groups of different brain topologies cannot be accurately represented by a sharp template with (ii) the mathematical results on the template’s bias as an estimate of the anatomy shared by the population. The framework of [35] is based on the quotient of the observed data by the action of a Lie group. The data in our case are the brain images, and the Lie group action is the action of diffeomorphisms on these images. Quotienting the images by the action of diffeomorphisms amounts to filtering out any information that is invariant under diffeomorphic deformations. Thus, the quotient gives the topology of the images’ level sets. This means that we could quantify the brain template’s asymptotic bias using a representation of its topology.

Quantifying the bias could enable us to decide when and where a sharply defined template makes sense. We want a sharp template in brain regions where the intersubject anatomical variability is low and a fuzzier template when this variability is higher. Alternatively, we could consider computing several sharp brain templates using mixtures. This discussion boils down to the following question: When is it reasonable to assume that a unique brain anatomy represents the whole subject population?

Furthermore, we could think about controlling the brain template’s asymptotic bias by constraining its topology. Topological representations of images have been used with various objectives in the literature. For example, [12] uses a topological representation for classification of autism versus normal brain images. Topological constraints are also used for segmentation where the reconstruction of the cortical surface needs to match the brain anatomy [21, 30, 31]. However, topological representation of images or topological constraints on images have not been used to study and enforce a statistical property, such as asymptotic unbiasedness.

Contributions and outline. We use a topological representation of images, the Morse–Smale (MS) complex, to investigate and control the asymptotic bias of the brain template. We make three main contributions in this paper.

First, we show how to combine geometry and topology to tackle a statistical problem in neuroimaging. We show how the MS complex is a computational representation of statistical concepts of the template computation procedure. Second, we analyze the template as an estimator of brain anatomy and quantify the asymptotic bias. This leads us to discuss the initial assumption of a unique anatomy. Third, we present an adaptation of the template computation algorithm that bounds the bias, through topological constraints, at the price of constructing a “smoother” template.

Section 1 presents the geometry and the topology of the template computation. We
emphasize the variables that describe the bias of the brain template. Section 2 presents the chosen computational representation of these variables through MS complexes. Section 3 leverages the previous computational model to spatially identify the biased regions of the template. We thus propose an adaptation of the template computation with topological constraints bounding the bias. In section 4 our methodology is used on the Open Access Series of Imaging Studies (OASIS) database of T1-weighted MR brain images.

1. Geometry and topology for template estimation. We show how geometry and topology combine to formalize the template computation algorithm and highlight required directions for further mathematical developments.

1.1. Geometrization of the action of diffeomorphisms on images.

Brain images. We consider 2D and 3D images, whose domain \( \Omega \subset \mathbb{R}^d \), with \( d = 2, 3 \), is supposed to be compact. We adopt the point of view of images as square-integrable functions \( I \) over the compact domain \( \Omega \); i.e., we write \( I \in L_2(\Omega) \), where \( L_2(\Omega) \) is a Hilbert space. The corresponding \( L_2 \) distance is invariant under volume preserving diffeomorphisms. Additionally, we assume that the images are in \( C^\infty(\Omega) \), which is \( C^\infty \) defined on the compact support \( \Omega \). For some of our results, we consider an image as a square-integrable function \( I \) such that all of its mixed partial derivatives exist in the weak sense and are square-integrable; i.e., \( I \) is in the Sobolev space \( H^\infty(\Omega) \). We denote \( \text{Img}(\Omega) \) as the set of images, referring to either \( L_2(\Omega) \) or \( H^\infty(\Omega) \).

As an illustration, we use the toy Hilbert space \( \mathbb{R}^2 \), where one point schematically represents one image; see Figure 1.

Diffeomorphisms. A diffeomorphism of \( \Omega \) is a differentiable map \( \phi : \Omega \to \Omega \) which is a bijection whose inverse \( \phi^{-1} \) is also differentiable. We consider two sets of diffeomorphisms.

On the one hand, we consider \( C^\infty(\Omega) \), i.e., the smooth diffeomorphisms that are identity outside a compact support. \( C^\infty(\Omega) \) can be seen as an infinite dimensional manifold [33] and forms an infinite dimensional Lie group [26]. Its Lie algebra \( V \) is the set of smooth vector fields with compact support [26]. We use this set of diffeomorphisms to present algebraic concepts.

On the other hand, we consider the set \( C_b(\mathbb{R}^d, \mathbb{R}^d) \) defined as \( C_b(\mathbb{R}^d, \mathbb{R}^d) = \{ \phi = \text{Id} + u \mid u \in C_b^1(\mathbb{R}^d, \mathbb{R}^d) \} \), where the subscript \( b \) refers to functions that are bounded with bounded derivatives. These diffeomorphisms are “small,” i.e., not too different from the identity. We use this set for our lemmas which need metric properties. If the specification between the two sets is not needed, we will refer to \( \text{Diff}(\Omega) \) to denote diffeomorphisms.

Action of diffeomorphisms on (brain) images. The Lie group of diffeomorphisms \( \text{Diff}(\Omega) \) acts on the space of images \( \text{Img}(\Omega) \) [38]: \( \rho : \text{Diff}(\Omega) \times \text{Img}(\Omega) \to \text{Img}(\Omega) \), \( (\phi, I) \mapsto \phi \cdot I = I \circ \phi^{-1} \).

This action is represented on Figure 1(a), which shows an image \( I \) and its diffeomorphic deformation.

Intuition and schematic representation on \( \mathbb{R}^2 \). The statistical analysis of this paper relies on geometric considerations in the Hilbert space of images \( \text{Img}(\Omega) \) endowed with the action of a Lie group of diffeomorphisms \( \text{Diff}(\Omega) \). Useful intuition is provided by figures, where

- \( \text{Img}(\Omega) \), the Hilbert space of images, is illustrated as \( \mathbb{R}^2 \), the 2D surface of the paper,
- \( \text{Diff}(\Omega) \), the Lie group of diffeomorphisms, is illustrated as \( SO(2) \), the 2D rotations, and we consider the fundamental action of \( SO(2) \) on \( \mathbb{R}^2 \).

Figure 1(b) shows this representation. The action of a diffeomorphism \( \phi \) on \( I \) is represented
by the blue curved arrow, i.e., by the action of a 2D rotation. The action transforms the image \( I \) into another image \( \phi \cdot I \), i.e., into a different point in the Hilbert space.

We note that \( \text{Img}(\Omega) \) with the action of \( \text{Diff}(\Omega) \) and \( \mathbb{R}^2 \) with the action of \( \text{SO}(2) \) have different properties. For example, \( \mathbb{R}^2 \) and \( \text{SO}(2) \) are finite dimensional and the action of \( \text{SO}(2) \) is isometric with respect to the Euclidean distance on \( \mathbb{R}^2 \). In comparison, \( \text{Img}(\Omega) \) and \( \text{Diff}(\Omega) \) are infinite dimensional and the action of \( \text{Diff}(\Omega) \) is not isometric with respect to the \( L_2 \) distance between images of \( \text{Img}(\Omega) \). Nevertheless, this schematic representation is useful in representing infinite dimensional spaces by finite dimensional ones, and the action is close to isometric as explained in the next paragraph.

**Figure 1.** Action of a diffeomorphism \( \phi \) on a brain image \( I \). (a) The brain image before and after the action of \( \phi \). (b) Schematic representation of the action of \( \phi \) on the brain image \( I \), represented as a dot in \( \mathbb{R}^2 \).

**Orbit \( O_I \) of a (brain) image \( I \).** Here, we consider \( \text{Diff}(\Omega) = C^\infty(\Omega) \). The orbit \( O_I \) of a brain image \( I \) is defined as all images reachable through the action of diffeomorphisms on \( I \):

\[
O_I = \{ I' \in \text{Img}(\Omega) | \exists \phi \in \text{Diff}(\Omega) \text{ s.t. } I' = I \circ \phi^{-1} \}.
\]

In Figure 2(a), images \( I_1 \) and \( I_2 \) belong to the same orbit, but \( I_3 \) belongs to a different orbit. We use \( \mathbb{R}^2 \) representing the space of images, with the action of \( \text{SO}(2) \) representing the action of diffeomorphisms on Figure 2(b). The blue dotted circle on Figure 2(b) represents \( O \), the orbit of \( I_1 \) and \( I_2 \). This orbit defines a submanifold of images: in this toy illustration, the submanifold is the blue dotted circle. The red point on Figure 2(b) represents \( O_{I_3} \), the orbit of the image \( I_3 \). This orbit contains only one point and is a submanifold of dimension 0.

