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# Learning the clustering of longitudinal shape data sets into a mixture of independent or branching trajectories

Vianney Debavelaere · Stanley Durrleman · Stéphanie Allassonnière · for the Alzheimers Disease Neuroimaging Initiative\*

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Abstract Given repeated observations of several subjects over time, i.e. a longitudinal data set, this paper introduces a new model to learn a classification of the shapes progression in an unsupervised setting: we automatically cluster a longitudinal data set in different classes without labels. Our method learns for each cluster an average shape trajectory (or representative curve) and its variance in space and time. Representative trajectories are built as the combination of pieces of curves. This mixture model is flexible enough to handle independent trajectories for each cluster as well as fork and merge scenarios. The estimation of such non linear mixture models in high dimension is known to be difficult because of the trapping states effect that hampers the optimisation of cluster assignments during training. We address this issue by using a tempered version of the stochastic EM algorithm. Finally, we apply our algorithm on different data sets. First, synthetic data are used to show that a tempered scheme achieves better convergence. We then apply our method to dif-

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\* Data used in preparation of this article were obtained from the Alzheimers Disease Neuroimaging Initiative (ADNI) database. As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: adni.loni.usc.edu. ferent real data sets: 1D RECIST score used to monitor tumors growth, 3D facial expressions and meshes of the hippocampus. In particular, we show how the method can be used to test different scenarios of hippocampus atrophy in ageing by using an heteregenous population of normal ageing individuals and mild cognitive impaired subjects.

**Keywords** Longitudinal data analysis · Mixture model · Branching population · Stochastic Optimization · Statistical Model · Riemannian manifold.

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#### 1 Introduction

The emergence of large longitudinal data sets (subjects observed repeatedly at different time points) has allowed the construction of different models improving the understanding of biological or natural phenomenon. Longitudinal studies have numerous applications: understating of the differences of progression in neurodegenerative disease such as Alzheimer's, chemotherapy monitoring, facial recognition, etc.. Such medical studies enable to retrieve the global progression of the disease while explaining the inter subject variability. In particular, it would be interesting to highlight the influence of a disease on a normal ageing process and to be able to differentiate those two processes. Clinicians are also interested in the possibility to detect the moment when a disease begins to manifest itself, i.e. the moment at which a subject branches from the normal

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dynamic. For instance, in the case of the Alzheimer's disease, we still do not know if the disease has a very early genesis, leading to a specific aging pattern from an early age or if it is a sudden deivation from the normal ageing process. Another example is the monitoring of tumors along treatment. Indeed, it is well known that the whole population will not react the same way to a given drug. Therefore, clustering patients would enable a specific care. In both situations, the evolution may not be smooth in the sense that the disease can show variations in dynamics according to the stage of its development. To tackle those problems, we consider that populations can follow different dynamics over time. Moreover, in order to detect subgroups with specific patterns, we implement an unsupervised clustering of the dataset. Here, our populations are therefore heterogeneous but without prior knowledge on the sub-groups composing them, thus preventing from the use of supervised approaches.

We design our model such that it is able to detect a certain fixed number of different dynamics in the population and, for each of them, to estimate a representative trajectory of that population together with the inter subjects variability. The difficulty is in fact further increased in this spatiotemporal setting since clustering may take various forms: sub-groups may follow independent trajectories, or they may follow trajectories that fork or merge at specific time-points. The former case is relevant to discover pathological sub-types having different disease course. The latter is interesting for a disease that is seen as a progressive deviation from a normal aging scenario.

Usually, shape spaces are built by considering shape data as points on a Riemannian manifold (Charon and Trouvé, 2013; Vaillant and Glaunès, 2005; Miller and Younes, 2001). In such shape spaces, descriptive (Donohue et al., 2014) or generative (Jedynak et al., 2012; Durrleman et al., 2013; Allassonnière et al., 2015) models have been constructed. To deform the shapes, the Large Deformation Diffeomorphic Metric Mapping (LD-DMM) framework is usually used. It allows us to compute the deformation from one shape to the other by coding deformations as geodesics on a Riemannian manifold and using flows of deformations (Miller et al., 2006). Given a data set of shapes, it is then possible to construct an atlas. An atlas is composed of a shape that is representative of the population, as well as the spatial variability within this population (Fletcher, 2013; Allassonnière and Kuhn, 2008; Lorenzen et al., 2005; Su et al., 2014). The next logical step is to handle longitudinal data sets. Once again, the trajectory of a shape from one time point to the other will be

constructed by using flows of diffeomorphisms (Bône et al., 2018; Lorenzi et al., 2011; Singh et al., 2016). In this framework, a longitudinal atlas consists of a representative trajectory, or template, and of the spatiotemporal variability of the population. The representative trajectory is a long-term scenario of changes informed by sequences of short-term individual data. It can be seen as a geodesic (Bône et al., 2018; Schiratti et al., 2017) or a piecewise geodesic (Allassonniere et al., 2017) curve on the manifold. All these methods however assumed that observations are drawn from an homogeneous population that may be summarized by a single representative trajectory. In this paper, we explain with more details and examples the work presented in (Debavelaere et al., 2019) where the population is supposed to contain a certain fixed number of unknown clusters. To tackle this problem, we construct a mixed-effect generative model. To estimate the different parameters, we choose to use a variant of the Expectation-Maximization algorithm called the Markov Chain Monte Carlo Stochastic Approximation Expectation Maximization algorithm (MCMC-SAEM) (Delyon et al., 1999; Allassonnière et al., 2010). However, using those algorithms in a clustering context leads to the problem of trapping states: changing class assignment is often more costly than adjusting the parameters of the current clusters, resulting in very few updates of class assignment during optimization. Solutions have already been presented in the case of cross sectional data sets analysis but at very high computational costs (Allassonnière and Kuhn, 2010). Here, we choose to introduce temperate distributions in our Expectation-Maximization algorithm to avoid being trapped in the initial labelling.

