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Topologically constrained template estimation via Morse-Smale complexes controls its statistical consistency

Abstract.

In most neuroimaging studies, one builds a brain template that serves as a reference anatomy for normalizing the measurements of each individual subject into a common space. Such a template should be representative of the population under study, in order to avoid biasing the 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 follows: it is 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, 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 quantifies spatially the brain template’s asymptotic bias. We identify the main variables controlling the inconsistency. This leads us to investigate the topology of the template’s intensity levels sets, represented by its Morse-Smale 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.

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 to compute a brain template [15]. A first practice selects one brain 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 towards this specific individual. Thus, the template fails at being a prototype of the population. This is why researchers consider the computation of an “unbiased template” that represents the mean anatomy better.

Such an “unbiased” template is often constructed by performing an iterative averaging of intensities and deformations [17, 24, 20]. One initializes with a template chosen among the subject images. Then, during each iteration, one registers the subjects to the current template, and computes the mean deformation. The new template is computed as the mean intensity of the subjects’ images, deformed with the mean deformation. This procedure does not favor any subject’s image if it does not end in 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 brain template. Computing a template is often the first step in medical image processing because of its many applications. The template is used as a standardized 3D coordinate frame where the subject brains can be compared. The subjects

44 are then characterized by their *spatial diffeomorphic deformations from the template*. These
45 deformations may serve for a statistical analysis of the subject shapes [6]. One studies the
46 normal and pathological variations of the subjects with respect to the template. The deforma-
47 tions also facilitate automated segmentation, by mapping the template’s already segmented
48 regions into each subject space.

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

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

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

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

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

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

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

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

103 Furthermore, we could think about controlling the brain template's asymptotic bias by
104 constraining its topology. Topological representations of images have been used with various
105 objectives in the literature. For example, [12] uses a topological representation of brain images
106 for classification of autism versus normals. Topological constraints have also been implemented
107 for segmentation where the reconstruction of the cortical surface needs to match the brain
108 anatomy [30, 31, 21]. However, topological representation of images or topological constraints
109 on images have not been used to study and enforce a statistical property, like asymptotic
110 unbiasedness.

111 *Contributions and Outline.* We use a topological representation of images - the Morse-
112 Smale complex - to investigate and control the asymptotic bias of the brain template. We
113 make three main contributions in this paper. First, we show how to combine geometry and
114 topology to tackle a statistical problem in neuroimaging. We provide conjectures at the
115 boundaries of the fields with sketches of their proofs. Second, we analyze the template as an
116 estimator of the brain anatomy and quantify the asymptotic bias. This leads us to discuss
117 the initial assumption of a unique anatomy. Third, we present an adaptation of the template
118 computation algorithm that bounds the bias, through topological constraints, at the price of
119 constructing a "smoother" template.

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

127 **1. Geometry and topology for template estimation .** This paper will not present mathe-
128 matical results, rather we show how geometry and topology combine to formalize the template
129 computation algorithm and highlight required directions for further mathematical develop-

130 ments.

131 **1.1. Geometrization of the action of diffeomorphisms on images.**

132 *Brain images.* We consider two- and three-dimensional images, whose domain $\Omega \subset \mathbb{R}^d$, with
 133 $d = 2, 3$, is supposed compact. We adopt the point of view of images as square-integrable
 134 functions I over the compact domain Ω , i.e. we write $I \in L_2(\Omega)$, where $L_2(\Omega)$ is a Hilbert
 135 space. The corresponding L_2 distance is invariant by volume preserving diffeomorphisms
 136 (volumorphisms). Additionally, we assume that the images are in $C^\infty(\Omega)$, which is C^∞ defined
 137 on the compact support Ω . We denote $\text{Img}(\Omega)$ the set of images.

138 To illustrate the following concepts, we use the toy Hilbert space \mathbb{R}^2 where one point
 139 schematically represents one image, see Figure 1.

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

142 On the one hand, we consider $C^\infty(\Omega)$, i.e. the smooth diffeomorphisms that are the
 143 identity outside a compact support. $C^\infty(\Omega)$ can be seen as an infinite dimensional manifold
 144 [33] and forms an infinite dimensional Lie group [26]. Its Lie algebra V is the set of smooth
 145 vector fields with compact support [26]. We use this set of diffeomorphisms to present algebraic
 146 concepts.

147 On the other hand, we consider the set $C_{\text{Id}}(\mathbb{R}^d, \mathbb{R}^d)$ defined as $C_{\text{Id}}(\mathbb{R}^d, \mathbb{R}^d) = \{\phi = \text{Id} +$
 148 $u \text{ for } u \in C_b^1(\mathbb{R}^d, \mathbb{R}^d)\}$, where the subscript “b” refers to functions that are bounded with
 149 bounded derivatives. These diffeomorphisms are “small”, i.e. not too different from the
 150 identity. We use this set to formulate mathematical conjectures which need metric properties.
 151 If the specification between the two sets is not needed, we will refer to $\text{Diff}(\Omega)$ to denote
 152 diffeomorphisms.

153 *Action of diffeomorphisms on (brain) images.* The Lie group of diffeomorphisms $\text{Diff}(\Omega)$ acts
 154 on the space of images $L_2(\Omega)$ [39]: $\rho : \text{Diff}(\Omega) \times \text{Img}(\Omega) \rightarrow \text{Img}(\Omega)$, $(\phi, I) \mapsto \phi \cdot I = I \circ \phi^{-1}$.
 155 This action is represented on Figure 1 (a), which shows an image I and its diffeomorphic
 156 deformation.

157 *Intuition and schematic representation on \mathbb{R}^2 .* The statistical analysis of this paper relies on
 158 geometric considerations in the Hilbert space of images $L_2(\Omega)$ endowed with the action of an
 159 Lie group of diffeomorphisms $\text{Diff}(\Omega)$. The intuition on the geometry in these abstract spaces
 160 will be given by a serie of figures, where:

161 $L_2(\Omega)$: Hilbert space of images is represented as \mathbb{R}^2 : 2D surface of the paper,
 162 $\text{Diff}(\Omega)$: Lie group of diffeomorphisms is represented as $SO(2)$: Lie group of 2D rotations.

164 and we consider the fundamental action of $SO(2)$ on \mathbb{R}^2 .

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

168 We note that $L_2(\Omega)$ with the action of $\text{Diff}(\Omega)$ and \mathbb{R}^2 with the action of $SO(2)$ have
 169 different properties. For example, \mathbb{R}^2 and $SO(2)$ are finite dimensional and the action of
 170 $SO(2)$ is isometric with respect to the Euclidean distance on \mathbb{R}^2 . In comparison, $L_2(\Omega)$ and
 171 $\text{Diff}(\Omega)$ are infinite dimensional and the action of $\text{Diff}(\Omega)$ is not isometric with respect to the

172 L_2 distance between images of $L_2(\Omega)$.

173 Nevertheless, we argue that our schematic representation makes sense for the following
 174 reasons. First, representing infinite dimensional spaces by finite dimensional ones is standard
 175 as it is difficult to draw infinite dimensions on a piece of paper. Second, we consider diffeo-
 176 morphisms that transform a *brain* image into another *brain* image, i.e. an image into one that
 177 looks similar. Therefore, we restrict ourselves to "small" diffeomorphisms. In this context, we
 178 will see that we can consider their action as being isometric.

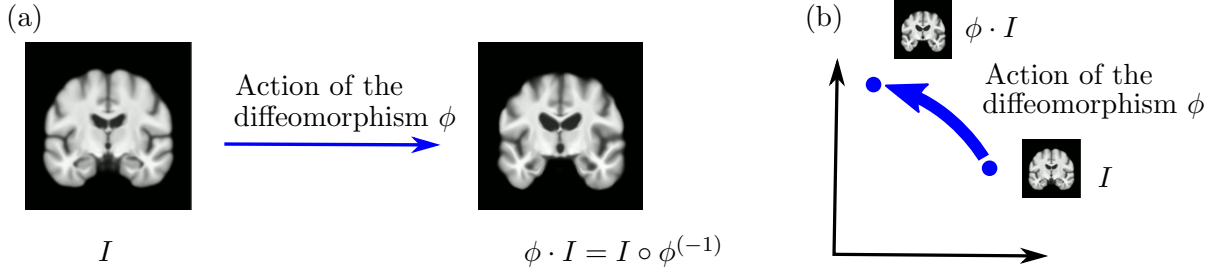


Figure 1. Action of a diffeomorphism ϕ on a brain image I . (a) the brain image before and after the action of ϕ , (b) schematic representation of the action of ϕ on the brain image I , represented as a dot in \mathbb{R}^2 .

179 **Orbit O_I of a (brain) image I .** Here, we consider $\text{Diff}(\Omega) = C^\infty(\Omega)$. The orbit O_I of a
 180 brain image I is defined as all images reachable through the action of diffeomorphisms on I :
 181 $O_I = \{I' \in \text{Img}(\Omega) | \exists \phi \in \text{Diff}(\Omega) \text{ s.t. } I' \circ \phi^{-1} = I\}$.

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

188 We note that the orbits may be infinite dimensional in the case of diffeomorphisms acting
 189 on $L_2(\Omega)$. Furthermore the orbits are not necessarily high-dimensional spheres as the action of
 190 the diffeomorphisms is not isometric. However, by considering only "small" diffeomorphisms
 191 acting on a given image I , we move locally on the orbit of image I . We could consider writing
 192 a Taylor expansion of the orbit around I [34], where the first order gives its tangent space
 193 and the second order is a high-dimensional sphere. Therefore, "small" diffeomorphisms are
 194 consistent with a representation of the images' orbits as spheres.