We note that the orbits may be infinite dimensional in the case of diffeomorphisms acting on \( L_2(\Omega) \). Furthermore, the orbits are not necessarily high-dimensional spheres as the action of the diffeomorphisms is not isometric. However, we consider diffeomorphisms that transform a brain image into another brain image, i.e., an image into one that looks similar. Therefore, these diffeomorphisms are “small.” Restricting ourselves to “small” diffeomorphisms enables us to consider their action as isometric.

However, by considering only “small” diffeomorphisms acting on a given image \( I \), we move locally on the orbit of image \( I \). We could consider writing a Taylor expansion of the orbit around \( I \) [34], where the first order gives its tangent space and the second order is a high-dimensional sphere. Therefore, “small” diffeomorphisms are consistent with a representation of the images’ orbits as spheres.

**Isotropy group \( G_I \) of a (brain) image \( I \).** Here, we consider \( \text{Diff}(\Omega) = C^\infty(\Omega) \). The isotropy group \( G_I \) of a brain image \( I \) is defined as the subgroup of \( \text{Diff}(\Omega) \) formed by the diffeomorphisms that leave \( I \) unchanged:

\[
G_I = \{ \phi \in \text{Diff}(\Omega) | I \circ \phi^{-1} = I \}.
\]

\( G_I \) describes the intrinsic
symmetry of the image $I$: the more symmetric is $I$, the larger its isotropy group. All images on the same orbit have conjugate isotropy groups. Moreover, the isotropy group (also called the stabilizer) and the orbit of an image are linked by the orbit-stabilizer theorem: $O_I \sim \text{Diff}(\Omega)/G_I$ in finite dimensions. The intuition is that the larger the isotropy group (and thus, the more symmetry the image has), the smaller the orbit. Figure 2(a) shows two brain images: the isotropy group of $I_1$ and $I_2$ is larger than the isotropy group of $I_3$ in the sense of inclusion. As a consequence, the orbit of $I_3$ is “smaller” than the orbit of $I_2$.

Again, we use the $\mathbb{R}^2$ analogy as an illustration. The notion of “isotropy group” dictates the dimension of a given orbit, i.e., whether we have a 1D submanifold like the blue dotted circle or a 0D submanifold like the red point in Figure 2(b). The isotropy group of the image at the blue point in Figure 2(b) is the identity. Only the identity leaves this image unchanged. The isotropy group of the image represented by the red point is the whole Lie group of 2D rotations. Any rotation leaves this point invariant.

Going back to diffeomorphisms, we note that the isotropy group may be of infinite dimension: the isotropy group of a uniform image, i.e., $I$ constant map over $\Omega$, is the whole group $\text{Diff}(\Omega)$. Nevertheless, the orbit-stabilizer theorem holds in infinite dimensions; therefore, we can rely on the intuition of “smaller” isotropy groups and “larger” orbits.

![Figure 2. Orbit and isotropy group of a brain image.](image)

(a) $I_1$ and $I_2$ belong to the same orbit: $I_2$ is a diffeomorphic deformation of $I_1$. They have conjugate isotropy groups. In contrast, $I_3$ belongs to a different orbit and has a different isotropy group. $I_3$ shows more symmetry than $I_1$ and $I_2$, and thus a larger isotropy group, whereas the more asymmetric details of $I_1$ and $I_2$ are the sign of a smaller isotropy group. (b) The orbit of $I_1$, $I_2$ is represented as the blue dotted circle, and the two images $I_1$, $I_2$ are points on this circle. The isotropy group is linked to the dimension of the image’s orbit. $I_1$, $I_2$ have a smaller isotropy group; they have a circle orbit. $I_3$ has a larger isotropy group; its orbit is itself, i.e., the red point at $(0,0)$.  

1.2. From geometry to topology.  

Topology of (brain) images. The topology of a brain image $I$ is defined as the topology of its level sets; these are the surfaces of $\Omega$ with constant intensity. “Topology” refers to properties that are preserved under smooth deformations [16], i.e., conserved by the action of
diffeomorphisms on $I$—for example, the number of holes, or the number of connected parts (see Figure 3(a)).

Geometry and topology combine as follows. Two images $I$ and $I'$ that are diffeomorphic deformations of each other, i.e., that are on the same orbit, have the same topology. The orbit $O_I$ itself represents the topology of image $I$ (and $I'$). The set of orbits $Q = \{O_I | I \in \text{Img}(\Omega)\}$, which is the quotient space of $\text{Img}(\Omega)$ by the action of $\text{Diff}(\Omega)$, is the set of the topologies.

Figure 3(b) shows how the space of images $\mathbb{R}^2$ is partitioned into orbits: blue circles and one red “singular circle,” the red point at $(0,0)$. Figure 3(b) also shows $\mathbb{R}_+$, the quotient space of $\mathbb{R}^2$ by the group of 2D rotations, which schematically represents the quotient space of the space of brain images $\text{Img}(\Omega)$ by the Lie group of diffeomorphisms $\text{Diff}(\Omega)$. Each of the four blue circles in $\mathbb{R}^2$ becomes a blue point in the quotient space $\mathbb{R}_+$.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3}
\caption{(a) Images in the same column have the same topology. Images in the same row have different topologies; one cannot be diffeomorphically deformed to match the other. (b) Top: Schematic representation of the space of images partitioned into orbits. The two different orbit types are in blue and red, respectively. Bottom: Schematic representation of the quotient space of brain images $\text{Img}(\Omega)$ by the Lie group of diffeomorphisms $\text{Diff}(\Omega)$. $Q = \mathbb{R}_+$ is stratified into one stratum $\mathbb{R}_+^*$ (corresponding to the stratum $\mathbb{R}^2 \setminus \{(0,0)\}$ in the space of brain images) and one stratum $\{0\}$ (corresponding to the stratum $(0,0)$ in the space $\mathbb{R}^2$).}
\end{figure}

Gathering brain images with similar topologies: Orbit types. By definition, two brain images are of the same orbit type if their isotropy groups are conjugate subgroups in the Lie group of diffeomorphisms. In particular, brain images that belong to the same orbit have the same orbit type. The type corresponding to the smallest isotropy group—in the sense of the inclusion among the subgroups of the diffeomorphism group—is sometimes called the principal type [1], which is the appellation we use here. For example, if the elements of an orbit have the group’s identity as their isotropy group, then the orbit is necessarily of principal type. Equivalently, the orbits of principal type are called principal orbits. Other orbits are called singular orbits.

The blue circles in Figure 3(b) have the same orbit type: the images on these orbits have the identity $\{Id\}$ of the Lie group as isotropy group. They are of principal type since the identity $\{Id\}$ is the smallest subgroup—in the sense of the inclusion—of the group of rotations.

Stratification of the space of topologies. In the space of brain images, we gather orbits of the same type: we gather the blue circles of Figure 3(b) into $\mathbb{R}^2 \setminus \{(0,0)\}$ on the one hand, and keep the red dot $(0,0)$ on the other hand. The orbit type itself is a submanifold of the space of brain images: $\mathbb{R}^2 \setminus \{(0,0)\}$ or $(0,0)$ in the schematic brain images space $\mathbb{R}^2$. Furthermore,
these orbit type submanifolds form a \textit{stratification}, meaning they fit together in a particularly nice way.

The quotient space $Q$ can also be naturally partitioned into manifolds, i.e., also as a stratification. $Q$ is not a manifold, but $Q$ is composed of manifold pieces, and those pieces are called strata. There is a partial ordering of the strata in the quotient space, using the inclusion [22].

1.3. Geometry of generative model and estimation procedure. In this subsection, we consider $\text{Diff}(\Omega) = C^1_b(\mathbb{R}^d, \mathbb{R}^d)$.