In this paper, we will first explain in section 2 the geometrical framework allowing us to compute the representative trajectories and deformations towards the subjects. Because this framework allows us to define our model by a finite number of parameters, we will present in section 3 the statistical model and the algorithm used to estimate those parameters. Finally, we will apply our work to different data sets. We will quantitatively validate it on simulated 2D data. We will then perform experiments on real data: we will work with 1D RECIST score used to monitor the growth of a tumor (Therasse et al., 2000), with a data set of 3D faces expressing different expressions and with a 3D data set of hippocampi of patients with or without Alzheimer's disease.

### 2 Geometrical model

#### 2.1 Construction of the representative trajectory

In the following, we consider a longitudinal data set of n subjects, each being observed  $k_i$  times:  $(y_{i,j})_{1 \le i \le n, 1 \le j \le k_i}$  at time  $(t_{i,j})_{1 \le i \le n, 1 \le j \le k_i}$ , where each observation  $y_{i,j}$  is a point of  $\mathbb{R}^d$ ,  $d \in \mathbb{N}$ .

We briefly recall the Large Deformation Diffeomorphic Metric Mapping (LDDMM) framework for shape matching (Miller et al., 2006). Given two shapes  $y_0$  and  $y_1$ , we want to solve the registration problem consisting in finding a diffeomorphism  $\phi_1$  that transforms  $y_0$  onto  $y_1$ . In the framework of LDDMM, diffeomorphisms are built as the flow of a velocity vector  $v_t$  over  $t \in [0, 1]$ :

$$\begin{cases} \frac{\partial \phi_t}{\partial t} = v_t \circ \phi_t \\ \phi_0 = Id \,. \end{cases}$$
(1)

We suppose here that our velocity fields belong to a Reproductive Kernel Hilbert Space V with kernel  $K_g$ . V is in fact the set of squared integrable functions regularized by the convolution by the kernel  $K_g$ . We place ourselves in the finite setting where, given a set of  $n_{cp}$  control points  $(c_{0,i})_{1 \leq i \leq n_{cp}}$  and momenta vectors  $(m_{0,i})_{1 \leq i \leq n_{cp}}$  in  $\mathbb{R}^d$ , we can define a velocity vector  $v_0 \in V$  at a point  $x \in \mathbb{R}^d$  by:

$$v_0(x) = \sum_{i=1}^{n_{cp}} K_g(c_{0,i}, x) m_{0,i} \,. \tag{2}$$

The value of  $v_0$  at a point x is obtained as the interpolation of the momenta at the control points.

We then say that  $\phi_1$  is a solution of the registration problem if it transforms  $y_0$  into  $y_1$  while minimizing the energy:

$$d(Id,\phi_1) = \int_0^1 \|v_t\|_V^2 dt, \qquad (3)$$

where  $\|.\|_V$  is the norm of the RKHS V. in particular, this implies that  $\phi_1$  defines a geodesic path.

It has been shown in (Miller et al., 2006) that if the initial velocity field  $v_0$  is the interpolation of momentum vectors at control points as in Eq. (2), then the velocity field minimizing Eq. (3) keeps the same form along the geodesic:

$$v_t(x) = \sum_{i=1}^{n_{cp}} K_g(c(t)_i, x) m(t)_i \,. \tag{4}$$

m(t) and c(t) are time dependent momenta and control points solutions of the Hamiltonian equations:

$$\begin{cases} \dot{c}(t) = K_g(t)m(t)\\ \dot{m}(t) = \nabla_{c(t)} \left(m(t)^T K_g(t)m(t)\right) \end{cases}$$
(5)

with initial conditions  $m(0) = (m_{0,k})_{1 \le k \le n_{cp}}$ ,  $c(0) = (c_{0,k})_{1 \le k \le n_{cp}}$  and where  $K_g(t)$  is the  $n_{cp} \times n_{cp}$  kernel matrix  $(K_g(c_i(t), c_j(t)))_{1 \le i,j \le n_{cp}}$ .

If a diffeomorphism solving this problem exists, we can then represent it by its set of control points and momenta at t = 0. In practice, we don't solve the exact registration problem but we relax the problem to find  $\phi_1$  the extreme-path diffeomorphism that warps  $y_0$  onto a shape as close as possible to  $y_1$  for a certain distance  $d_{\epsilon}$ . Depending on the application, we place ourselves in the current (Vaillant and Glaunès, 2005) or varifold (Charon and Trouvé, 2013) framework, allowing us to compute the distance  $d_{\epsilon}$  between shapes without any point correspondence.

To sum up, given a set of initial control points, the initial velocity is parametrized by the momentum vectors attached to them (see Eq. (2)). By integrating the Hamiltonian equations (5), one can compute the evolution of those control points and momenta over time and obtain the velocity vector at any time t (Eq. (4)). By integrating the flow equation (1), we can obtain the diffeomorphism  $\phi_1$  deforming the ambient space. By applying this diffeomorphism at a point cloud or mesh  $y_0$ , we are finally able to deform it.