195 **Isotropy group G_I of a (brain) image I .** Here, we consider $\text{Diff}(\Omega) = C^\infty(\Omega)$. The isotropy
 196 group G_I of a brain image I is defined as the subgroup of $\text{Diff}(\Omega)$ formed by the diffeomor-
 197 phisms that leave I unchanged: $G_I = \{\phi \in \text{Diff}(\Omega) | I \circ \phi^{-1} = I\}$. G_I describes the intrinsic
 198 symmetry of the image I : the more symmetric is I , the larger its isotropy group. All im-
 199 ages on the same orbit have conjugate isotropy groups. Moreover, the isotropy group (also
 200 called the stabilizer) and the orbit of an image are linked by the orbit-stabilizer theorem:
 201 $O_I \sim \text{Diff}(\Omega)/G_I$ in finite dimensions. The intuition is that the larger the isotropy group (and
 202 thus, the more symmetry the image has), the smaller the orbit. Figure 2(a) shows two brain

203 images: the isotropy group of I_1 and I_2 is larger than the isotropy group of I_3 , in the sense of
 204 inclusion. As a consequence, the orbit of I_3 is “smaller” than the orbit of I_2 .

205 We use again the representation of \mathbb{R}^2 to illustrate this notion. The notion of “isotropy
 206 group” dictates the dimension of a given orbit, i.e. whether we have a 1-dimensional subman-
 207 ifold like the blue dotted circle or a 0-dimensional submanifold like the red point on Figure 2
 208 (b). The isotropy group of the image at the blue point on Figure 2(b) is the identity. Only the
 209 identity leaves this image at the same place. The isotropy group of the image represented by
 210 the red point is the whole Lie group of 2D rotations. Any rotation leaves this point invariant.

211 Going back to diffeomorphisms, we note that the isotropy group may be of infinite dimen-
 212 sion: the isotropy group of a uniform image, i.e. I constant map over Ω , is the whole group
 213 $\text{Diff}(\Omega)$. Nevertheless, the orbit-stabilizer theorem holds in infinite dimensions therefore we
 214 can rely on the intuition of “smaller” isotropy groups and “larger” orbits.

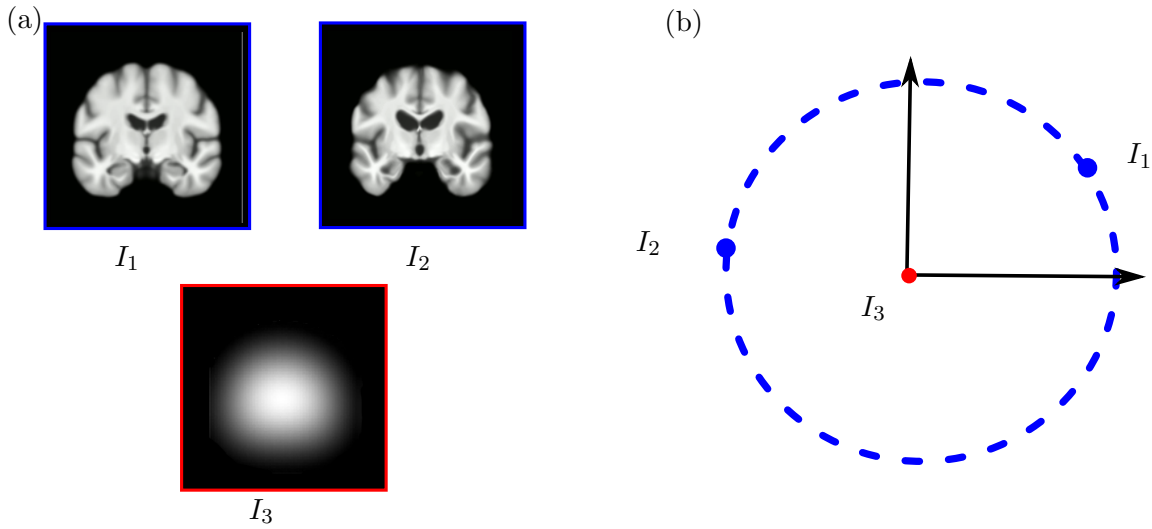


Figure 2. Orbit and isotropy group of a brain image. (a) I_1 and I_2 belong to the same orbit: I_2 is a diffeomorphic deformations of I_1 . They have conjugate isotropy groups. In contrast, I_3 belong to a different orbit and has a different isotropy group. I_3 shows more symmetry than I_1 and I_2 , thus a larger isotropy group, whereas the more asymmetric details of I_1 , 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 $(0, 0)$.

215 1.2. From geometry to topology.

216 **Topology of (brain) images.** The topology of a brain image I is defined as the topology of
 217 its level sets, these surfaces of Ω with constant intensity. topology refers to properties that are
 218 preserved under smooth deformations [16], i.e. conserved by the action of diffeomorphisms on
 219 I : for example, the number of holes, or the number of connected parts, see Figure 3(a).

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

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

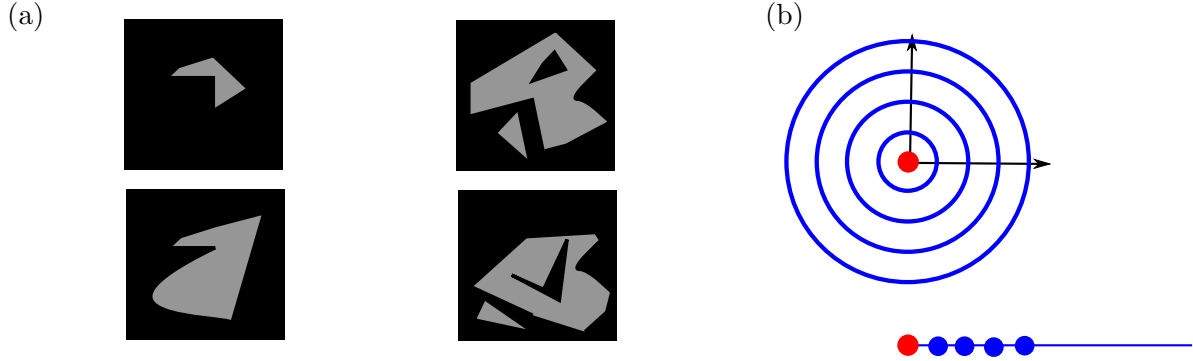


Figure 3. (a) Images in the same column have same topology, images in the line have different topologies: one cannot be diffeomorphically deformed to match the other. (b) Top: schematic representation of the space of images partitioned into orbits. The two different orbit types are in blue and red respectively. Bottom: schematic representation of the quotient space of brain images $\text{Img}(\Omega)$ by the Lie group of diffeomorphisms $\text{Diff}(\Omega)$.

229 **Gathering brain images with similar topologies: orbit types.** By definition, two brain images
 230 are of the same *orbit type* if their isotropy groups are conjugate subgroups in the Lie group of
 231 diffeomorphisms. In particular, brain images that belong to the same orbit have same orbit
 232 type. The type corresponding to the smallest isotropy group - in the sense of the inclusion
 233 among the subgroups of the diffeomorphism group - is sometimes called the principal type [1].
 234 We use this appellation in this paper. For example, if an orbit has type the identity of the
 235 group of diffeomorphisms, then it is necessarily of principal type. Equivalently, the orbits of
 236 principal type are called *principal orbits*. Other orbits are called *singular orbits*.

237 The blue circles on Figure 3(b) have same orbit type: the images on these orbits have the
 238 identity $\{Id\}$ of the Lie group as isotropy group. They are of principal type since the identity
 239 $\{Id\}$ is the smallest subgroup - in the sense of the inclusion - of the group of rotations.

240 **Stratification of the space of topologies.** In the space of brain images, we can gather orbits
 241 of same orbit type: we gather the blue circles of Figure 3(b) into $\mathbb{R}^2 \setminus \{(0,0)\}$ on the one
 242 hand, and keep the red dot $(0,0)$ on the other hand. The orbit type itself is a submanifold
 243 of the space of brain images: $\mathbb{R}^2 \setminus \{(0,0)\}$ or $(0,0)$ in the schematic brain images space \mathbb{R}^2 .
 244 Furthermore, these orbit type submanifolds form a *stratification*, meaning they fit together in
 245 a particularly nice way [38].

246 The quotient space Q is also naturally partitioned into manifolds, and this partitioning is
 247 also a stratification. All in all, Q is *not* a manifold, but Q composed of manifold pieces, and
 248 those pieces are called strata. There is a partial ordering of the strata in the quotient space,
 249 using the inclusion [22].

250 Figure 3(b) uses the analogy of \mathbb{R}^2 as the space of images and $SO(2)$ as the Lie group
 251 acting on it. It shows the orbits grouped by orbit type: the color blue denotes one orbit type

252 and the color red another orbit type. We see for example that $Q = \mathbb{R}_+$ is stratified into one
 253 stratum being \mathbb{R}_+^* - corresponding to the stratum $\mathbb{R}^2 \setminus \{(0,0)\}$ in the space of brain images -
 254 and one stratum being $\{0\}$ - corresponding to the stratum $(0,0)$ in the space of brain images.

255 **1.3. Geometry of generative model and estimation procedure.** In this subsection, we
 256 consider: $\text{Diff}(\Omega) = C_b^1(\mathbb{R}^d, \mathbb{R}^d)$.