\textbf{Generative model.} The $n$ brain images $I_1, \ldots, I_n$ are interpreted with a generative deformable model: $I_i = \phi_i \cdot T + \epsilon_i$, $i = 1, \ldots, n$, where each image $I_i \in \text{Img}(\Omega)$ is a diffeomorphic deformation $\phi_i \in \text{Diff}(\Omega)$ of a unique brain anatomy $T$, to which noise $\epsilon_i$ is added. The parameter $T$ represents the brain anatomy shared by the population. The transformations $\phi_i$ and the noises $\epsilon_i$ are i.i.d. realizations of random variables. The transformations $\phi_i$ follow a general distribution, for example a Gaussian distribution, in a finite dimensional subspace of the Lie group, and the $\epsilon_i$’s represent Gaussian noise on the space of images [28, 36]. We denote $\sigma^2$ its variance.

The model can be interpreted by a three-step generative procedure illustrated schematically in Figure 4. First, there is only the shared anatomy $T$. Second, the template $T$ is deformed with the diffeomorphism $\phi_i$ and gives a brain image $\phi_i \cdot T$. Third, we represent the measurement noise with $\epsilon_i$, which gives the observed brain image $I_i$.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Schematic illustration of the generative model of the brain images data. As before, the space of the brain images is represented by the plane $\mathbb{R}^2$. (a) First step of the generative model: Generate a brain anatomy. One usually assumes that there is a unique brain anatomy: $T$, in green. (b) Second step of the generative model: Generate a deformation $\phi_i \in \text{Diff}(\Omega)$ which is used to deform the template. The brain image $\phi_i \cdot T$ belongs to the orbit of $T$, represented by the green circle. (c) Third step of the generative model: Generate noise $\epsilon_i$ in the space of images. The brain image $\phi_i \cdot T + \epsilon_i$ does not belong to the orbit of $T$ anymore.}
\end{figure}

\textbf{Computing the template: An estimation procedure.} Computing the brain template amounts to inverting the generative model: given the data, we want to estimate the parameter $T$. The transformations $\phi$ are hidden variables of the model. The natural statistical procedure for estimating $T$ in this context is the Expectation-Maximization (EM) algorithm [13]. The EM algorithm is an iterative procedure that maximizes the log-likelihood of the generative model.
with hidden variables. The EM algorithm gives an asymptotically unbiased and consistent estimation of the brain anatomy $T$.

In practice, the EM algorithm can be computationally expensive, especially when dealing with tridimensional images. Most neuroimaging pipelines rely on an approximation of the EM algorithm called “Fast Approximation with Modes” in [2]. It runs as follows. Initialize the estimate with $\hat{T} = I_1$, i.e., one of the brain images from the database. Then, iterate the following two steps until convergence [24]:

$$
\begin{align}
(1) & \quad \hat{\phi}_i = \underset{\phi \in \text{Diff}(\Omega)}{\text{argmin}} \ d_{\text{Img}(\Omega)}(\hat{T}, \phi \cdot I_i) + \lambda \text{Reg}(\phi), \quad \forall i \in \{1, \ldots, n\}, \\
(2) & \quad \hat{T} = \underset{T \in \text{Img}(\Omega)}{\text{argmin}} \sum_{i=1}^{n} d_{\text{Img}(\Omega)}(T, \hat{\phi}_i \cdot I_i)^2.
\end{align}
$$

Step (1) is an estimation $\hat{\phi}_i$ of the diffeomorphisms $\phi_i$, and an approximation of the E-step of the EM algorithm. In practice, each brain image $I_i$ is registered to the current template estimate and the $\hat{\phi}_i$ is the result of this registration. The term Reg is a regularization that ensures that the optimization has a solution. Showing that the estimates $\hat{\phi}_i$ and $\hat{T}$ exist is beyond the scope of this paper.

Step (2) is the M-step of the EM algorithm: the maximization of the surrogate in the M-step amounts to the maximization of the variance of the projected data. This computes the updated template estimate as the mean intensity of the subject images $I_i$, deformed with the mean deformation of the $\hat{\phi}_i$’s.

The registration step (1) amounts to aligning the $n$ subject images by transporting them onto their orbit (see Figure 5(b)), i.e., projecting them in the quotient space (see Figure 5(c)). Step (2) averages the $n$ registered images (see Figure 5(d)).

**Figure 5.** Geometrization of an iteration of the template’s computation: (a) $n$ subject images (black squares); (b) the $n$ images are registered, and they travel on their orbit (the blue circles) to alignment; (c) registered images; (d) the empirical brain template $\hat{T}$ (in yellow) is computed as the Fréchet mean of the $n$ registered images. How far is it from the unique anatomy $T$ of the generative model (in green)? Can we quantify $B_n$?

**Evaluation of the procedure:** Definition of asymptotic bias $B_\infty$. We evaluate the template $\hat{T}$ as an estimator of the unique brain anatomy $T$ (see Figure 5(d)) given $n$ observations $I_i$, $i = 1, \ldots, n$. We note that in other papers, $T$ may be called the template directly and $\hat{T}$ the template’s estimate.
We consider two measures of the accuracy of this estimator, its variance $V_n^2$ and bias $B_n$, which are defined as

$$V_n^2 = \mathbb{E}((\hat{T} - \mathbb{E}(\hat{T}))^2) \quad \text{and} \quad B_n = \mathbb{E}(\hat{T} - T).$$

The bias for $n$ images $B_n$ is illustrated in Figure 5. We are interested in the asymptotic behavior $n \to +\infty$, i.e., when the number of brain images goes to infinity. One would expect that the procedure converges to the brain anatomy $T$ it is designed to estimate. When the estimator converges, its variance is asymptotically zero: $V_\infty^2 = 0$.

1.4. Geometry of the template estimate.

Estimation procedure interpreted as the Fréchet mean in the quotient space. We consider the estimation procedure of (1.1). First, we note that the regularization term in step (1) forces the diffeomorphisms to be small, i.e., to be close to the identity and close to having an isometric action on the images. Second, we could consider the subgroup of diffeomorphisms that leave a volume form $V$ invariant (often used to model incompressible fluids in continuum mechanics). In this case, using $y = \phi^{-1}(x)$ and the fact that the volume form is conserved, (1.2)

$$d(\phi \cdot I_1, \phi \cdot I_2)^2 = \int_\Omega (I_1 \circ \phi^{-1}(x) - I_2 \circ \phi^{-1}(x))^2dV(x) = \int_\Omega (I_1(y) - I_2(y))^2dV(y) = d(I_1, I_2)^2,$$

and the action is thus isometric.

In both of the above two frameworks, it is thus reasonable to trade the regularization term for the assumption that the action is isometric in our model.

First, we model the two steps of the estimation procedure as follows:

1. $\hat{\phi}_i = \arg\min_{\phi \in G} d_M(\hat{T}, \phi \cdot I_i) \quad \forall i \in \{1, \ldots, n\},$

2. $\hat{T} = \arg\min_{T \in M} \sum_{i=1}^n d_M(T, \hat{\phi}_i \cdot I_i)^2,$

where $M$ is a generic Riemannian manifold and $G$ is a Lie group acting on $M$ isometrically.

This converges to a local minimum because it decreases at each step and is bounded below by zero. The estimator computed with this procedure is (1.3)

$$\hat{T} = \arg\min_{T \in M} \sum_{i=1}^n \min_{\phi \in G} d_M^2(T, \phi \cdot I_i).$$

The term $\min_{\phi \in G} d_M^2(T, \phi \cdot I_i)$ is the distance in the quotient space between $T$ and $I_i$. Thus (1.3) defines the Fréchet mean on the quotient space [36].

The study of the set of solutions of the iterative algorithms is an interesting direction of research but beyond the scope of this paper. However, we point out that the existence and uniqueness of the solution are linked to the question of whether the Fréchet mean exists and is unique in the quotient space, which is studied in [4, 25].
Asymptotic bias $B_\infty$ and curvature. We show in [35] that the asymptotic bias is nonzero: $B_\infty \neq 0$. For an infinite number of brain images $n \to +\infty$, the estimate converges, but not to the brain anatomy $T$ it was designed for. We compute a Taylor expansion of the asymptotic bias $B_\infty$ around the noise $\sigma = 0$ in the case of a finite dimensional manifold and isometric Lie group action [34]:

$$B_\infty = \frac{\sigma^2}{2} H(T) + O(\sigma^3) + \epsilon(\sigma),$$

where $H(T)$ denotes the mean curvature vector of the template’s orbit. There is no bias when there is no measurement error $\sigma = 0$. It was observed experimentally that the bias was dependent on the measurement error [2].