Given initial control points  $c_0$  and time  $t_0$ , this defines an exponential operator:  $Exp_{c_0,t_0,t}(m_0) = \phi_t$  and a finite dimensional subgroup of diffeomorphisms  $M = \{Exp_{c_0,t_0,1}(m_0)|m_0 \in \mathbb{R}^{n_{c_p} \times d}\}.$ 

We now come back to the longitudinal framework. Instead of matching one shape onto another, we want to construct a representative trajectory, or template, from which we will derive the individual trajectories of the subjects using the tools and methods previously introduced. A usual way to solve this problem is to model the representative trajectory as the action of a geodesic in M on an initial shape. However, to deal with possible change of dynamics in the population, we do not represent it as a geodesic but as a piecewise geodesic curve  $\gamma_0$  i.e. as a combination of K different geodesics following each other, generalizing the work done in (Allassonniere et al., 2017) in dimension 1. In particular, each of the geodesics defining  $\gamma_0$  describes a dynamic of the population, different from the others, on a particular time segment.

We now formalize this: we introduce a subdivision of  $\mathbb{R}$ :

 $(t_{R,1} < \dots < t_{R,K-1} < t_{R,K} := +\infty)$  where  $(t_{R,k})_{1 \le k \le K-1}$ are called rupture times i.e. times when the representative curve switches from one geodesic to another. It is at those times that the population switches from one dynamic to the other. Given a set of initial control points  $c_1 \in \mathbb{R}^{n_{cp} \times d}$ , of rupture times  $t_R \in \mathbb{R}^{K-1}$ , an initial shape  $x_1$  and K momenta  $(m_0, m_1, \dots, m_{K-1})$ , we define the representative trajectory as:

$$\begin{cases} \gamma(t)(x_1) = \operatorname{Exp}_{c_1, t_{R,1}, t_{R,1} - t}(m_0) \cdot x_1 \mathbb{1}_{t \le t_{R,1}} \\ + \sum_{k=1}^{K-1} \operatorname{Exp}_{c_k, t_{R,k}, t - t_{R,k}}(m_k) \cdot x_k \mathbb{1}_{t_{R,k} \le t \le t_{R,k+1}} \\ \text{with, for } k \ge 2: \\ c_k = \operatorname{Exp}_{c_{k-1}, t_{R,k-1}, t_{R,k} - t_{R,k-1}}(m_{k-1}) \cdot c_{k-1} \\ x_k = \operatorname{Exp}_{c_{k-1}, t_{R,k-1}, t_{R,k} - t_{R,k-1}}(m_{k-1}) \cdot x_{k-1} \end{cases}$$

Here, the  $c_k$  and  $x_k$  are respectively the position of the control points and the value of the representative curve at times  $t_{R,k}$ . For  $k \geq 2$ , they are fixed to assure the continuity of the trajectory.

It can be noticed that the first rupture time has a particular role as we must define a geodesic before it, determining the trajectory from  $-\infty$  to the first rupture time and another after it, determining the trajectory from the first rupture time to the second. The control points  $c_1$  and momenta  $m_0$ ,  $m_1$  are used to compute the velocities at the time  $t_{R,1}$  defining the geodesic before and after it. The other momenta  $m_2, ...m_{K-1}$  and control points  $c_2, ...c_{K-1}$  define the subsequent geodesics.

#### 2.2 Deformations towards the subjects

From this representative trajectory featuring the group characteristic path, we want to derive individual trajectories following different behaviour. To achieve this goal, we take into account both spatial and temporal differences by introducing a time reparametrization and a diffeomorphic spatial deformation. Indeed, each individual can follow its own rhythm of progression, different from the representative curve and varying from one time segment to another, hence the need to introduce time reparametrizations.

For each subject i, let  $\xi_{i,0}, ..., \xi_{i,K-1}$  be acceleration coefficients and  $\tau_{i,0}, ..., \tau_{i,K-1}$  time shifts. We write for every subject i:

$$\psi_{i,0}(t) = t_{R,1} - e^{\xi_{i,0}} \left( t_{R,1} - t + \tau_{i,0} \right)$$

and, for each time segment  $k \ge 1$ ,

$$\psi_{i,k}(t) = t_{R,k} + e^{\xi_{i,k}} \left( t - t_{R,k} - \tau_{i,k} \right) \,.$$

 $\psi_{i,k}$  codes the temporal reparametrization of the subject *i* on the time segment *k*. Once again, a first time

reparametrization must be defined before the first rupture time.

The time shifts  $\tau_{i,k}$  allow the subjects to be at different stage of evolution while the acceleration factors  $\xi_{i,k}$  allow an inter-subject variability in the pace of evolution on each geodesic (quicker evolution if  $\xi_{i,k} > 0$ , slower if  $\xi_{i,k} < 0$ ).

Each subject has its own rupture times  $t_{R,i,k}$  representing the times the subject *i* goes through a change of dynamic and such that  $t_{R,k} = \psi_{i,k}(t_{R,i,k})$  i.e.  $t_{R,i,k} = t_{R,k} + \tau_{i,k}$ . To assure the continuity of the time reparametrization at each of those rupture times, we also fix all the time shifts but  $\tau_{i,0}$  by continuity conditions: we impose for all  $k \psi_{i,k-1}(t_{R,i,k}) = \psi_{i,k}(t_{R,i,k})$ , i.e.:  $\tau_{i,0} = \tau_{i,1}$  and, for  $k \in [|2, K - 1|]$ ,

$$\tau_{i,k} = \tau_{i,k-1} + (t_{R,k} - t_{R,k-1})(e^{-\xi_{i,k-1}} - 1).$$
(6)

From now on, we note  $\tau_i = \tau_{i,0}$ . Finally, we set:

$$\psi_i(t) = \psi_{i,0}(t) \mathbb{1}_{t \le t_{R,i,1}} + \sum_{k=1}^{K-1} \psi_{i,k}(t) \mathbb{1}_{t_{R,i,k} \le t \le t_{R,i,k+1}}.$$