257 *Generative model.* The n brain images I_1, \dots, I_n are interpreted with a generative de-
 258 formable model: $I_i = \phi_i \cdot T + \epsilon_i, i = 1 \dots n$, where each image $I_i \in \text{Img}(\Omega)$ is a diffeomorphic
 259 deformation $\phi_i \in \text{Diff}(\Omega)$ of a unique brain anatomy T , to which noise ϵ_i is added. The pa-
 260 rameter T represents the brain anatomy shared by the population. The transformations ϕ_i 's
 261 and the noises ϵ_i 's are i.i.d. realizations of random variables. The transformations ϕ_i 's follow
 262 a general law, which could be for example a Gaussian law in a finite-dimensional subspace of
 263 the Lie group and the ϵ_i 's represent Gaussian noise on the space of images. We denote σ^2 its
 264 variance. Definitions of distributions on finite dimensional Riemannian manifolds are taken
 265 from [36] and the Gaussian distributions for infinite dimensional spaces from [28].

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

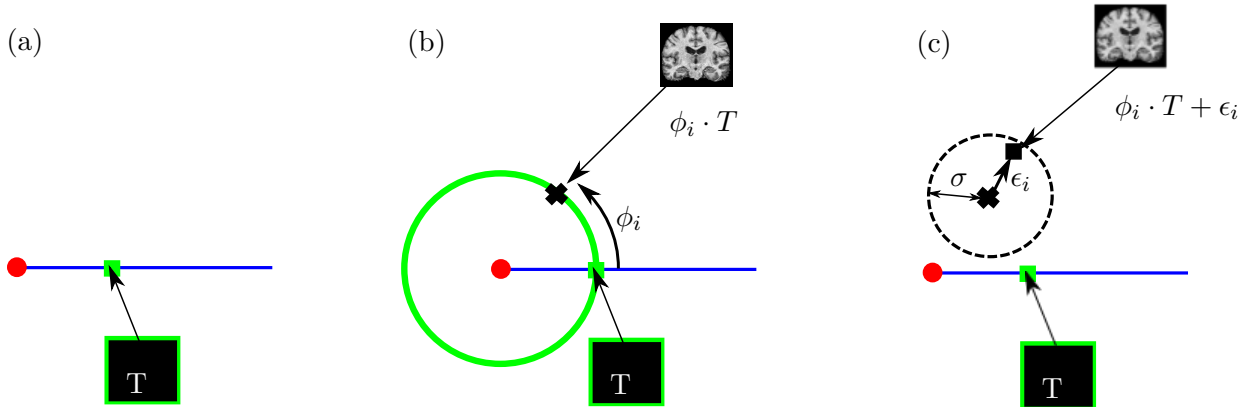


Figure 4. Schematic illustration of the generative model of the brain images data. As before, the space of brain images is represented by the plane \mathbb{R}^2 . (a) First step of the generative model: generate a brain anatomy. One usually assumes that there is a unique brain anatomy: T , in green. (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 ϵ_i in the space of images. The brain image $\phi_i \cdot T + \epsilon_i$ does not belong to the orbit of T anymore.

270 *Computing the template: an estimation procedure.* Computing the brain template amounts
 271 to invert the generative model: given the data, we want to estimate the parameter T . The
 272 transformations ϕ 's are hidden variables of the model. The natural statistical procedure to
 273 estimate T in this context is the Expectation-Maximization (EM) algorithm [13]. The EM is
 274 an iterative procedure that maximizes the log-likelihood of the generative model with hidden
 275 variables. As such, the EM gives an asymptotically unbiased and consistent estimation of the

276 brain anatomy T .

277 In practice, one does not use the EM algorithm because it is computationally expensive,
 278 especially when dealing with tridimensional images. Most neuroimaging pipelines rely on *an*
 279 *approximation of* the Expectation-Maximization algorithm to estimate the brain anatomy,
 280 called “Fast Approximation with Modes” in [2]. It runs as follows. Initialize the estimate
 281 with $\hat{T} = I_1$, i.e. one of the brain images from the database. Then, iterate the following two
 282 steps until convergence [24]:

$$283 \quad (1) \quad \hat{\phi}_i = \operatorname{argmin}_{\phi \in \operatorname{Diff}(\Omega)} d_{\operatorname{Img}(\Omega)}(\hat{T}, \phi \cdot I_i) + \lambda \operatorname{Reg}(\phi), \quad \forall i \in \{1, \dots, n\},$$

$$284 \quad (2) \quad \hat{T} = \operatorname{argmin}_{T \in \operatorname{Img}(\Omega)} \sum_{i=1}^n d_{\operatorname{Img}(\Omega)}(T, \hat{\phi}_i \cdot I_i)^2.$$

285

286 Step (1) is an estimation $\hat{\phi}_i$ of the diffeomorphisms ϕ_i , and an approximation of the E-step
 287 of the EM algorithm. In practice, each brain image I_i is registered to the current template
 288 estimate and the $\hat{\phi}_i$ is the result of this registration. The term Reg is a regularization that
 289 ensures that the optimization has a solution. Showing that the estimates $\hat{\phi}_i$'s and \hat{T} exist is
 290 technical and beyond the scope of this paper.

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

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

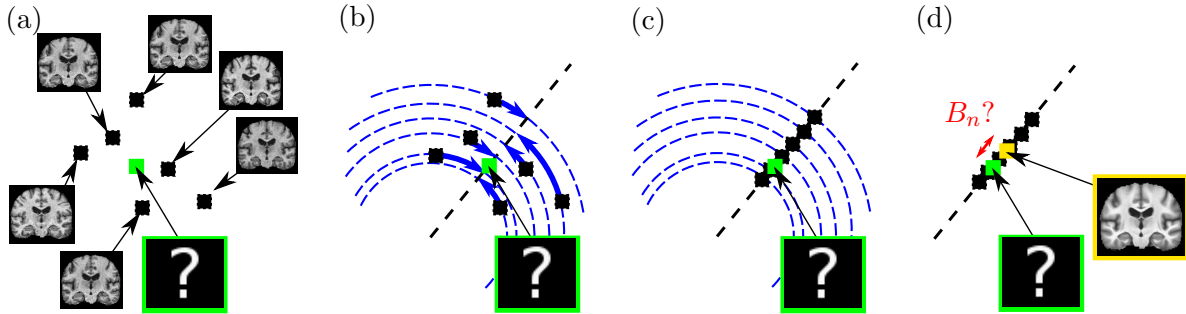


Figure 5. Geometrization of an iteration of the template’s computation: (a) n subjects images (black squares); (b) the n images are registered, they travel on their orbit (the blue circles) to get aligned; (c) registered images; (d) the empirical brain template \hat{T} (in yellow) is computed as the 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 ?

298 *Evaluation of the procedure: definition of asymptotic bias B_∞ .* We evaluate the template
 299 \hat{T} as an estimator of the unique brain anatomy T (see Figure 5 (d)) given n observations I_i ,
 300 $i = 1 \dots n$. We note that in other papers, T may be called the template directly and \hat{T} the
 301 template’s estimate.

302 We consider two measures of the accuracy of this estimator: its variance V_n^2 and bias B_n ,
 303 which are defined as:

$$304 \quad V_n^2 = \mathbb{E}((\hat{T} - \mathbb{E}(\hat{T}))^2) \quad \text{and} \quad B_n = \mathbb{E}(\hat{T} - T).$$

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

310 1.4. Geometry of the template estimator's evaluation.

311 *Estimation procedure interpreted as the Fréchet mean in the quotient space.* We consider
 312 the estimation procedure of Equation 1.3. First, we note that the regularization term in step
 313 (1) forces the diffeomorphisms to be small, i.e. to be close to the identity and close to have
 314 an isometric action on the images. Second, we could consider the group of volumorphisms,
 315 the subgroup of diffeomorphisms that leave a volume form V invariant and is used to model
 316 incompressible fluids in continuum mechanics. In this case, using $y = \phi^{-1}(x)$ and the fact
 317 that the volume form is conserved:

$$318 \quad (1) \quad d(\phi \cdot I_1, \phi \cdot I_2)^2 = \int_{\Omega} (I_1 \circ \phi^{-1}(x) - I_2 \circ \phi^{-1}(x))^2 dV(x) = \int_{\Omega} (I_1(y) - I_2(y))^2 dV(y) = d(I_1, I_2)^2$$

319 and the action is thus isometric.

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

322 First, we model the estimation procedure as follows.

$$323 \quad (1) \quad \hat{\phi}_i = \operatorname{argmin}_{\phi \in G} d_M(\hat{T}, \phi \cdot I_i), \quad \forall i \in \{1, \dots, n\},$$

$$324 \quad (2) \quad \hat{T} = \operatorname{argmin}_{T \in M} \sum_{i=1}^n d_M(T, \hat{\phi}_i \cdot I_i)^2.$$

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

327 This converges to a local minimum because it decreases at each step a cost bounded below
 328 by zero. The estimator computed with this procedure is:

$$329 \quad (2) \quad \hat{T} = \operatorname{argmin}_{T \in M} \sum_{i=1}^n \min_{\phi \in G} d_M^2(T, \phi \cdot I_i).$$

330 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
 331 Equation 2 defines the Fréchet mean on the quotient space [36].

332 The study of the set of solutions of algorithms in Equation 1.3 and Equation 1.4 is an
 333 interesting direction of research but beyond the scope of this paper. However, we point out
 334 that the existence and uniqueness of the solution of algorithm 1.4 is linked to the question
 335 of whether the Fréchet mean exists and is unique in the quotient space, which is studied for
 336 example in [25, 4].