The coefficient $H(T)$ depends on the template $T$ that is being estimated. We investigate this dependency in the geometric framework of subsection 1.2. Assume that there exists a fixed point $o$ of the Lie group action, i.e., a point that is invariant under the whole Lie group. Consider the orbit $O_T$ of $T$. As the action is isometric, the orbit belongs to a geodesic sphere $S_d$ with center $o$ and radius $d$. A geodesic sphere of radius $d$ in a manifold—like a hypersphere of radius $d$ in $\mathbb{R}^m$—has a mean curvature vector whose norm is $|H(T)| = \frac{(m-1)d}{d}$. If we write the template’s bias in terms of $d$ units, then the asymptotic bias depends on $\left(\frac{d}{\sigma}\right)^2$. In other words, the distance of the template to the singularity $o$ at the scale of the noise $\sigma$ governs the asymptotic bias $B_\infty$. Our approach is to compute the asymptotic bias by estimating the geometric parameters. Conversely, one could infer the geometric parameters, like the external curvature of orbits for different Lie groups, from the asymptotic bias known on simulated examples.

Figure 6 shows the intuition behind this. In Figure 6(a), $\mathbb{R}^2$ schematically represents the space of brain images—the black squares represent brain images from the database, and the green square is $T$—and the green circle is the orbit of $T$. The dotted circles, which have their centers on the template’s orbit, represent the probability distribution of the (2D isotropic) Gaussian noise in the generative model. More precisely, they represent the level sets at $\sigma$ of the noise distribution. The curvature $H(T)$ controls the area in grey in Figure 6, which is the area inside the Gaussian level set that is outside $T$’s orbit. This area is greater than the area inside $T$’s orbit. As a consequence, the probability that the brain images are generated “outside” $T$’s orbit is higher than the probability that they are generated inside $T$’s orbit.

Figure 6(b) shows the registration step of the template estimation: there is a higher probability that the registered images are away from $T$, as if repulsed by the singularity around which the orbits warp. When one averages the registered images, one sees that the template’s estimate becomes biased as it will systematically give an image that is further away than $T$ from the quotient space’s singularity, i.e., from the red dot.

Quantifying the asymptotic bias $B_\infty$ of the brain template. In neuroimaging, the manifold is the space of brain images $\text{Img}(\Omega)$ and the Lie group is the group of diffeomorphisms $\text{Diff}(\Omega)$: they are both infinite dimensional. We assume that we can apply the geometry of [34] because $B_\infty$ appears in the same way in infinite dimension; see Figure 7.

First, [34] studies the bias when the dimension of the manifold increases. They consider the finite dimensional manifold $M = \mathbb{R}^m$ with the action of $SO(m)$, i.e., a generalization of
Figure 6. Schematic illustration of the asymptotic bias in the template computation algorithm of neuroimaging. (a) The images generated with the model described above have a higher probability of being “outside” (with respect to the curvature) of the template’s orbit. (b) The registration during the template’s estimation aligns the images. The distribution of images is unbalanced with respect to the real template.

Figure 7. Image from [34]. Take $M = \mathbb{R}^m$ with the action of $SO(m)$. The template’s bias increases with $\sigma$ and is more important as $m$ increases: The blue curve shows the asymptotic bias for $m = 2$, the pink curve shows that for $m = 10$, and the yellow curve shows that for $m = 20$.

The toy example $\mathbb{R}^2$ with the action of $SO(2)$ in our illustrations. We show in [34] that $B_\infty$ increases when $m$ increases; see Figure 7.

There is an asymptotic bias in an infinite dimensional Hilbert space [3]. The asymptotic behavior of the bias when the noise level $\sigma$ tends to infinity is given by [14]; see Figure 8. Although the 1D signals have been discretized for the numeric implementation, they represent
Figure 8. Image from [14]. The real signal is shown in blue. The template, computed with $n = 10^5$ observations simulated with Gaussian noise with $\sigma = 10$, is shown in red. There is an asymptotic bias in the estimation of signal.

1D functions that are elements of an infinite dimensional Hilbert space.

Ultimately, [9] gives a lower bound of the asymptotic bias for shapes of curves in 2D, where the terms depend on derivatives of the functions representing the curve. These can be interpreted as the derivatives of the action of translations, which lead to the curvature of the orbit of the given function under the translations’ action. We assume that, given these illustrative examples, the intuition provided by [34] applies to neuroimaging and that the bias depends on the ratio $\left(\frac{\sigma}{d}\right)^2$.

2. Computational representation of geometry and topology. We show in this section how the MS complexes can be used to encode the topology and enable the estimation of the geometric parameters $d$ and $\sigma$ previously introduced.

2.1. Definition of Morse–Smale complexes for (brain) images.

Morse–Smale (intensity) functions. A real-valued smooth map $I : \Omega \rightarrow \mathbb{R}$ is a Morse function if all its critical points are nondegenerate (the Hessian matrix is nonsingular) and no two critical points have the same function value. The intensity function $I$ representing a bi- or tridimensional brain image is a Morse function, at least after a convolution with a smoothing Gaussian [11]. In the following, $I$ represents a brain image. Morse theory traditionally analyzes the topology of a manifold by studying the Morse functions on that manifold. Here,
the manifold is known: it is the image domain \( \Omega \). We are not interested in the topology of \( \Omega \) but rather in the topology of the functions \( I \) themselves; that is, we would like to know the distribution of their critical points. Figure 9(a) shows a 2D slice of a 3D brain image \( I \), where the intensity is represented as the height: the maxima are in red, and the minima are in blue.

![Figure 9](image)

**Figure 9.** (a) Intensity \( I \) on a 2D brain image visualized as height: Maxima are in red, and minima are in blue. This is an MS function \( I : \Omega = \mathbb{R}^2 \rightarrow \mathbb{R} \). (b) Persistences \( p_1 < p_2 \) of two pairs min-max. A threshold \( p_1 < p < p_2 \) divides the domain into three regions (pink, violet, and green), while \( p < p_1 \) divides it into five regions (pink, violet, brown, turquoise, and green). (c) Computational representation of the geometry: Regions on a 2D domain, induced by an MSC with threshold \( p = 0.1 \): (i) The MS graph represents the geometry's class of the image. (ii) The labeled MS graph represents the image's orbit under the diffeomorphisms.

We introduce the notions of integral lines, ascending and descending manifolds that are needed to define the MS (intensity) functions. An integral line is a maximal path in the image domain \( \Omega \) whose tangent vector corresponds to the intensity gradient \( \nabla I \), the gradient of \( I \), at every point. This notion comes from autonomous ordinary differential equations, where it represents the trajectory of a system verifying

\[
\frac{dx}{dt}(x) = \nabla I(x).
\]

Each integral line starts and ends at critical points of \( I \), where the gradient \( \nabla I \) is zero. Ascending \( A(x_i) \) and descending \( D(x_j) \) manifolds of respective extrema \( x_i \) and \( x_j \) are defined as

\[
A(x_i) = \{ x \in \Omega \mid \text{The integral line going through } x \text{ ends at } x_i \},
\]

\[
D(x_j) = \{ x \in \Omega \mid \text{The integral line going through } x \text{ starts at } x_j \}.
\]

Take the two manifolds \( A(x_i) \) and \( D(x_j) \) in \( \Omega \) and assume they intersect at a point \( p \in \Omega \). Let \( T_A \) (resp., \( T_D \)) denote the set of all vectors tangent to \( A(x_i) \) (resp., \( D(x_j) \)) at \( p \). If every vector in \( \Omega \) is the sum of a vector in \( T_A \) and a vector in \( T_D \), then \( A(x_i) \) and \( D(x_j) \) are said to intersect transversely at the point \( p \). The intensity function \( I \) defining the brain image is Morse–Smale (MS) if the ascending and descending manifolds only intersect transversely. We assume in the following that all brain images \( I \) are MS.