As proposed in (Bône et al., 2018), we will account the space variability by using exp-parallelizations, i.e. the generalization of parallelism to geodesically complete manifolds (Schiratti et al., 2015). More precisely, we introduce for each subject *i* a space-shift momentum  $w_i$ . We note  $P_{\gamma}^{(w)}$  the parallel transport which transports any vector  $w \in \mathbb{R}^{n_{cp} \times d}$  along the trajectory  $\gamma$ . Practically, we compute it using the fanning scheme (Louis et al., 2017). Then, to code the deformation field at a time *t*, we transport the momentum *w* along the curve  $\gamma(t)$  and then compute the flow given by this new momentum. The given trajectory is the exp-parallelization of  $\gamma$  by  $w_i$ . Hence, we define:

$$\eta_t(w) = \operatorname{Exp}_{\gamma(t)(c_1), 0, 1}(P_{\gamma(t)}(w))$$

Finally, given  $x_1$  the value of the representative curve at the first rupture time, the deformation of the representative curve  $\gamma$  by the space shift w is given by:

$$\gamma_w(t) = \eta_t(w) \circ \gamma(t) \circ x_1 \, .$$

We summarize the space deformation process on Fig. 1 by computing the exp-parallelization of a geodesic on a sphere and on Fig 2 by presenting an example in a space of shapes.

We model this space shift as a linear combination of  $n_s$  sources: we suppose that  $w = A_{(m_0,...,m_{K-1})^{\perp}} s$  with  $A_{(m_0,...,m_1)^{\perp}}$  a  $n_{cp} \times n_s$  matrix called the modulation matrix and  $s \in \mathbb{R}^{n_s}$  the sources. By projecting all the columns of  $A_{(m_0,...,m_{K-1})^{\perp}}$  on  $(m_0,...,m_{K-1})^{\perp}$  for the

 $\overline{n}$ 



**Fig. 1** Example of parallel transport on a sphere. On the left, we draw the geodesic  $\gamma$  and the momenta to transport w. On the center, we transport w along  $\gamma$ . On the right, we compute the exp-parallelization of  $\gamma$ by w.



Fig. 2 Samples from a piecewise geodesic (top) and a parallel deformation (bottom). The red momenta codes the template evolution, lowering then raising an arm after the rupture time. The blue momenta is transported along the piecewise geodesic and defines the deformation frame.

metric  $K_g$ , we impose orthogonality between the space shifts and the momentum vectors. It has been shown in (Schiratti et al., 2017) that this condition is necessary to assure the identifiability of the model by preventing a confusion between the space shifts and the acceleration factors. Finally, we deform the template  $\gamma(t)(x_1)$  by setting:

$$\gamma_i(t) = \gamma_w(\psi_i(t)) \,.$$

#### 2.3 Mixture and branching process

This construction builds a piecewise geodesic model of progression. We now propose an extension for the analysis of heterogeneous populations. More precisely, we suppose there exists N different representative curves in a given population, each of the subjects *i* being in the cluster cl(i) defined by the particular representative curve  $\gamma^{cl(i)}$ . This representative curve comes with its own set of rupture times  $(t_{R,1}^{cl(i)} < \ldots < t_{R,K-1}^{cl(i)})$ , initial shape  $x_1^{cl(i)}$ , control points  $c_1^{cl(i)}$ , momenta  $(m_0^{cl(i)}, \ldots,$ 

$$A_{K-1}^{cl(i)}$$
) and modulation matrix  $A_{(m_0^{cl(i)},...,m_{K-1}^{cl(i)})^{\perp}}^{cl(i)}$ .

This mixture framework enables to compare and test hypothesis on the clusters. For instance, some of the time segments can be shared by several clusters. This imposes the representative curves of these clusters on these time segments to be the same. In particular, if we want some of the clusters to be equal on the first time segment, we impose  $t_{R,1}^k$ ,  $x_1^k$ ,  $c_1^k$  and  $m_0^k$  to be the same for these clusters. This allows us to handle populations forking or merging at the rupture times. The rupture times will then not only be times when a change of dynamic occurs but also times when the population will fork or merge.

#### **3** Statistical Model and estimation

#### 3.1 Statistical Model

In the previous part, we have presented a complex geometrical model allowing us to compute global trajectories and the deformations towards subjects. Those global trajectories can take a wide variety of forms. But, in all cases, our model is parametrized by a finite number of parameters. Hence, we can define a mixed effects statistical model allowing us to estimate those different parameters. We note:

$$z_{pop}^{r} = (m_{0}^{r}, (m_{k}^{r}, t_{R,k}^{r})_{1 \le k \le K-1}, x_{1}^{r}, c_{1}^{r}, A_{(m_{0}^{r}, \dots, m_{K-1}^{r})^{\perp}}^{r})$$

the population parameters of the cluster r and

$$z_i = ((\xi_{i,k})_{0 \le k \le K-1}, t_{R,i,0}, s_i)$$

the deformation parameters of the subject i with  $\xi_i$  the acceleration parameters,  $s_i$  the sources and  $t_{R,i,0}$  the first individual rupture time. As all the time shifts but the first one are fixed by continuity conditions (cf Eq. (6)), all subsequent individual rupture times are fixed by an expression depending only of the first individual rupture time, the acceleration parameters and the global rupture times of the cluster.

We suppose that the subject i is obtained as a noisy deformation of the representative curve  $\gamma^{cl(i)}$ :  $\forall i \in [|1, n|], \forall j \in [|1, k_i|],$ 

$$y_{i,j}|cl(i), z_{pop}^{cl(i)}, z_i \sim \mathcal{N}(\gamma_i(t_{i,j}), \sigma^2 Id)$$

We also suppose that the deformation parameters  $z_i$  verify:

$$z_i | cl(i) \sim \mathcal{N}(\mu^{cl(i)}, \Sigma^{cl(i)})$$

where for all cluster r,  $\Sigma^r$  is a positive-definite matrix and  $\mu^r = (0, ..., 0, t_{R,0}^r)$ . Unlike in (Debavelaere et al.,

n

2019), we suppose that the first rupture time of each piecewise-geodesic  $t_{R,0}^r$  is not a random variable but a parameter of our model, defined as the mean of the law of the individual rupture times. Indeed, those individual rupture times are here considered as random variables, while in (Debavelaere et al., 2019) we only considered the time-shifts. It allows to accelerate the computation time of each iteration while improving the stability of our algorithm.