337 *Asymptotic bias B_∞ and curvature.* We show in [35] that the asymptotic bias is non zero:
 338 $B_\infty \neq 0$. For an infinite number of brain images $n \rightarrow +\infty$, the estimate converges, but not
 339 to the brain anatomy T it was designed for. We compute in [35] a Taylor expansion of the
 340 asymptotic bias B_∞ around the noise $\sigma = 0$, in the case of a finite dimensional manifold and
 341 isometric Lie group action [34]:

$$342 \quad (3) \quad B_\infty = \frac{\sigma^2}{2} H(T) + \mathcal{O}(\sigma^3) + \epsilon(\sigma)$$

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

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

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

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

372 *Quantifying the asymptotic bias B_∞ of the brain template.* In neuroimaging, the manifold is
 373 the space of brain images $\text{Img}(\Omega)$ and the Lie group is the group of diffeomorphisms $\text{Diff}(\Omega)$,
 374 both infinite dimensional. This paper assumes that we can apply the geometry of [34], because
 375 there are indications that B_∞ appears in the same fashion in infinite dimension, see Figure 7.

376 First, [34] studies the bias when the dimension of the manifold increases. They consider
 377 the finite dimensional manifold $M = \mathbb{R}^m$ with the action of $SO(m)$, i.e. a generalization of

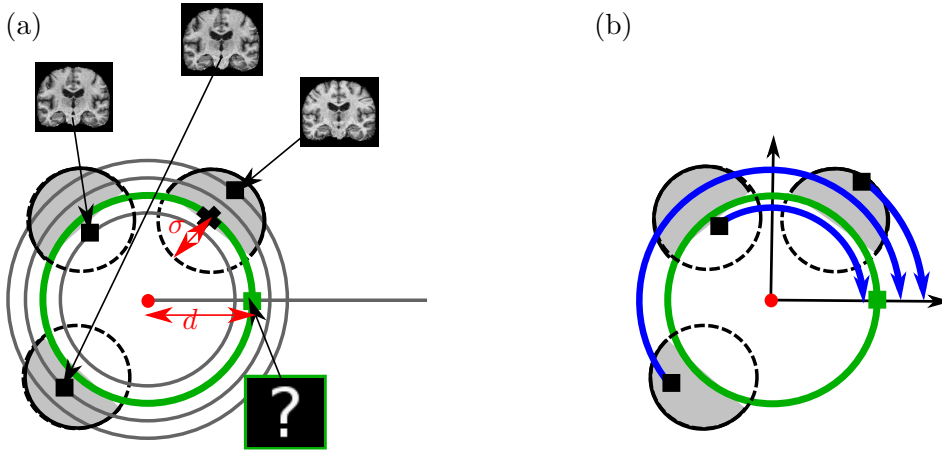


Figure 6. Schematic illustration of the asymptotic bias in the template computation algorithm of neuroimaging. (a) The images generated with the model described above have a higher probability to be “outside” (with respect to the curvature) of the template’s orbit. (b) The registration during template’s estimation aligns the images. The distribution of images is unbalanced with respect to the real template.

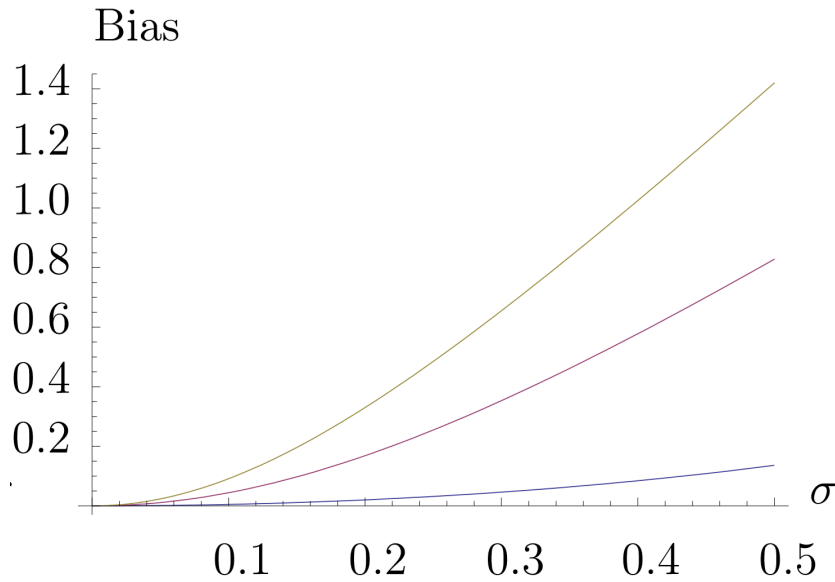


Figure 7. Image from [34]. Take $M = \mathbb{R}^m$ with the action of $SO(m)$. The template’s bias increases with σ and is more important as m increases: the blue curve shows the asymptotic bias for $m = 2$, the pink curve for $m = 10$ and the yellow curve for $m = 20$.

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

380 Then, the work of [3] shows that there exists an asymptotic bias in an infinite dimensional
 381 Hilbert space. The work of [14] provided an asymptotic behavior of the bias when the noise
 382 level σ tends to infinity. This bias is exemplified on examples of template of signals in [14],

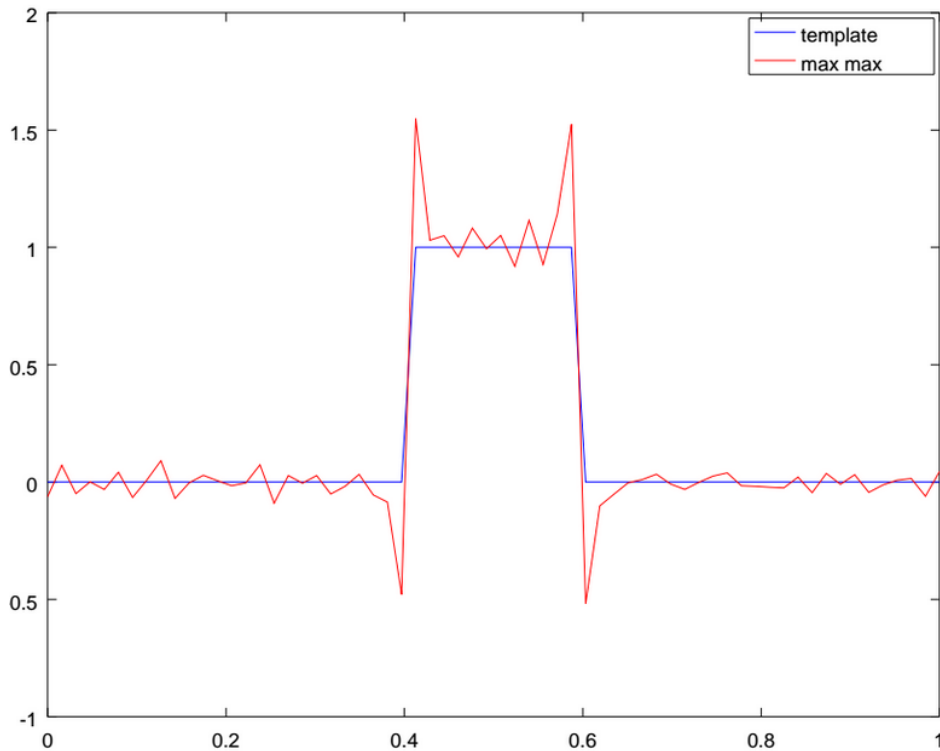


Figure 8. Image from [14]. The real signal is shown in blue. The template, computed with $n = 10^5$ observations simulated with Gaussian noise with $\sigma = 10$, is shown in red. There is an asymptotic bias in the estimation of signal.

383 see Figure 8. Although the 1D signals are discretized for the numeric implementations, they
 384 represent 1D functions that are elements of an infinite dimensional Hilbert space.

385 Ultimately, [9] gives a lower bound of the asymptotic bias for shapes of curves in 2D,
 386 where terms depend on derivatives of the functions representing the curve. These derivatives
 387 can be interpreted as the derivative of the action of translations, which leads to the curvature
 388 of the orbit of the given function under the translations' action. As a consequence of these
 389 examples, we assume that the intuition provided by [34] applies to neuroimaging and that the
 390 bias depends on the ratio $(\frac{\sigma}{d})^2$.

391 **2. Computational representation of geometry and topology .** Now that we have seen
 392 that the geometrization of template estimation leads us to investigate the topology of images,
 393 we show in this section how the Morse-Smale complexes can be used to encode the topology
 394 and help the estimation of the geometric parameters d and σ previously introduced.

395 2.1. Definition of Morse-Smale complexes for (brain) images.