**Morse–Smale complex and persistence.** The MS complex of an MS function is the set of intersections \( A(x_i) \cap D(x_j) \), over all combinations of extrema \( (x_i, x_j) \) \[19\]. The MS complex includes regions (i.e., submanifolds of \( \Omega \)) of dimensions 0 through \( D \), where \( D \) is the dimension of the domain \( \Omega \), i.e., \( D = 2 \) or \( D = 3 \) for our purposes. The MS complex of \( I \) is a partition
of the domain $\Omega$ into regions defined by the set of integral lines that share common starting and ending points. The interior of each region is monotonic with respect to the intensity $I$: a region contains no critical points and has a single local minimum and maximum on its boundary; see, for example, Figure 9(c)(ii), where the maximum $I_{\text{max}}$ and minimum $I_{\text{min}}$ are shown on the boundary of the grey region. The MS complex can also be seen as a graph on the brain image domain $\Omega$ whose nodes are the critical points of the brain image intensity.

The persistence of a critical point $x_i$ of $I$ is the amount of change in intensity $I$ required to remove this critical point:

$$p(x_i) = |I(x_i) - I(n(x_i))|,$$

where $n(x_i)$ is the critical point closest to $x_i$ in intensity, among the critical points connected to $x_i$ by an integral line [16]. The persistence of $x_i$ is a measure of its significance as a critical point, i.e., importance of the topological feature. Figure 9(b) illustrates the definition of persistence on a 1D example. The function represented has four critical points: two minima and two maxima. The figure shows how they pair, as well as their persistence. On the $x$-axis, colors show the regions of the corresponding 1D MS complex.

Beside this usual definition of persistence of a critical point, we define here the persistence of a region of the MS complex as the amount of change in intensity required to remove this region from the MS complex more precisely,

$$p(\text{region}) = |I_{\text{max}} - I_{\text{min}}|,$$

where $I_{\text{max}}$ and $I_{\text{min}}$ are, respectively, the maximum and the minimum intensity of this region. In contrast to the definition of the persistence of a critical point, we do not rely on the saddle points, but only on the extrema.

**Hierarchy of Morse–Smale complexes.** The notion of persistence of a region enables the definition of a hierarchy of MS complexes of one brain image $I$ [16, 19]. One uses the ordering given by persistence to successively remove topological features from the image $I$. One starts with the MS complex of the brain image $I$ defined above and one recursively removes the critical points with minimal persistence. This leads to a nested series of successively simplified MS complexes. At each level, some of the MS regions are merged into a single region. Ultimately the MS complex consists of only one region which is the entire domain $\Omega$.

Persistence introduces a notion of scale at which the MS complex of $I$ is considered. Only the nodes whose persistence is above the threshold are kept. Figure 9(b) shows that the 1D domain is partitioned differently when the threshold $p$ is below $p_1$ or between $p_1$ and $p_2$. We say that an MS complex is represented at a given persistence level. At the scale of the persistence threshold $p$, the intensity is considered monotonic on each region of the MS.

We note that this MS hierarchy is different from a Gaussian scale space (GSS) hierarchy of images [37]. The latter takes critical points across smoothing scales and not across persistence levels.

**2.2. Computing Morse–Smale complexes of (brain) images in practice.** The previous definitions are relevant to (continuous) MS theory and apply strictly for a continuous intensity function $I$. Nevertheless, the MS complex, introduced in terms of ascending and descending
manifolds, can be computed for discrete brain images as follows [16]. We choose the approach of line integrals to compute the MS complex. Other approaches such as Delaunay triangulation may also be considered [12].

**Computing the Morse–Smale complex of a brain image.** We compute the MS complex of a brain image, which will later be the brain template image. Our input is \( \{ \mathbf{x}_i, I_i \} \), i.e. the intensity values \( \{ I_i \} \) on a grid \( \{ \mathbf{x}_i \} \) of \( \Omega \). We compute the integral lines of the intensity gradient, which we then gather to get the regions of the MS complex. For each element of the grid \( \mathbf{x}_i \), following the gradient \( \nabla I \) leads to computing the integral line going through \( \mathbf{x}_i \) and in particular its starting and ending points [16]. The domain \( \Omega \) can be approximated via a \( k \) nearest-neighbor graph, and one computes the integral lines by considering the connectivity of the graph. Then, elements \( \mathbf{x}_i \) with the same starting and ending points belong to the same MS region. This gives the partition of the domain \( \Omega \) and therefore the MS complex. We remark that the \( \mathbf{x}_i \)'s necessarily belong to a 3D (for a tridimensional image) component of the MS complex because the 0D, 1D, and 2D components have measure zero.

Figure 9(c) shows the MS complex of the 2D slice of a 3D brain image for level of persistence of \( p = 0.1 \). The image’s 2D domain is divided into different regions, represented by the different colors. The quadrant shows part of the underlying MS graph. The red dot represents a maximum in intensity, and the blue dot, a minimum. They are nodes of the underlying graph on the domain \( \Omega \).

**Morse–Smale graph and labeled Morse–Smale graph.** There are two ways of representing the MS graph corresponding to the computed MS complex. Both will be useful for analyzing the template’s asymptotic bias. One can consider the graph as the set of nodes and edges, without any intensity information at the nodes. We simply call this graph the Morse–Smale (MS) graph: this is the graph illustrated in Figure 9(c)(i). Alternatively, one can label the nodes with the intensity information. We call this graph the labeled Morse–Smale (MS) graph: this is the graph illustrated on Figure 9(c)(ii). Both of these graphs are oriented, the edges being directed in the direction of the intensity gradient from one node to the next.

**2.3. Template’s computation and Morse–Smale complexes.** We show how the MS complex of an image can represent its geometry through its isotropy group.

**Lie algebra of the isotropy group and intensity gradient of the brain template.** The template is an image \( I \in \text{Img}(\Omega) \). We consider the space of images \( \text{Img}(\Omega) = H^\infty(\Omega) \) and the Lie group of diffeomorphisms \( \text{Diff}(\Omega) = C^\infty(\Omega) \) and its Lie algebra \( V \); see subsection 1.1.

**Lemma 2.1.** Take an image \( I \in H^\infty(\Omega) \) and \( \epsilon > 0 \). Consider the set

\[
V_I = \{ v \in V \ s.t.: I \circ \text{Exp}(tv) = I \forall |t| < \epsilon \}.
\]

By construction, the exponential of the elements of \( V_I \) is in the isotropy group of \( I \). For \( v \in V_I \), we have

\[
\forall x \in \Omega, \quad \nabla I(x)^T.v(x) = 0.
\]

**Proof.** Take \( v \in V_I \) and \( |t| < \epsilon \). Its group exponential is a diffeomorphism in the isotropy group \( G_I \), which can be written

\[
\phi = \exp(tv) = Id + tv + \mathcal{O}(t^2).
\]
Then, the equation above leads to

\[ I(x) = I(x - tv(x) + \mathcal{O}(t^2)), \]
\[ I(x) = I(x) - DI(x). (tv(x)) + \mathcal{O}(t^2), \]
\[ 0 = DI(x). (tv(x)) + \mathcal{O}(t^2). \]

The identification of the coefficients in this Taylor expansion leads to

\[ \nabla I(x). v(x) = 0. \]

A vector field of \( V_I \), which is in the Lie algebra of the isotropy group of the image \( I \), is orthogonal to the image's gradient at any point \( x \) of the image’s domain \( \Omega \).

We note that this lemma does not give a characterization of the vector fields in \( V_I \). It gives the inclusion \( V_I \subset \{ v|\forall x \in \Omega, \nabla I(x).v(x) = 0 \} \). Thus, it allows us to control the complexity of \( V_I \) and thus of some of the isotropy group’s Lie algebra.

To understand the intuition behind this result, consider an image with constant intensity. In this case, there are no restrictions a priori on the vector fields of the Lie algebra of the image’s isotropy group. Thus, the isotropy group is as large as it can be. The isotropy group of an image with constant intensity is the whole group of diffeomorphisms.

**Intensity gradient and MS graph.** We now present a lemma showing that the MS graph can be used to represent the isotropy group of an image.

**Lemma 2.2.** Take two images \( I_1, I_2 \in H^\infty(\Omega) \) that are Morse functions. If \( I_1 \) and \( I_2 \) have the same MS graph, regardless of the nodes’ positions and intensities, then the level sets of \( I_1 \) can be continuously mapped to the level sets of \( I_2 \).