The cluster r is drawn with a probability  $p^r$  i.e.

$$cl(i) \sim \sum_{r=1}^{N} p^r \delta_r$$

and finally, we suppose  $z_{pop}^r \sim \mathcal{N}(\bar{z}_{pop}^r, v_{pop})$  where  $v_{pop}$  are small fixed variances so that our model belongs to the curved exponential family. Finally, our model is defined with parameters  $\theta = ((t_{R,0}^r, \Sigma^r, p^r, \bar{z}_{pop}^r)_{1 \leq r \leq N}, \sigma)$ .

For effectiveness in the high dimension low sample size setting, we work in the Bayesian framework and set as priors:

$$\begin{cases} t_{R,0}^r \sim \mathcal{N}(\overline{t_{R,0}^r}, v_{t_R}) \\ \Sigma_r \sim \mathcal{W}^{-1}(V, m_{\Sigma}) \\ \sigma \sim \mathcal{W}^{-1}(v, m_{\sigma}) \\ p \sim \mathcal{D}(\alpha) \\ \overline{z}_{pop}^r \sim \mathcal{N}(\overline{z}_{pop}^r, \overline{v}_{pop}) \end{cases}$$
(7)

where  $\mathcal{W}$  is the inverse Wishart distribution,  $\mathcal{D}$  is the Dirichlet distribution and  $\overline{t_{R,0}^r}$ ,  $v_{t_R}$ , V,  $m_{\Sigma}$ , v,  $m_{\sigma}$ ,  $\alpha$ ,  $\overline{z_{nan}^r}$  and  $\overline{v_{pop}}$  are hyperparameters of the model.

Finally, if we note  $\Lambda$  the dimension of the space in which the residuals  $||y_{i,j} - \gamma_i(t_{i,j})||^2$  are computed, the complete log-likelihood writes:

$$\begin{split} \log q(y, z_{pop}, z, c, \theta) &= \\ &- \sum_{i=1}^{n} \left( \sum_{j=1}^{k_{i}} \frac{1}{2\sigma^{2}} \|y_{i,j} - \gamma^{cl(i)}(t_{i,j})\|^{2} - \frac{Ak_{i}}{2} \log(\sigma^{2}) \right) \\ &- \frac{1}{2} \sum_{r=1}^{N} (z_{pop}^{r} - \bar{z}_{pop}^{r})^{T} v_{pop}^{-1} (z_{pop}^{r} - \bar{z}_{pop}^{r}) \\ &- \frac{1}{2} \sum_{i=1}^{n} \left( (z_{i} - \mu^{cl(i)})^{T} (\Sigma^{cl(i)})^{-1} (z_{i} - \mu^{cl(i)}) \right) \\ &- \log |\Sigma^{cl(i)}| \right) + \sum_{i=1}^{n} \log p^{c(i)} + \sum_{r=1}^{N} \alpha \log p^{r} \\ &+ \sum_{r=1}^{N} \left( \frac{m_{\Sigma}}{2} (\log |V| - \log |\Sigma_{r}|) - tr(V\Sigma_{r}^{-1}) \right) \end{split}$$

$$+ m_{\sigma} \log\left(\frac{v}{\sigma}\right) - \frac{m_{\sigma}}{2} \left(\frac{v}{\sigma}\right)^{2} \\ - \frac{1}{2} \sum_{r=1}^{N} (\bar{z}_{pop}^{r} - \bar{\bar{z}}_{pop}^{r})^{T} \bar{v}_{pop}^{-1} (\bar{z}_{pop}^{r} - \bar{\bar{z}}_{pop}^{r}) \\ - \sum_{r=1}^{N} \frac{(t_{R,0}^{r} - \overline{t_{R,0}^{r}})^{2}}{2v_{t_{R}}^{2}} + cste .$$
(8)

Our model belongs to the curved exponential family with sufficient statistics defined for all class r as:

$$S_{1}^{r}(y, z, z_{pop}) = z_{pop}^{r} \qquad S_{2}^{r}(y, z, z_{pop}) = \sum_{i=1}^{n} \mathbb{1}_{cl(i)=r}$$

$$S_{3}(y, z, z_{pop}) = \sum_{i=1}^{n} k_{i}$$

$$S_{4}^{r}(y, z, z_{pop}) = \sum_{i=1}^{n} \mathbb{1}_{cl(i)=r} \left( \Sigma_{cl(i)}^{-1} \right)_{N,N}$$

$$S_{5}^{r}(y, z, z_{pop}) = \sum_{i=1}^{n} \mathbb{1}_{cl(i)=r} (z_{i} - \mu_{i})^{t} (z_{i} - \mu_{i})$$

$$S_{6}^{r}(y, z, z_{pop}) = \sum_{i=1}^{n} \mathbb{1}_{cl(i)=r} \left( \Sigma_{cl(i)}^{-1} \right)_{N} (\xi_{i,0}, \dots, \xi_{i,N-1}, t_{R,i,0})$$

$$S_{7}(y, z, z_{pop}) = \sum_{i=1}^{n} \sum_{j=1}^{k_{i}} \|y_{i,j} - \gamma_{i}(t_{i,j})\|^{2}$$
(9)

with  $\left(\Sigma_{cl(i)}^{-1}\right)_N$  the  $N^{th}$  column of  $\Sigma_{cl(i)}^{-1}$  and  $\mu_i = (0, ..., 0, t_{R,0}^r)$ .