396 *Morse-Smale (intensity) functions.* A real-valued smooth map $I : \Omega \rightarrow \mathbb{R}$ is a *Morse function*
 397 if all its critical points are non-degenerate (the Hessian matrix is non-singular) and no two
 398 critical points have the same function value. The intensity function I representing a bi- or
 399 tri-dimensional brain image is a Morse function, at least after a convolution with a smoothing

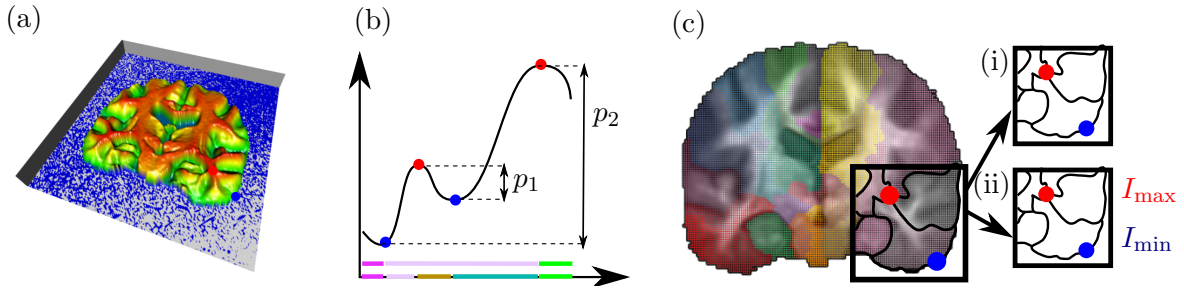


Figure 9. (a) Intensity I on a 2D brain image visualized as height: maxima are in red, minima in blue. This is a Morse-Smale function $I : \Omega = \mathbb{R}^2 \rightarrow \mathbb{R}$. (b) Persistences $p_1 < p_2$ of two pairs min-max. A threshold $p_1 < p < p_2$ divides the domain into 3 regions (pink, violet, green), while $p < p_1$ divides it in 5 regions (pink, violet, brown, turquoise, green). (c) Computational representation of the geometry: Regions on a 2D domain, induced by a MSC with threshold $p = 0.1$: (i) The MS graph represents the isotropy group's class of the image, (ii) the labeled MS graph represents the image's orbit under the diffeomorphisms

400 Gaussian [11]. In the following, I represents a brain image. *Morse theory* traditionally
 401 analyzes the topology of a manifold by studying the Morse functions on that manifold. Here,
 402 the manifold is known: it is the image domain Ω . We are not interested in the topology of Ω
 403 but rather in the topology of the functions I themselves, that is: we would like to know the
 404 distribution of their critical points. Figure 9(a) shows a 2D slice of a 3D brain image I , where
 405 the intensity is represented as the height, to better emphasize its maxima and minima: the
 406 maxima are in red and the minima in blue.

407 We introduce the notions of integral lines, ascending and descending manifolds that are
 408 needed to define Morse-Smale (intensity) functions. An *integral line* is a maximal path in the
 409 image domain Ω whose tangent vector correspond to the intensity gradient ∇I , the gradient
 410 of I , at every point. This notion comes from autonomous ordinary differential equation, where
 411 it represents the trajectory of a system verifying:

$$412 \quad (4) \quad \frac{dx}{dt}(x) = \nabla I(x)$$

413 Each integral line starts and ends at critical points of I , where the gradient ∇I is zero.
 414 *Ascending* $A(x_i)$ and *descending* $D(x_j)$ manifolds of respective extrema x_i and x_j are defined
 415 as:

$$416 \quad A(x_i) = \{x \in \Omega \mid \text{The integral line going through } x \text{ ends at } x_i\}$$

$$417 \quad D(x_j) = \{x \in \Omega \mid \text{The integral line going through } x \text{ starts at } x_j\}$$

419 Take the two manifolds $A(x_i)$ and $D(x_j)$ in Ω and assume they intersect at a point $p \in \Omega$.
 420 Let T_A (resp. T_D) denotes the set of all vectors tangent to $A(x_i)$ (resp. $D(x_j)$) at p . If every
 421 vector in Ω 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
 422 to intersect transversely at the point p . The intensity function I defining the brain image
 423 is *Morse-Smale* if the ascending and descending manifolds only intersect transversely. We
 424 assume in the following that all brain images I are Morse-Smale.

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

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

$$438 \quad (5) \quad p(x_i) = |I(x_i) - I(n(x_i))|$$

439 where $n(x_i)$ is the critical point closest to x_i in intensity, among the critical points connected
 440 to x_i by an integral line [16]. The persistence of x_i is a measure of its significance as a critical
 441 point, i.e. importance of the topological feature. Figure 9(b) illustrates the definition of
 442 persistence on a 1D example. The function represented has 4 critical points: two minima and
 443 two maxima. The figure shows how they pair, as well as their persistence. On the x -axis,
 444 colors show the regions of the corresponding 1D Morse-Smale complex.

445 Beside this usual definition of persistence of a critical point, we define here the *persistence*
 446 *of a region of the Morse-Smale complex* as the amount of change in intensity required to
 447 remove this region from the MS complex, and more precisely:

$$448 \quad (6) \quad p(\text{region}) = |I_{\max} - I_{\min}|$$

449 where I_{\max} and I_{\min} are respectively the maximum and the minimum in intensity of this
 450 region. In contrast to the definition of the persistence of a critical point, we do not rely on
 451 the saddle points, but only on the extrema i.e. the minima and maxima.

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

460 The persistence introduces a notion of scale at which the Morse-Smale complex of I is
 461 considered. One keeps only the nodes whose persistence is above the threshold. Figure 9(b)
 462 shows that the one dimensional domain is partitioned differently if one takes a threshold p
 463 below p_1 or between p_1 and p_2 . We say that a Morse-Smale complex is represented at a
 464 given persistence level. At the scale of the persistence threshold p , the intensity is considered
 465 monotonic on each region of the MS.

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

469 **2.2. Computing Morse-Smale complexes of (brain) images in practice.** The previous
 470 definitions are relevant to (continuous) Morse-Smale theory and apply strictly for a continuous
 471 intensity function I . Nevertheless, the MS complex, introduced in terms of ascending and
 472 descending manifolds, can be computed for discrete brain images as follows [16]. We choose
 473 the approach of line integrals to compute the Morse-Smale complex. Other approaches may
 474 also be considered like the Delaunay triangulation [12].

475 *Computing the Morse-Smale of a brain image.* We compute the Morse-Smale complex of a
 476 brain image, which will later be the brain *template* image. Our input are $\{x_i, I_i\}$, i.e. the in-
 477 tensity values $\{I_i\}$ on a grid $\{x_i\}$ of Ω . We compute the integral lines of the intensity gradient,
 478 which we then gather to get the regions of the Morse-Smale complex. For each element of the
 479 grid x_i , following the gradient ∇I leads to computing the integral line going through x_i and
 480 in particular its starting and ending points [16]. The domain Ω can be approximated via a
 481 k nearest-neighbor graph and one computes the integral lines by considering the connectivity
 482 of the graph. Then, elements x_i 's with same starting and ending points belong to the same
 483 Morse-Smale region. This gives the partition of the domain Ω and therefore the Morse-Smale
 484 complex. We remark that x_i 's necessarily belong to a 3-dimensional (for a tridimensional im-
 485 age) component of the Morse-Smale complex because the 0-, 1- and 2-dimensional components
 486 have measure zero.

487 Figure 9(c) shows the Morse-Smale complex of the 2D slice of a 3D brain image for level
 488 of persistence of $p = 0.1$. The image's 2D domain is divided in different regions, represented
 489 by the different colors. The quadrant shows part of the underlying Morse-Smale graph. The
 490 red dot represents a maximum in intensity, and the blue dot a minimum of intensity. They
 491 are nodes of the underlying graph on the domain Ω .

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

501 **2.3. Template's computation and Morse-Smale complexes.** We show how the MS com-
 502 plex of an image can represent its geometry and in particular isotropy group.

503 *Lie algebra of the isotropy group and intensity gradient of the brain template.* The template
 504 is an image $I \in \text{Img}(\Omega)$. We consider the Lie group of diffeomorphisms $\text{Diff}(\Omega) = C^\infty(\Omega)$ and
 505 its Lie algebra V , see Subsection 1.1.

506 **Lemma 1.** *Take $\epsilon > 0$ and consider the Lie algebra:*

507 (7)
$$V_I = \{v \in V \text{ s.t.}: I \circ \text{Exp}(tv) = I, \forall |t| < \epsilon\}$$

508 *By construction, the exponential of the elements of V_I are in the isotropy group of I . For*
 509 *$v \in V_I$, we have:*

$$510 \quad (8) \quad \forall x \in \Omega, \quad \nabla I(x)^T \cdot v(x) = 0$$

511 ***Proof.** Take $v \in V_I$ and $|t| < \epsilon$. Its group exponential is a diffeomorphisms in the isotropy*
 512 *group G_I , which can be written:*

$$513 \quad \phi = \exp(tv) = Id + tv + \mathcal{O}(t^2)$$

515 Then, the equation above leads to:

$$516 \quad I(x) = I(x - tv(x) + \mathcal{O}(t^2))$$

$$517 \quad I(x) = I(x) - DI(x) \cdot (tv(x)) + \mathcal{O}(t^2)$$

$$518 \quad 0 = DI(x) \cdot (tv(x)) + \mathcal{O}(t^2)$$

520 The identification of the coefficients in this Taylor expansion leads to:

$$521 \quad \nabla I(x) \cdot v(x) = 0$$

523 A vector field of V_I , which is in the Lie algebra of the isotropy group of the image I , is
 524 perpendicular the image's gradient at any point x of the image's domain Ω . ■

525 We note that this lemma does not give a characterization of the vector fields in V_I . It gives
 526 the inclusion: $V_I \subset \{v | \forall x \in \Omega, \nabla I(x) \cdot v(x) = 0\}$. Thus, it allows to control the complexity of
 527 V_I , and thus of some of the isotropy group's Lie algebra. It represents a first step towards the
 528 following conjecture.