This implies that the partition of the domain \( I_1 \) induced by its MS can be continuously mapped to the partition of the domain of \( I_2 \). Taking a cell \( C \subset \Omega \) of the partition of the domain of \( I_2 \), there exists a diffeomorphism \( \psi \) and a function \( \kappa \) such that

\[
\forall x \in C, \quad \nabla I_2(x) = \kappa(x).d^*\psi(x).\nabla I_1 \circ \psi(x).
\]

**Proof.** The images \( I_1 \) and \( I_2 \) have the same MS graph when the nodes’ and edges’ positions in the images’ domain \( \Omega \) are not taken into account. We consider \( G_1, G_2 \) the MS graphs of \( I_1, I_2 \) with their nodes’ and edges’ positions on the domain \( \Omega \). The graph \( G_1 \) can be diffeomorphically deformed on the graph \( G_2 \) of \( I_2 \). We take \( \psi_1 \) a diffeomorphism that realizes the graphs’ matching.

Now, \( I_1 \circ \psi_1^{-1} \) and \( I_2 \) share the same MS graph \( G_2 \) when the nodes’ and edges’ positions on \( \Omega \) are taken into account. However, this graph is not labeled as the nodes’ intensities are not taken into account. We consider one cell \( C \) of the graph \( G_2 \), where the nodes “max” and “min” corresponding to the maximum and the minimum in intensity do not have intensity labels.

We take the image \( \tilde{I}_2 \mid C \) defined on the cell \( C \) obtained by setting \( \tilde{I}_2(\text{max}) = 1 \) and \( \tilde{I}_2(\text{min}) = 0 \) on the nodes “max” and “min” and rescaling the image gradient by \( (I_2(\text{max}) - I_2(\text{min}))^{-1} \).

We take the image \( I_1 \circ \psi_1^{-1} \mid C \) built similarly. This operation does not change the position of

\[
\forall x \in C, \quad \nabla I_2(x) = \kappa(x).d^*\psi(x).\nabla I_1 \circ \psi(x).
\]
the integral lines of the images $I_1 \circ \psi_1^{-1}$ and $I_2$. Now, the images $\tilde{I}_2|_C$ and $I_1 \circ \psi_1^{-1}|_C$ are diffeomorphic. We take $\psi_2|_C$ as the diffeomorphism that registers $I_1 \circ \psi_1^{-1}|_C$ to $\tilde{I}_2|_C$. $\psi_2|_C$ also continuously maps the integral lines of $I_1 \circ \psi_1^{-1}|_C$ to the integral lines of $\tilde{I}_2|_C$, and therefore the integral lines of $I_1 \circ \psi_1^{-1}$ to the integral lines of $I_2$ on the cell $C$.

Now we consider the set of integral lines of $I_2$ on the whole domain $\Omega$ and the map $\psi_2 = \cup_C \psi_2|_C$ defined on the set of integral lines. The map $\psi_2$ is obtained by gluing the $\psi_2|_C$’s on the edge of the graph; we can do this because the integral line defining the border of a cell is left (globally) invariant by each $\psi_2|_C$ of the neighboring cells $C$’s. Thus, $\psi_2$ is well defined and continuous on the set of integral lines of $I_2$.

We write $\psi = \psi_1 \circ \psi_2$. From the above, $I_1 \circ \psi^{-1}$ and $I_2$ have the same integral lines. Therefore, $\psi$ also maps the level sets of $I_1$ to the level sets of $I_2$.

Now we go back to a cell $C \subset \Omega$ of the partition of the domain of $I_1$ induced by its MS complex. On this cell, there exists a function $f$ such that

\begin{equation}
I_2 = f \circ I_2 \circ \psi|_C.
\end{equation}

The function $f$ gives the mapping of intensity levels on each level set and $\psi$ is the map built above. Differentiating this equation with the chain rule gives

\begin{equation}
dI_1 = df(I_2 \circ \psi).dI_2 \circ \psi.d\psi,
\end{equation}

where $df(I_2 \circ \psi)$ is a scalar which we note $\kappa$. Taking the adjoint gives

\begin{equation}
\nabla I_1 = \kappa.\nabla I_2 \circ \psi.d^*\psi.
\end{equation}

In other words, if two images $I_1$, $I_2$ have the same MS graph, then $I_1$ can be diffeomorphically deformed so that its intensity gradient is parallel at every point to the intensity gradient of $I_2$. From Lemma 2.1, the sets $\{v_1|\forall x \in \Omega, \nabla I_1(x).v_1(x) = 0\}$ and $\{v_2|\forall x \in \Omega, \nabla I_2(x).v_2(x) = 0\}$ control the isotropy groups of $I_1$ and $I_2$. If $I_1$ and $I_2$ have the same MS graph, any vector field in the first set can be diffeomorphically deformed to get a vector field in the second set, and conversely. As a consequence, the MS graph represents the image’s isotropy group. From section 1, we know that the isotropy group controls, in turn, the orbit type of the image, i.e., to which stratum the image belongs.

Furthermore, we note that we could have considered the labeled MS graph of the image, i.e., the MS graph with intensities at the nodes; see Figure 9(c)(ii). The labeled MS graph controls the orbit of the image: images in the same orbit have the same topology but also the same intensities.

3. **Topology quantifies and controls the template’s asymptotic bias.** This section gathers the elements of sections 1 and 2 to quantify the asymptotic bias in the brain template computation. We use MS complexes to quantify, and then control, the bias.
3.1. Quantify the template inconsistency.

Understand and estimate the geometric parameter \( d \). The distance \( d \) is the distance of the current image to a brain image with a larger isotropy group, measured in sum of squared differences of intensities; see Figure 6. How can we measure this distance \( d \) locally on the template’s image? From section 1, we know that the isotropy group becomes larger when the image is “more symmetric.” From section 2, we know that the isotropy group becomes larger when the image topology becomes simpler. Thus, the distance \( d \) is a distance in intensity from the template image to a similar image with simpler topology.

We want to express this distance locally on the template image. Modifying the intensity locally on the template image modifies the image itself and may simplify its topology. For example, modifying the intensity locally in a region of the image can suppress a min-max pair and the image becomes “more symmetric.” Thus we describe the distance \( d \) locally on the image by the amount of intensity needing to be changed in this region, so that the topology is simplified.

We quantify the local intensity needed to simplify the template image’s topology using the MS complex representation of section 2. Suppose we know the MS complex of the template image. The intensity needed to simplify the image’s topology is, by definition, the intensity needed to simplify the MS graph. We consider the partition of the image’s domain \( \Omega \) induced by the MS complex. For each region of the partition, the intensity needed to simplify the topology can be represented by the intensity needed to remove the min-max pair of the region:

\[
d(\text{region}) = \max_{\text{region}} - \min_{\text{region}} = p_F(\text{region}).
\]

This quantifies the importance of the region as a representative of the brain anatomy: if the intensity difference between the region’s min and max is low, then one can assume that this min-max pair has been created by chance because of the noise on the images. We see that the notion of persistence defined in section 2 estimates the first geometric parameter \( d \).

Understand and estimate the geometric parameter \( \sigma \). Now we turn to the second geometric parameter that causes asymptotic bias: the standard deviation \( \sigma \) of the noise (see again (1.4) and Figure 6). The standard deviation \( \sigma \) of the noise is a parameter of the generative model that has produced the observed images of the subjects’ brain anatomies. The parameter \( \sigma \) is unknown, but it can be estimated from the observed images. Since we want to compute the asymptotic bias locally, we are interested in estimating the parameter \( \sigma \) locally.