#### 3.2 Estimation

To estimate the parameters  $\theta$ , we want to compute a maximum a posteriori estimator by using a stochastic version of the Expectation Maximization algorithm known as MCMC-SAEM (Allassonnière and Kuhn, 2010). It consists in the following steps: (i) simulation of  $(z, z_{pop}, cl)$ , (ii) stochastic approximation of the sufficient statistics of the curved exponential model and (iii) maximization using the updated stochastic approximation. We can remark that the joint distribution is in the curved exponential family which guaranties the convergence of the MCMC-SAEM algorithm, as proven in (Allassonnière et al., 2010).

Concerning the sampling, we simulate  $(z, z_{pop}, cl)$ as an iterate of an ergodic Monte Carlo Markov Chain with stationary distribution  $q(z_{pop}, z, cl|y, \theta)$ . More precisely, we use a symmetric random walk Monte-Carlo Markov Chain within Gibbs sampler with adapted variance.

We then compute a stochastic approximation of the sufficient statistics using Eq. (9) and a decreasing positive sequence of step size  $\Delta_k$ : if *m* is the current iteration of our algorithm,  $1 \leq r \leq N$  and  $1 \leq k \leq 7$ , we compute  $s_{m,k}^r = s_{m-1,k}^r + \Delta_{m-1}(S_k(y, z, z_{pop}) - s_{m-1,k}^r)$ . Finally, the update of the parameters  $\theta$  in the maxi-

mization step of the MCMC-SAEM at iteration m can be derived: for all  $1 \le r \le N$ ,

$$\begin{cases} \bar{z}_{pop}^{r} = \frac{\bar{v}_{pop} s_{m,1}^{r} + v_{pop} \bar{z}_{pop}^{r}}{v_{pop} + \bar{v}_{pop}} \\ t_{R,0}^{r} = \frac{v_{t_{R}} s_{m,6}^{r} + \overline{t_{R,0}^{r}}}{v_{t_{R}} s_{m,4}^{r} + 1} \\ \Sigma_{r} = \frac{s_{m,5}^{r} + m_{\Sigma} V}{s_{m,2}^{r} + m_{\Sigma}} \\ \sigma^{2} = \frac{s_{m,7}^{r} + m_{\sigma} v}{A s_{m,3}^{r} + m_{\sigma}} \\ p^{r} = \frac{s_{m,2}^{r} + \alpha}{n + \alpha N} \end{cases}$$
(10)

The intricate update of the parameters  $t_{R,0}^r$  and  $\Sigma_r$  is solved by iterative replacement.

However, using the algorithm as presented above yields to bad results in exploring the support of the conditional probability distribution. This issue is known as trapping states: once a label is given to an observation, the probability of changing to another is almost zero. This leads to no change of class after a few iterations. To solve this problem, we use a tempered version of the MCMC-SAEM. Instead of targetting  $q(c|y,\theta)$  in the MCMC step, we rather sample from an ergodic Markov Chain with density  $\frac{1}{C(T_k)}q(c|y,\theta_k)^{\frac{1}{T_k}}$  where k is the current iteration of the algorithm,  $T_k$  is a sequence of temperature converging towards 1 and  $C(T_k)$  is the normalizing constant. The higher the temperature, the flatter the distribution and the more the clusters are likely to explore the entire set.

Finding a good distribution of temperatures such that meaningful representative curves are found without immediately fixing the clusters nor forcing them to move throughout the whole algorithm is quite difficult. Several choices have been proposed in (Allassonnière and Chevallier, 2019) but we choose here a distribution that takes into account the current state of the algorithm. For each subject *i* and each cluster *k*, we set  $\tau_i^k = \log\left(\frac{q(cl_i)=j}{q(cl_i)=k}\right)$  where cl(i) is the cluster of the subject *i*, *j* the index of that cluster during the previous iteration and *q* is the complete log likelihood.  $\tau_i^k$  is in fact the logarithm of the acceptance rate of the MCMC-SAEM

algorithm for the subject i to go from the cluster j to the cluster k. We then take:

$$T = \begin{cases} \frac{\operatorname{Median}(\tau)}{\lceil \operatorname{iter}/10 \rceil} \frac{5 - \operatorname{iter}\%10}{5} + 1 - \frac{5 - \operatorname{iter}\%10}{5} \\ & \text{if iter}\%10 < 5 \\ 1 \text{ otherwise} \end{cases}$$
(11)

where % is the modulo operator and iter is the current iteration.

Such a distribution of temperature allows the representative curves to fix themselves when iter $\%10 \ge 5$  while forcing the clusters to explore the whole space when iter%10 < 5.

If this temperature scheme allows us to observe meaningful clusters, as showed later in section 4, it must be remarked that it depends of the acceptance rate  $\tau$  and so of the previous state of the algorithm. The convergence of tempered SAEM algorithms has already been proven in (Allassonnière and Chevallier, 2019) and can easily be generalized in the case where the temperature depends of the previous state of the algorithm. However, for the MCMC-SAEM case used here, the geometric ergodicity of the Markov Chain should be proven in order to conclude that the algorithm converges.

#### 3.3 Initialization and influence of the hyperparameters

Now that we have presented the algorithm estimating  $\theta$ , we interest ourselves in its initialization and in the influence of the choice of the hyperparameters.

Concerning the initialization, all the representative trajectories of the different clusters are chosen equals by building a constant trajectory equal to the first observation of the first subject at all times. Similarly, we initialize the individual parameters such that there is no deformation towards the subjects. Hence, at first, all individual trajectories are equals.