529 **Conjecture 1.** *The Lie algebra of the isotropy group G_I of the brain image I is constituted*
 530 *of vector fields that are everywhere perpendicular to the image's gradient.*

531 **Sketch of Proof 1.** *The proof will study the relations between the following three sets of*
 532 *vector fields:*

- 533 - the Lie algebra \mathfrak{g}_I of G_I ,
- 534 - the set $V_I = \{v \in V \text{ s.t.: } I \circ \text{Exp}(tv) = I, \forall |t| < \epsilon\}$,
- 535 - the set $V_\perp = \{v | \forall x \in \Omega, \nabla I(x) \cdot v(x) = 0\}$.

537 • *Proving $\mathfrak{g}_I = V_I$ by proving the double inclusion: (a) $\mathfrak{g}_I \subset V_I$ and (b) $V_I \subset \mathfrak{g}_I$.*

538 *The inclusion (a) may be difficult to prove directly because of the lack of characterization*
 539 *of the infinite dimensional Lie algebra \mathfrak{g}_I . The inclusion (b) could make use of the above*
 540 *Lemma which shows that $\text{Exp}(V_I) \subset G_I$. We need to use the group logarithm in order to*
 541 *transform an inclusion on Lie groups into an inclusion on Lie algebra. The group logarithm is*
 542 *defined as the reciprocal of the group exponential, on its domain of bijectivity. As the domain*
 543 *of bijectivity is not well characterized in the general case, it is difficult to make use of this.*

544 • *Proving $V_I = V_\perp$ by proving the double inclusion: (a) $V_I \subset V_\perp$ and (b) $V_\perp \subset V_I$.*

545 *The inclusion (a) is proven in Lemma 1. The inclusion (b) may be proven in two steps.*
 546 *First, we would write the full Taylor expansion of $I \circ \text{Exp}(tv)$ where v is an element of V_\perp and*

547 show that the orders above the 1st give 0. At this point, the expression of the Taylor expansion
 548 is unclear, as well as if the condition $v \perp \nabla I$ is sufficient to make the orders above the 1st
 549 make 0. In a second step, we would need to translate the inclusion written in terms of Lie
 550 groups as an inclusion written in terms of Lie algebra, which is not trivial according to the
 551 paragraph above.

552 To understand the intuition behind this conjecture, consider a uniform image, i.e. with
 553 a constant intensity. In this case, there is no restrictions a priori on the vector fields of the
 554 Lie algebra of the image's isotropy group. Thus, the isotropy group is as large as it can be.
 555 We get that the isotropy group of an image with constant intensity is the whole group of
 556 diffeomorphisms.

557 **Intensity gradient and MS graph.** We now present a lemma showing that the MS graph can
 558 be used to computationally represent the isotropy group of an image. Take two images I_1 and
 559 I_2 . Assume that their MS graphs are the same, regardless of the nodes' positions.

560 **Lemma 2.** *Assume we can map the level sets of I_1 to the level sets of I_2 . This implies that*
 561 *we can map the partition of the domain I_1 induced by its Morse-Smale to the partition of the*
 562 *domain of I_2 .*

563 *Take a part $w \subset \Omega$ of this partition. There exists a diffeomorphism ψ and a function κ*
 564 *such that: $\nabla I_2(x) = \kappa(x).d^*\psi(x).\nabla I_1 \circ \psi(x), \forall x \in w$.*

565 **Proof.** We consider a part $w \subset \Omega$ of the partition of the domain of I_1 induced by its
 566 Morse-Smale complex. On this part, there exists a function f such that:

$$567 \quad (9) \quad I_1 = f \circ I_2 \circ \psi$$

568 The function f gives the mapping of intensity levels on each level set. Differentiating the
 569 previous equation with the chain rule gives:

$$570 \quad (10) \quad dI_1 = df(I_2 \circ \psi).dI_2 \circ \psi.d\psi$$

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

$$572 \quad (11) \quad \nabla I_1 = \kappa.\nabla I_2 \circ \psi.d^*\psi \quad \blacksquare$$

573 This lemma is the first step towards the following conjecture.

574 **Conjecture 2.** *Two images with same MS graphs have same isotropy group.*

575 **Sketch of Proof 2.** *The images I_1 and I_2 have the same MS graph. The graph of I_1 , taken*
 576 *with the nodes and edges positions on Ω , can be diffeomorphically deformed on the graph of*
 577 *I_2 . We take ψ_1 a diffeomorphism that realizes the graphs' matching.*

578 *Now, $I_1 \circ \psi_1^{(-1)}$ and I_2 share the same MS graph, taken with the nodes and edges' positions*
 579 *on Ω . We consider one cell of this graph.*

580 *We consider the integral lines of the respective gradients $\nabla \psi_1.\nabla I_1 \circ \psi_1$ and ∇I_2 on the*
 581 *cell. Both define a "parallel" partition of the cell. As a consequence, the set of integral lines*
 582 *of the gradient of $I_1 \circ \psi_1^{(-1)}$ can be mapped diffeomorphically to the set of integral lines of the*
 583 *gradient of I_2 . We take ψ_2 a diffeomorphism that realizes the matching of the integral lines.*

584 *At this step, the notion of parallel partition would need to be written as a definition, together*
 585 *with the proof of the existence of ψ_2 .*

586 *Here, we would need to combine the ψ_2 's obtained on the different cells of the MS complex*
 587 *into one transformation on Ω that we also write ψ_2 . A study of the behavior of ψ_2 on the*
 588 *edges of the MS complex should show that ψ_2 is itself a diffeomorphism on Ω . Then, we write*
 589 *$\psi = \psi_2 \circ \psi_1$. At the end of this step, I_1 is transformed to $I_1 \circ \psi^{(-1)}$.*

590 *The gradients of $I_1 \circ \psi^{(-1)}$ and I_2 share the same integral lines. Therefore ψ also maps*
 591 *the level sets of I_1 to the level sets of I_2 . Using Lemma 2, we conclude.*

592 In others words: if two images I_1, I_2 have the same MS graph, then I_1 can be diffeo-
 593 morphically deformed so that its intensity gradient is parallel at every point to the intensity
 594 gradient of I_2 .

595 From Lemma 1, the sets $\{v_1 | \forall x \in \Omega, \nabla I_1(x) \cdot v_1(x) = 0\}$ and $\{v_2 | \forall x \in \Omega, \nabla I_2(x) \cdot v_2(x) = 0\}$
 596 control the isotropy groups of I_1 and I_2 . If I_1 and I_2 have same MS graph, any vector field
 597 in the first set can be diffeomorphically deformed to get a vector field in the second set, and
 598 conversely. As a consequence, the MS graph represents the image's isotropy group. From
 599 Section 1, we know that the isotropy group controls, in turn, the orbit's type of the image i.e.
 600 to which stratum the image belongs.

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

605 **3. Topology quantifies and controls the template's asymptotic bias.** This Section gath-
 606 ers the elements of Sections 1 and 2 to quantify the asymptotic bias in the brain template
 607 computation. We use Morse-Smale complexes to quantify, and then control, the bias.

608 3.1. Quantify the template inconsistency.

609 *Understand and estimate the geometric parameter d .* The distance d is the distance of
 610 the current image to a brain image with larger isotropy group, measured in sum of squared
 611 differences of intensities, see Figure 6. How can we measure this distance d locally on the
 612 template's image? From Section 1, we know that the isotropy group becomes larger when the
 613 image is "more symmetric". From Section 2, we know that the isotropy group becomes larger
 614 when the image topology becomes simpler. Thus, the distance d is a distance in intensity
 615 from the template image to a similar image with simpler topology.

616 We want to express this distance locally on the template image. Modifying the intensity
 617 locally on the template image modifies the image itself and may simplify its topology. For
 618 example, modifying the intensity locally in a region of the image can suppress a min-max pair
 619 and the image becomes "more symmetric". Thus we describe the distance d locally on the
 620 image by the amount of intensity needed to be changed in this region, so that the topology is
 621 simplified.

622 We quantify the local intensity needed to simplify the template image's topology using
 623 the Morse-Smale complex representation of Section 2. Let be given the Morse-Smale complex
 624 of the template image. The intensity needed to simplify the image's topology is, by definition,
 625 the intensity needed to simplify the Morse-Smale graph. We consider the partition of the

626 image's domain Ω induced by the Morse-Smale complex. For each region of the partition,
 627 the intensity needed to simplify the topology can be represented by the amount of intensity
 628 needed to remove the min-max pair of the region:

$$629 \quad (12) \quad \hat{d}(\text{region}) = \hat{T}_{\max} - \hat{T}_{\min} = p_{\hat{T}}(\text{region})$$

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

634 *Understand and estimate the geometric parameter σ .* Now we turn to the second geometric
 635 parameter that causes the asymptotic bias: the standard deviation σ of the noise, see again
 636 Equation 3 and Figure 6. The standard deviation σ of the noise is a parameter of the generative
 637 model that we assume has produced the observed images of the subjects brain anatomies. The
 638 parameter σ is unknown but it can be estimated from the observed images. Since we want to
 639 compute the asymptotic bias locally, we are interested in estimating the parameter σ locally,
 640 and for example on a region of the Morse-Smale complex of the template image. We estimate
 641 it as the average of the variability in intensity of the registered images in the region:

$$642 \quad (13) \quad \hat{\sigma}(\text{region}) = \frac{1}{\#x} \sum_{x \in \text{region}} \hat{\sigma}(x),$$

643 where $\hat{\sigma}(x)$ is the variability in intensity of the registered images at the voxel x , and serves as
 644 an estimate of the noise at this voxel. This quantifies the amount of noise in this region. The
 645 larger the standard deviation σ of the noise, the more chances for the template to show min-
 646 max pairs that appeared by chance. One could use other estimator of the standard deviation,
 647 for example the sample standard deviation. Future work may investigate these estimators and
 648 their impact on the estimator of the template's bias.