We first estimate \( \sigma^2 \) at a given voxel \( x \in \Omega \):

\[
\hat{\sigma}^2(x) = \frac{1}{n-1} \sum_{i=1}^{n} (I_i(x) - T(x))^2,
\]

where \( T \) is the template, i.e., the average of the registered images, and \( I_i \) refers to the \( i \)th image registered to \( T \). In other words, \( \hat{\sigma}^2(x) \) is the standard unbiased estimate of the intensity variance at voxel \( x \) of the registered images. Assuming that the voxel intensities are independent, we estimate \( \sigma^2 \) locally on a region of the MS complex of the template image by

\[
\hat{\sigma}^2(\text{region}) = \frac{1}{\#x} \sum_{x \in \text{region}} \hat{\sigma}^2(x).
\]
Thus, \( \hat{\sigma}(\text{region}) = \sqrt{\hat{\sigma}^2(\text{region})} \) quantifies the noise on the brain images in a specific region of the brain. The larger the standard deviation \( \sigma \) of the noise, the higher the chance for the template to show min-max pairs appearing by chance. The independence assumption on the intensities is a strong one, and other estimates of the standard deviation could be used. Future work is needed to investigate these estimators and their impact on the estimate of the template’s bias.

**Compute the asymptotic bias using the persistence of the whitened brain template.** The local estimates of the geometric parameters \( d \) and \( \sigma \) enable us to estimate the asymptotic bias locally on a brain region:

\[
\hat{B}_\infty(\text{region}) = \left( \frac{d(\text{region})}{\hat{\sigma}(\text{region})} \right)^{-2}.
\]

We emphasize here that \( \hat{B}_\infty \) is an estimate of the asymptotic bias \( B_\infty \) (of the brain template estimation) and is not exact. We link the estimate \( \hat{B}_\infty \) to the definition of persistence in the MS complex framework.

First, we define the whitened brain template estimate \( \hat{t} \) of \( \hat{T} \) as

\[
\forall x \in \Omega, \quad \hat{t}(x) = \frac{\hat{T}(x)}{\hat{\sigma}(x)}.
\]

In other words, we divide the brain template intensity of each voxel \( x \) by the estimation of the standard deviation of the noise at this voxel \( \hat{\sigma}(x) \). This whitens the noise all over the brain template.

We further assume that \( \hat{\sigma}(\text{region}) \simeq \hat{\sigma}(\text{max}) \) and similarly that \( \hat{\sigma}(\text{region}) \simeq \hat{\sigma}(\text{min}) \), where \( \hat{\sigma}(\text{max}), \hat{\sigma}(\text{min}) \) are the variabilities at the respective min and max of the MS complex. In other words, we assume that the noise does not vary “too much” from a voxel to another in a given region. This assumption holds for a region of one voxel or a few voxels but is a stronger requirement for larger regions.

We assume that the critical points of \( \hat{t} \) are close to the critical points of \( \hat{T} \) and consider the MS complex of the whitened template. We can write

\[
\hat{B}_\infty(\text{region}) \simeq \left( \frac{\hat{T}_{\text{max}}}{\hat{\sigma}(\text{max})} - \frac{\hat{T}_{\text{min}}}{\hat{\sigma}(\text{min})} \right)^{-2} = \left( \hat{t}(\text{max}) - \hat{t}(\text{min}) \right)^{-2} = p_t(\text{region})^{-2},
\]

where we recognize the persistence \( p_t(\text{region}) \) of the corresponding region of the whitened template \( \hat{t} \). This links the estimation of the asymptotic bias to the persistence of the whitened template’s MS complex. This shows how a topological property of the image in fact represents a statistical property of this image as the estimate of the brain template.

**Hierarchy of the whitened template.** The persistence of the whitened template quantifies locally the asymptotic bias, i.e., how far the brain template is from the unique brain anatomy of the generative model. Is there a statistical interpretation of the hierarchies of MS complexes, introduced in section 2? Let us consider another MS of the whitened template’s hierarchy, i.e., an MS computed at a given persistence threshold \( p_{\text{threshold}} \). There is an asymptotic bias.
threshold corresponding to it, which we can write \( p_{\text{threshold}}^{-1/2} \). The regions kept in the new MS complex are those having a persistence higher than the persistence threshold \( p_{\text{threshold}} \), i.e., those having an asymptotic bias lower than the asymptotic bias threshold \( p_{\text{threshold}}^{-1/2} \).

Therefore, if we can impose the topology of the brain template to match the new MS complex of threshold \( p_{\text{threshold}}^{-1/2} \), we control its asymptotic bias. This means that we preserve only the min-max pairs shown on the MS graph chosen. It eliminates the min-max pairs that have been created by chance, because the noise on the images was at a level similar to the intensity signal on these regions. The next subsection explains how to impose the topology of a given MS on the template’s image.

### 3.2. Controlling the template’s asymptotic bias by constraining its topology.

We are given the template’s image and we want to force its asymptotic bias to be below a threshold, so that it is closer to estimating the anatomy of the database, i.e., the anatomy shared by the brains. The development above suggests computing the MS complex with a persistence threshold corresponding to the desired bias threshold. Then, enforcing the template’s topology to match the MS complex will control its asymptotic bias. This enforcement procedure is called “topological denoising.”

#### 3.2.1. Topological denoising.

Topological denoising is a procedure for smoothing an image, like our template image, while preserving topological features [18, 23]. The input of the procedure is the intensity function defining the template \( \hat{T} : \Omega \to \mathbb{R} \) and an MS complex with intensity values at its nodes. Enforcing the template’s topology to match the MS complex means that we compute \( \hat{T}^\prime : \Omega \to \mathbb{R} \) which is a smoothed version of original template estimate \( \hat{T} \) containing only the intensity min-max pairs specified by the MS complex chosen. In terms of intensity, \( \hat{T}^\prime \) should be as close as possible to the original template estimate \( \hat{T} \). The values and positions of the MS extrema are preserved, while all other extrema are removed from the brain template estimate. Such a procedure provides control over the topology of the brain image \( \hat{T} \).

Formally, the original topological denoising problem is written as the minimization [23]

\[
\arg\min_{T^\prime} \sum_{x_i \in \Omega} ||\hat{T}(x_i) - T^\prime(x_i)||^2 + \int_{\Omega} ||\Delta T^\prime||^2
\]

s.t. \( T^\prime(x_i) = \hat{T}(x_i) \) for \( x_i \) a node of the MS complex,

\( T^\prime(x_j) > T^\prime(x_i) \) for \( x_j \) neighbor of \( x_i \) and \( x_i \) minimum,

\( T^\prime(x_j) < T^\prime(x_i) \) for \( x_j \) neighbor of \( x_i \) and \( x_i \) maximum,

\( T^\prime(x_i) > \min_{\text{neighbor } x_j} T^\prime(x_j) \) for \( x_i \) not an extremum,

\( T^\prime(x_i) < \max_{\text{neighbor } x_j} T^\prime(x_j) \) for \( x_i \) not an extremum.

The nonlinear inequality constraints make this optimization problem hard to solve. The solution suggested by [23] is to compute a representative function \( u \) that verifies the last four
inequality constraints. Given this function \( u \), the topological denoising problem becomes

\[
\arg\min_{T'} \sum_{x_i \in \Omega} ||\hat{T}(x_i) - T'(x_i)||^2 + \int_{\Omega} ||\Delta T'||^2 \\
\text{s.t. } T'(x_i) = \hat{T}(x_i) \text{ for } x_i \text{ a node of the MS complex,} \\
(T'(x_i) - T'(x_j))(u(x_i) - u(x_j)) > 0, \text{ for } (x_i, x_j) \text{ a pair of neighbors,}
\]

where the last constraint means that the direction of \( T' \) shall be aligned with the direction of \( u \). This alternative optimization problem is easily solved [23].

The representative function \( u \) can be computed by solving the Dirichlet problem

\[
\arg\min_{u} \int_{\Omega} ||\nabla u||^2 \\
\text{s.t. } u(x_i) = 0 \text{ for } x_i \text{ a minimum,} \\
u(x_i) = 1 \text{ for } x_i \text{ a maximum.}
\]

Minimizers of the Dirichlet energy are harmonic functions, and their properties guarantee that \( x_i \) and \( x_j \) are minima and maxima and that \( u \) contains no other extrema inside the MS regions. We refer the reader to [23] for further details.

Figure 10 shows examples of topological denoising. The topology to be enforced is represented by the red and blue dots, which are nodes of the MS complex: red for intensity maxima and blue for intensity minima. In the left example, the circle motifs that were inducing undesirable minima and maxima are removed. In the right example, two of the initial four maxima in the center of the image are removed too. Only the topology dictated by the input MS complex is preserved.