The influence of the different parameters defining the priors is shown in the update of  $\theta$  (cf Eq. (10)). All those updates can in fact be seen as barycenters between a quantity defined by the sufficient statistics and another depending on the prior. For instance,  $\bar{z}_{pop}^r$ is the barycenter between  $S_1^r(y, z)$  and  $\bar{z}_{pop}^r$  with respective weight  $\frac{\bar{v}_{pop}}{\bar{v}_{pop}+v_{pop}}$  and  $\frac{v_{pop}}{\bar{v}_{pop}+v_{pop}}$ . Hence, we can choose the prior to influence the final value of  $\bar{z}_{pop}^r$  and also choose the weight given to this a priori. Similar remarks can be done with all parameters.

## Algorithm 1: MCMC-SAEM algorithm

**Data:**  $(y_{i,j}), (t_{i,j})$ , total number of iterations  $\overline{K}$ ,  $s_0 = 0$  and  $(\Delta_k)_{k \in \mathbb{N}}$  a decreasing positive step size sequence

for  $1 \leq k \leq K$  do

Sample  $(z_{pop}, z)$  using a single step of a Symmetric Random-Walk Metropolis Hastings within Gibbs sampler targeting the posterior distribution  $q(z_{pop}, z|y, \theta_k)$ .

Compute  $T_k$  using Eq. 11 and sample c using a single step of a Symmetric Random-Walk Metropolis Hastings within Gibbs sampler targeting the posterior distribution  $\frac{1}{T_c}q(c|y,\theta_k)$ .

Compute the stochastic approximation  $s_k = s_{k-1} + \Delta_{k-1}(S(z, z_{pop}, y) - s_{k-1})$  where S are the sufficient statistics given by Eq. 9.

Update the parameters  $\theta_k$  to maximize the posterior likelihood  $q(\theta|y)$  using Eq. 10:  $\theta_k = \hat{\theta}(s_k).$ 

Finally, we must also choose the kernel used to compute the deformations. Here, we take a Gaussian kernel:  $K_g(x, y) = \exp\left(\frac{\|x-y\|_2^2}{\sigma_g^2}\right)$ . We choose the kernel width  $\sigma_g$  in the range of the distance between the control points such that the whole shape can be deformed smoothly.

The final algorithm is summarized below.

### 4 Results

#### 4.1 2D simulated data

We first test our algorithm on simulated data mimicking the shape of a dancing man. We create 100 subjects by deforming a branching piecewise-geodesic representative curve with two components. More precisely, we draw three random momenta. We first apply one of them on a fixed shape to obtain the first common component and then we apply the two others momenta on the same fixed shape to obtain the two distinct components forking at the rupture time. We then create our 100 individuals by sampling random accelerations, time shifts and space shifts. Finally, we add a gaussian noise of variance 0.02 to each subject and apply our algorithm to find the two clusters, the representative curves and the spatiotemporal deformations towards the data sequence of each subject. Results in Fig. 3 show that there is only little differences between the true and estimated representative trajectories (left), and no noticeable differences between the true and reconstructed observations. To quantify the reconstruction error, we compute the varifold norm of the errors for all subjects along the iterations on Fig. 4 (left).

97% of the subjects are classified in their right cluster. As for the others subjects, in most cases, no measurement is done after the rupture time or the second acceleration coefficient is so small that the shape practically does not vary after the rupture time, which explains why the algorithm cannot find the right cluster. We also show the necessity of using tempered distributions by plotting the error of classification with and without temperature on Fig. 4 (right). The oscillations we see on those figures are due to the oscillating evolution of the temperature. We can see that the classification and hence the final reconstructions are better with tempered distributions.

Finally, we launch the algorithm on the same data set 10 times to compute the errors on the estimation of the different parameters. We can first remark that, on average, 96.88% of the subjects are well classified with a standard deviation of 2.08 over the 10 runs.

On the table 1, we display the relative errors of the individual parameters. All those errors are below 10%, with particular good estimation for the individual rupture times. The high standard deviation observed is in fact due to the badly classed subjects. Indeed, for those subjects, the individual parameters often take absurd values: practically null accelerations, large rupture times, etc..

On the table 2, we present the errors of reconstruction for the varifold norm. We can remark that both the subjects and the templates are very well reconstructed. The error on the template is a bit higher due to the repercussion of the small errors in the temporal reparametrization. Indeed, the small errors in accelerations can cause the time lines between the real template and the estimated one to differ causing small errors when comparing them at the same time point.

We also present the errors on our parameters table 3. Here, we can remark the very poor estimation of  $\Sigma$ . Once again, this is due to the presence of badly classed subjects having absurd individual parameters provoking, for example, a very high variance in the estimated individual rupture times. If we try to compute the estimated  $\Sigma$  taking into account only the subjects in the correct cluster, we then find more correct results: an error of 8.12% with a standard deviation of 3.97.

Finally, we test the ability of our model to predict new data by using cross validation. We create 100 new



Fig. 3 In red, the exact simulated data, in black, the results given by our algorithm. On the left, the representative curves that split up at a certain rupture time. On the right side, two subjects given with their reconstructions.



Fig. 4 Left: evolution of the varifold distances between the subjects and their reconstructions. Right: percentage of error in the classification along the first 100 iterations. With tempered distribution, the oscillating temperature coerces a lot of subjects to change classes. After 500 iterations, the error is 31.3% smaller.