649 *Compute the asymptotic bias using the persistence of the whitened brain template.* The local
 650 estimates of the geometric parameters d and σ enable us to estimate the asymptotic bias
 651 locally on a brain region:

$$652 \quad (14) \quad \hat{B}_{\infty}(\text{region}) = \left(\frac{\hat{d}(\text{region})}{\hat{\sigma}(\text{region})} \right)^{-2},$$

653 We emphasize here that \hat{B}_{∞} is an *estimate* of the asymptotic bias B_{∞} (of the brain template
 654 estimation), and not an exact computation.

655 We link the estimate \hat{B}_{∞} to the definition of persistence in the Morse-Smale complex
 656 framework. First, we define the *whitened brain template estimate* \hat{t} of \hat{T} as:

$$657 \quad (15) \quad \forall x \in \Omega, \quad \hat{t}(x) = \frac{\hat{T}(x)}{\hat{\sigma}(x)}.$$

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

661 We assume that the critical points of \hat{t} are close to the critical points of \hat{T} and consider the
 662 Morse-Smale complex of the whitened template. We further assume that: $\hat{\sigma}_{\text{region}} \simeq \hat{\sigma}(\text{max}) \simeq$
 663 $\hat{\sigma}(\text{min})$, where $\hat{\sigma}(\text{max}), \hat{\sigma}(\text{min})$ are the variabilities at the respective min and max of the
 664 Morse-Smale complex. We can write:

$$665 \quad (16) \quad \hat{B}_{\infty}(\text{region}) \simeq \left(\frac{\hat{T}_{\text{max}}}{\hat{\sigma}(\text{max})} - \frac{\hat{T}_{\text{min}}}{\hat{\sigma}(\text{min})} \right)^{-2} = (\hat{t}(\text{max}) - \hat{t}(\text{min}))^{-2} = p_{\hat{t}}(\text{region})^{-2},$$

666 where we recognize the persistence $p_{\hat{t}}(\text{region})$ of the corresponding region of the whitened
 667 template \hat{t} . This links the estimation of the asymptotic bias to the persistence of the whitened
 668 template's Morse-Smale complex. This shows how a topological property of the image in fact
 669 represents a statistical property of this image as the estimate of the brain template.

670 **Hierarchy of the whitened template.** The persistence of the whitened template quantifies
 671 locally the asymptotic bias, i.e. how far the brain template is from the unique brain anatomy
 672 of the generative model. Is there a statistical interpretation of the hierarchies of Morse-Smale
 673 complexes, introduced in Section 2? Let us consider another Morse-Smale of the whitened
 674 template's hierarchy, i.e. a Morse-Smale computed at a given persistence threshold $p_{\text{threshold}}$.
 675 There is an asymptotic bias threshold that corresponds, which we can write: $p_{\text{threshold}}^{-1/2}$. The
 676 regions kept in the new Morse-Smale are those having a persistence higher than the persistence
 677 threshold $p_{\text{threshold}}$, i.e. those having an asymptotic bias lower than the asymptotic bias
 678 threshold $p_{\text{threshold}}^{-1/2}$.

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

685 **3.2. Controlling the template's asymptotic bias by constraining its topology.** We are
 686 given the template's image and we want to force its asymptotic bias to be below a threshold,
 687 so that it is closer to estimating the anatomy of the database, i.e. the anatomy shared by
 688 the subject brains. The development above suggests to compute the Morse-Smale complex
 689 with a persistence threshold corresponding to the desired bias threshold. Then, enforcing
 690 template's topology to match the Morse-Smale complex will control its asymptotic bias. This
 691 enforcement procedure is called "Topological denoising".

692 **3.2.1. Topological denoising.** Topological denoising is a procedure for smoothing an im-
 693 age, like our template image, while preserving topological features [23, 18]. The input of the
 694 procedure is the intensity function defining the template $\hat{T} : \Omega \rightarrow \mathbb{R}$ and a MS complex with
 695 intensity values at its nodes. Enforcing the template's topology to match the MS complex
 696 means that we compute $\hat{T}' : \Omega \rightarrow \mathbb{R}$ which is a smoothed version of original template estimate
 697 \hat{T} containing only the intensity min-max pairs specified by the MS complex chosen. \hat{T}' should
 698 be otherwise as close as possible to the original template estimate \hat{T} in terms of intensity. The
 699 values and positions of the MS extrema are preserved, while all other extrema are removed

700 from the brain template estimate. Such procedure provides control over the topology of the
701 brain image \hat{T} .

702 Formally, the original Topological denoising problem is written as the minimization [23]:

$$\begin{aligned}
703 \quad & \operatorname{argmin}_{T'} \sum_{x_i \in \Omega} \|\hat{T}(x_i) - T'(x_i)\|^2 + \int_{\Omega} \|\Delta T'\|^2 \\
704 \quad & \text{s.t. } T'(x_i) = \hat{T}(x_i) \text{ for } x_i \text{ a node of the MS complex} \\
705 \quad & T'(x_j) > T'(x_i) \text{ for } x_j \text{ neighbor of } x_i \text{ and } x_i \text{ minimum} \\
706 \quad & T'(x_j) < T'(x_i) \text{ for } x_j \text{ neighbor of } x_i \text{ and } x_i \text{ maximum} \\
707 \quad & T'(x_i) > \min_{\text{neighbor } x_j} T'(x_j) \text{ for } x_i \text{ not an extremum} \\
708 \quad & T'(x_i) < \max_{\text{neighbor } x_j} T'(x_j) \text{ for } x_i \text{ not an extremum.} \\
709
\end{aligned}$$

710 The non linear inequality constraints make this optimization problem hard to solve. The
711 solution suggested by [23] is to compute a *representative function* u that verifies the last four
712 inequality constraints. Given this function u , the topological denoising problem becomes:

$$\begin{aligned}
713 \quad & \operatorname{argmin}_{T'} \sum_{x_i \in \Omega} \|\hat{T}(x_i) - T'(x_i)\|^2 + \int_{\Omega} \|\Delta T'\|^2 \\
714 \quad & \text{s.t. } T'(x_i) = \hat{T}(x_i) \text{ for } x_i \text{ a node of the MS complex} \\
715 \quad & (T'(x_i) - T'(x_j))(u(x_i) - u(x_j)) > 0, \text{ for } (x_i, x_j) \text{ a pair of neighbors,}
\end{aligned}$$

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

719 The representative function u can be computed by solving the Dirichlet problem:

$$\begin{aligned}
720 \quad & \operatorname{argmin}_u \int_{\Omega} \|\nabla u\|^2 \\
721 \quad & \text{s.t. } u(x_i) = 0 \text{ for } x_i \text{ a minimum} \\
722 \quad & u(x_i) = 1 \text{ for } x_i \text{ a maximum.} \\
723
\end{aligned}$$

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

727 Figure 10 shows examples of topological denoising. The topology to be enforced is repre-
728 sented by the red and blue dots, which are nodes of the MS complex: red for intensity maxima
729 and blue for intensity minima. On the left example, the circle motifs that were inducing un-
730 desirable minima and maxima are removed. On the right example, two of the initial four
731 maxima in the center of the image are removed too. Only the topology dictated by the input
732 Morse-Smale complex is preserved.

733 3.2.2. Integrating the topological denoising in the template computation pipeline.

734 The original template's computation is performed with the algorithm of [24] and use the LCC

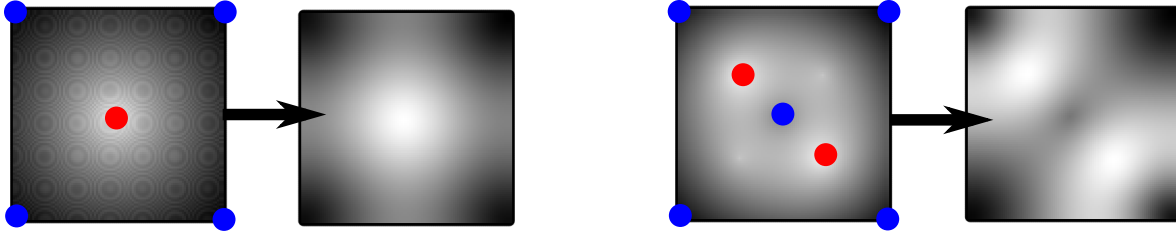


Figure 10. Topological denoising on two toy examples. We impose topological constraints on the initial images, on the left in both cases: minima in blue and maxima in red. The arrows denote the action of the topological denoising and point to the output image.

735 Log-demons for the registrations [29]. We adapt it by adding a Topological denoising step, in
 736 order to control the template’s asymptotic bias.