Figure 10. Topological denoising on two toy examples. We impose topological constraints on the initial images, which are on the left in both cases: Minima are in blue, and maxima are in red. The arrows denote the action of the topological denoising and point to the output image.

3.2.2. Integrating the topological denoising in the template computation pipeline. The original template’s computation is performed with the algorithm of [24] and uses the LCC Log-demons for the registrations [29]. We adapt it by adding a topological denoising step that controls the template’s asymptotic bias.

Algorithm 3.1 shows the adapted procedure. One initiates with the template being one of the subject images: \( \hat{T}_1 = I_1 \). At each iteration \( k \) of the template’s computation, one registers the subject images to the current template \( \hat{T}_k \) and performs the average of the registered
images’ intensities to get a first version of the updated template $\hat{T}_{k+1}$. So far, this matches
the usual template estimation procedure. Our adaptation is what follows. The MS complex
of the updated template $\hat{T}_{k+1}$ is computed using the R package msr [16]. Then, the updated
template $\hat{T}_{k+1}$ is smoothed using topological denoising; see Figure 12. These steps are iterated
until convergence.

Algorithm 3.1. Controlled brain template estimation.
Input: Images $\{I_i\}_{i=1}^n$, noise variance $\sigma^2$, persistence threshold $p_{\text{threshold}}$
Initialization:
$\hat{T}_1 = I_1$ (one of the subjects images)
$k = 1$
Repeat:
Nonlinearly register the images to $\hat{T}_k$, i.e., compute $\phi^i_k$: $J^i_k \simeq I^i \circ \phi^i_k$
Compute the mean deformation: $\bar{\phi}_k$
Register subject image: $L^i_k = I^i \circ \phi^i_k \circ \bar{\phi}^{-1}_k$
Compute the mean intensity image for template iteration: $\hat{T}^i_{k+1} = \frac{1}{n} \sum_{i=1}^n L^i_k$
Compute the MS complex of $\hat{T}^i_{k+1}$ at persistence level $p$
Topological denoising of $T^i_{k+1}$ using the MS complex
$k \leftarrow k + 1$
until convergence: $||\hat{T}_k - \hat{T}_{k+1}|| < \epsilon$
Output: $\hat{T}_k$

The main parameter controlling this adapted procedure is the asymptotic bias threshold,
i.e., the persistence threshold $p_{\text{threshold}}$ for the MS complex computation. The next section
discusses the choice of this parameter $p_{\text{threshold}}$. Varying the threshold $p_{\text{threshold}}$ leads to the
construction of a hierarchy of templates. The other parameter is $\sigma$, which is the noise on the
subject images. Either it is given through the experimental design, or it is estimated using
the variability of the registered subject images, as we did in section 2.

4. Experimental results. This section presents experimental results on the quantification
of the template’s asymptotic bias and the adapted algorithm that bounds this bias. We use
the Open Access Series of Imaging Studies (OASIS) database consisting of 136 T1 weighted
MR images of brains [32].

4.1. Quantification of the template inconsistency. We quantify the asymptotic bias
locally on the brain template computed from the OASIS database with the usual procedure.
This shows how faithfully the computed template represents human brain anatomy for the
neuroimaging studies.

First, we produce maps showing the local asymptotic bias directly with a color code
superimposed on the original tridimensional template image; see Figure 11. We call these
maps the asymptotic bias maps. Green indicates a low asymptotic bias for the region, and red
indicates a high asymptotic bias on the region.

The scale for the color code corresponds to a logarithmic scale, and more precisely to
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SNR_{dB}, where

\begin{equation}
SNR_{dB} = 10 \log_{10} \left[ \left( \frac{d}{\sigma} \right)^2 \right].
\end{equation}

The scale is thus in dB, as the decibel is the logarithmic unit that expresses the ratio of two values of a physical quantity, which is the squared intensity in our case. This unit emphasizes that the quantification of the asymptotic bias depends on a signal-to-noise ratio (SNR). Indeed, one can consider that the signal is \( d \), which is the template’s intensities representing the brain anatomies, and the “noise” is \( \sigma \), the intersubject variability after registration. The larger the SNR, the lower the asymptotic bias on the brain template.

We compute several maps; see (c)–(e) in Figure 11 for the same brain template. The difference between the maps is the MS complexes’ persistence threshold used to compute the asymptotic bias. The threshold is increased from left to right in Figure 11(c)–(e). Increasing the threshold makes more and more regions appear, and these are more and more biased: they become orange-red.

The asymptotic bias maps have the following interpretation with respect to neuroimaging. The maps show regions, in orange-red, where the template’s brain structures are small with respect to the subjects’ variability in the database. In these orange-red regions, it is not reasonable to have a sharply defined template, because the structures may have appeared by chance, by registration of noise between the different subjects. In other words, the maps reveal brain regions where the assumption of a unique anatomy in the subject population may break down.

4.2. Topological denoising for a consistent template.

**Choice of the persistence threshold.** Each map of Figure 11(c)–(e) represents the asymptotic bias of the brain template we would obtain if we were constraining the image to the topology of the corresponding MS. The persistence threshold gives a way of investigating the trade-off between asymptotic unbiasedness and sharpness of the template. On the one hand, a complex topology, i.e., a low persistence threshold, implies an important asymptotic bias on the template, which may not faithfully represent the brain anatomy shared by the subjects in the OASIS database. On the other hand, a topology that is too simple, i.e., a high persistence threshold, has no chance of representing a brain anatomy at all. If we want to look at small brain structures, we have to allow for some precision in the topology.

Therefore, which topology shall we choose in this trade-off of asymptotic unbiasedness versus sharpness? If the local intensity of the computed template is below the noise, there is no hope of computing a consistent template. As in the 1D example of [2], if the noise is of the same order of magnitude as the signal, the template may estimate the noise instead of the signal. Thus it makes sense to choose an inconsistency threshold between \(-1\) and 0 dB that expresses the limit situation where signal (intensity on the brain image) and noise are of the same order of magnitude.

**Applying topological denoising to control the brain template’s bias.** We apply the methodology of section 3.2 to enforce the asymptotic bias to be below a threshold, using topological denoising. Enforcing the unbiasedness in the procedure enables us to build the template of Figure 12. As a proof of concept, we have run it on the subject coronal slices of the OASIS
database. Following the development above, we bound the asymptotic bias by setting the SNR threshold to $-0.8 \text{ dB}$. We observe that the brain regions that were the more biased, i.e., those in orange-red in Figure 11, are now blurred. Thus, topological denoising decides where the sharply defined brain template makes sense as a representative of the shared brain anatomy, and blurs it where it does not.

One could be interested in a template that would be sharp and unbiased. In this case, one could consider dropping the assumption of a unique anatomy and consider multiple templates, i.e., use a mixture model. Further work is needed to investigate the construction of a stratified template, which would add a new stratification every time a region’s asymptotic bias crosses the threshold $B_\infty \sim 1\text{ dB}$.

**Conclusion and perspectives.** Computations of templates have been used in the medical imaging literature for at least 15 years. This paper considers these computations as the estimation of a unique anatomy shared by the population. We have presented a topological method to quantify the asymptotic bias of the template. This is, to the best of our knowledge, the first attempt to assess the bias of such procedures.

Our methodology builds a bridge between the diffeomorphic registration framework of medical imaging and MS theory. This link is an interesting application of topology in itself. As such, this paper opens the door to mathematical developments at the boundary of differential geometry and topology.
Our MS framework identifies biased regions in the brain template in section 3. In these regions, a sharp template might not be desirable. We control the template’s asymptotic bias by adding a topological denoising step in its iterative computation, creating a trade-off between sharpness and unbiasedness. Our methodology is illustrated on a real database of 136 brain images in section 4. It shows how the topological denoising blurs the regions that were the most biased. We control the template’s bias at the price of dropping its sharpness.

It would be very interesting to be able to keep both the unbiasedness and the sharpness of the brain template. In fact, the template being biased can be seen as an indication that the assumption of a unique anatomy within the population should be relaxed. One could think about estimating a mixture of several templates or stratified templates. Each of the templates would represent only a subset of the brain population. This subset would have a lower variability. Therefore, the parameter \( \sigma \) and the bias will both be decreasing. This will allow for sharper templates that are still unbiased.

REFERENCES