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

Algorithm 1 Controlled brain template estimation

Input: Images $\{I_i\}_{i=1}^n$, noise variance σ^2 , persistence threshold $p_{\text{threshold}}$

Initialization:

$\hat{T}_1 = I_1$ (one of the subjects images)

$k = 1$

Repeat:

Non-linearly register the images to \hat{T}_k , i.e. compute $\phi_k^i: J_k^i \simeq I^i \circ \phi_k^i$

Compute the mean deformation: $\bar{\phi}_k$

Register subject image: $L_k^i = I^i \circ \phi_k^i \circ \bar{\phi}_k^{-1}$

Compute the mean intensity image for template iteration: $\hat{T}_{k+1} = \frac{1}{n} \sum_{i=1}^n L_k^i$

Compute the MS complex of \hat{T}_{k+1} at persistence level p

Topological denoising of T_{k+1} using the MS complex

$k \leftarrow k + 1$

until convergence: $\|\hat{T}_k - \hat{T}_{k+1}\| < \epsilon$

Output: \hat{T}_k

745 The main parameter controlling this adapted procedure is the asymptotic bias threshold,
 746 i.e. the persistence threshold $p_{\text{threshold}}$ for the MS complex computation. The next section
 747 discusses the choice of this parameter $p_{\text{threshold}}$. Varying the threshold $p_{\text{threshold}}$ leads to the
 748 construction of a hierarchy of templates. The other parameter is σ , which is the noise on the

749 subject images. Either one knows it from the experimental design, or one estimates it with
750 the variability of the registered subject images, as we did in Section 2.

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

755 **4.1. Quantification of the template inconsistency.** We quantify the asymptotic bias
756 locally on the brain template computed from the OASIS database with the usual procedure.
757 This shows how faithfully the computed template represents human brain anatomy for the
758 neuroimaging studies.

759 First, we produce maps showing the local asymptotic bias directly with a color code
760 superimposed on the original tridimensional template image, see Figure 11. We call these
761 maps the *asymptotic bias maps*. A green color indicates a low asymptotic bias for the region
762 and a red color indicates a high asymptotic bias on the region.

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

$$765 \quad (17) \quad \text{SNR}_{\text{dB}} = 10 \log_{10} \left[\left(\frac{d}{\sigma} \right)^2 \right].$$

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

772 We compute several maps, see (c)-(d)-(e) on Figure 11 for the same brain template. The
773 difference between the maps is the Morse-Smale complexes’s persistence threshold used to
774 compute the asymptotic bias. The threshold is increased from left to right on Figure 11 (c)-
775 (d)-(e). Increasing the threshold makes more and more regions appear and these are more
776 and more biased: they become colored in orange-red.

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

784 **4.2. Topological denoising for a consistent template.**

785 *Choice of the persistence threshold.* Each map of Figure 11 (c)-(d)-(e) represents the asymp-
786 totic bias of the brain template we would obtain if we were constraining the image to the
787 topology of the corresponding Morse-Smale. The persistence threshold gives a way to inves-
788 tigate the trade-off between asymptotic unbiasedness and sharpness of the template. On the

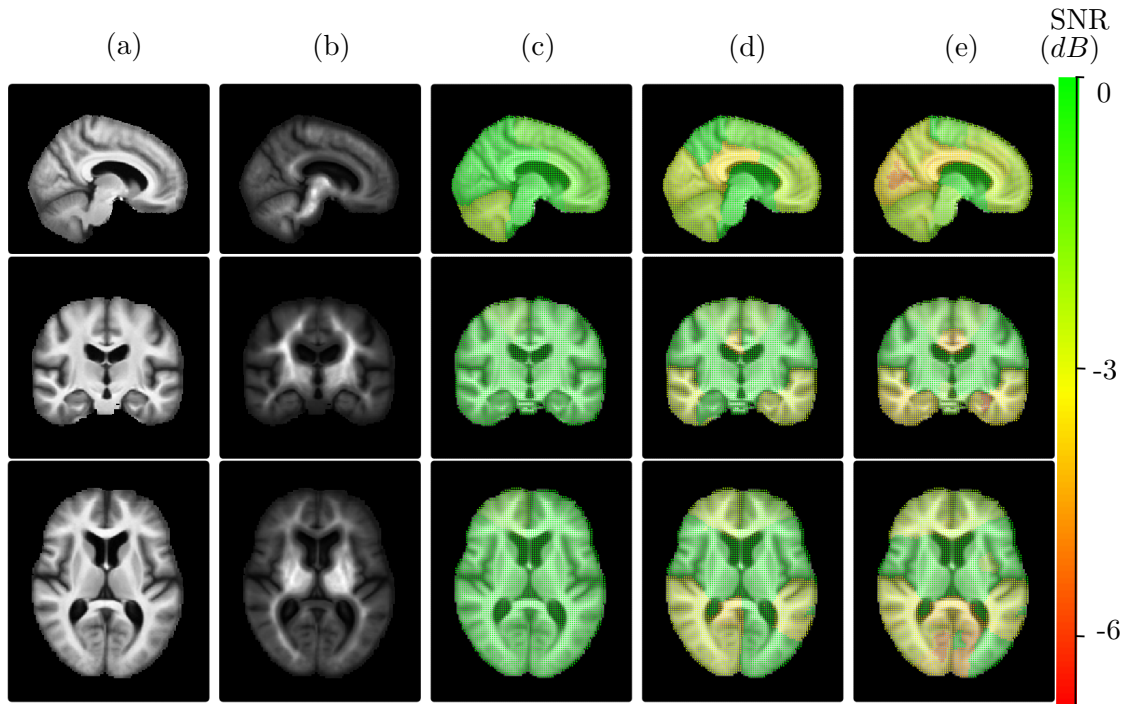


Figure 11. Investigation of the template's consistency as an estimator of a unique anatomy. (a) Template. (b) Template whitened by the intersubject variability. (c) Region-wise inconsistency for a threshold = 1.3, (d) for threshold = 2, (e) for threshold = 4 (dimensionless).

789 one hand, a complex topology - i.e. a low persistence threshold - implies an important asymptotic bias on the template, which may not represent faithfully the brain anatomy shared by
 790 the subjects in the OASIS database. On the other hand, a topology that is too simple - i.e. a
 791 high persistence threshold - has no chance of representing a brain anatomy at all. If we want
 792 to look at small brain structures, we have to allow for some precision in the topology.
 793

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

801 *Applying topological denoising to control the brain template's bias.* We apply the methodol-
 802 ogy of Section 3.2 to enforce the asymptotic bias to be below a threshold, using Topological
 803 denoising. Enforcing the unbiasedness in the procedure enables us to build the template of
 804 Figure 12. As a proof of concept, we have run it on the subject coronal slices of the OASIS
 805 database. Following the development above, we bound the asymptotic bias by setting the
 806 SNR threshold to -0.8 dB. We observe that the brain regions that were the more biased - i.e.

807 in orange-red in Figure 11 are now blurred. Thus, Topological denoising decides where the
 808 sharply defined brain template makes sense as a representative of the shared brain anatomy,
 809 and blurs it where it does not.

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

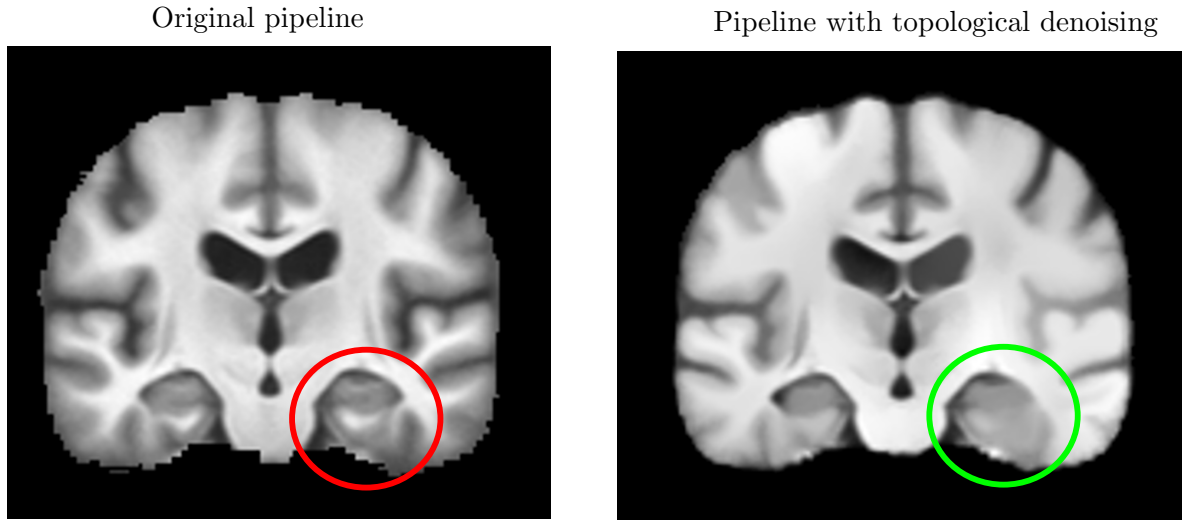


Figure 12. Results of Topological Denoising integration in the pipeline for the template's estimation. Left: Template from pipeline without topological denoising. Right: Template with the topologically constrained pipeline. Inconsistent regions from Figure 11 are now blurred.

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

820 Our methodology builds a bridge between the diffeomorphic registration framework of
 821 Medical Imaging and Morse-Smale theory. This link is an interesting application of topology
 822 in itself. There are some limitations from the technical point of view as we provide sketches of
 823 proofs for our conjectures. As such, this paper opens the door to mathematical developments
 824 at the boundary of Differential geometry and topology.

825 Our Morse-Smale framework identifies biased regions in the brain template in Section 3. In
 826 these regions, a sharp template might not be desirable. We control the template's asymptotic
 827 bias by adding a Topological Denoising step in its iterative computation, creating a trade-off
 828 between sharpness and unbiasedness. Our methodology is illustrated on a real database of
 829 136 brain images in Section 4. It shows how the Topological Denoising blurs the regions that

830 were the most biased. We control the template's bias at the price of dropping its sharpness.

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

838

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