$\xi_{i,0}$	$\xi_{i,1}$	$t_{R,i,0}$
$5.89\%_{\pm 7.01}$	$8.60\%_{\pm 10.7}$	$0.76\%_{\pm 1.61}$

**Table 1** Mean and standard deviation of the relativeerrors for the temporal parameters.

Subjects	Templates
$1.23\%_{\pm 1.96}$	$5.56\%_{\pm 2.60}$

**Table 2** Mean and standard deviation of the errors ofreconstruction for the subjects and templates.



**Table 3** Mean and standard deviation of the errors on the parameters  $\theta$ .

subjects deformed from the same representative curve as before. We then ask our algorithm to classify and reconstruct the trajectories while fixing the parameters and the representative curve by those learned previously. This time, 91% of the subjects are well classified and the error of reconstruction is only 0.84% with a standard deviation of 1.93. Hence, our model can process new data without problem, proving that we have no problem of overfitting or selection bias.

We want now to test hypothesis about the heterogeneity of the population. We run our algorithm supposing first that the two representative trajectories are different. We then run it again supposing that their first component is the same and that they fork at the rupture time. To select the model, we first compute the log-likelihood ratio test. However, in this case, this test is not enough to determine which model to choose. Indeed, with two independent representative curves, the algorithm can reconstruct the subjects as precisely as with branching representative curves. Hence, the difference between the likelihoods of the two models is too small to conclude and the test unstable between runs. To overcome this problem, we choose to compute the Bayesian Information Criterion (BIC):

$$BIC = ln(n)m - 2ln(q(y, z, \theta))$$

where m is the total number of parameters involved in the model.

This criterion takes into account the complexity of the model by adding a penalty proportional to the number of parameters involved. Hence, we will penalize the model with two independent trajectories (as it involves more parameters) even if the reconstruction is similar. This time, we have there is a difference of 2.98% between the two BIC criterions, leading us to choose, as expected, the model with branching representative curves.

#### 4.2 1D RECIST scores

In this 1D case, shapes are just curves on  $\mathbb{R}$  and we work with a logistic metric. The parallel transport is just a translation of the geodesic. That is why we rather considerate another space reparametrization, as done in (Allassonniere et al., 2017): for all classes *i* and all components *l*, we set:

$$\phi_{i,l}(x) = \gamma^{cl(i)}(t_R^{cl(i)}) + e^{\rho_i^l} \left( x - \gamma^{cl(i)}(t_R^{cl(i)}) \right) + \delta_i^l \,.$$

 $\rho_i^l$  is a dilatation factor and  $\delta_i^l$  is a translation factor. As with the time reparametrization, all the translation factors but the first one are fixed by continuity conditions and we note  $\delta_i^0 = \delta_i$ . Finally, our individual curve is defined by deforming spatially each component of  $\gamma^{cl(i)}$ by  $\psi_{i,l}$  and temporally by  $\phi_{i,l}$ .

With only two components, the piecewise geodesics for the logistic metric can be parameterized, for all class r, by:

$$\begin{cases} \gamma_{1}^{r}(t) = \frac{\gamma_{init}^{r} + \gamma_{escap}^{r} e^{a_{r}t + b_{r}}}{1 + e^{a_{r}t + b_{r}}} \\ \gamma_{2}^{r}(t) = \frac{\gamma_{fin}^{r} + \gamma_{escap}^{r} e^{-(c_{r}t + d_{r})}}{1 + e^{-(c_{r}t + d_{r})}} \\ \gamma_{1}^{r}(t) = \gamma_{1}^{r}(t)\mathbb{1}_{]-\infty, t_{R}^{r}]} + \gamma_{2}^{r}(t)\mathbb{1}_{]t_{R}^{r}, +\infty[}, \end{cases}$$
(12)

with  $\gamma_{init}^r, \gamma_{escap}^r, \gamma_{fin}^r \in \mathbb{R}$ . We fix  $a_r, b_r, c_r$  and  $d_r$  by asking the geodesics  $\gamma_{0,r}^1$  and  $\gamma_{0,r}^2$  to be  $\nu$ -near their geodesics at an initial time  $t_0^r$ , at the rupture time  $t_R^r$  and at a final time  $t_1^r$  (see (Allassonniere et al., 2017) for more details). Hence, rather than sampling momenta and control points, we will sample  $z_{pop}^r =$  $(\gamma_{init}^r, \gamma_{escap}^r, \gamma_{fin}^r, t_0^r, t_1^r)$ . This whole process is summarized Fig. 5.



**Fig. 5** Model description. In blue, the template with the different parameters defining it and in orange one subject obtained by deforming it. Here,  $t_0 = 0$ , the rupture points are represented by diamonds and the final times  $t_1$  by stars.

We test the algorithm on real data. We consider a database of patients suffering from the metastatic kidney cancer and taking antiangiogenic drugs. They come on a regular basis at the hospital to check the tumor evolution. Two behaviours are expected in the population: for all patients, the tumor first regresses. But then, for some, it stabilizes while for others the tumor size increases again forcing to change the treatment. The RECIST score is a feature that measures the tumor size and is used in the majority of clinical trials evaluating cancer treatments for objective response in solid tumors. Our dataset consists in the evaluation of the RECIST score for 176 patients with an average of 7 visits per subject and an average duration of 90 days between consecutive visits.

First, we launch our algorithm looking for two different representative curves. The result is displayed on the first line of figure 6. Our algorithm is indeed able to explain the variability of the population. However, it seems that our algorithm favours size over response dynamic as a clustering feature: small initial tumors (blue curve, 28% of the patients) are separated from big initial tumors (orange curve, 72% of the patients). For example, the orange reconstructed trajectory (top right plot) is classified with the blue template (top left plot) even if the treatment stays effective.

To overcome this trivial differentiation based on the tumor initial size, we ask the two templates to be the same until the rupture time using a branching process. This time, on the second line of figure 6, we really see two different behaviours: for one of the template, the RECIST score increases a lot more (blue curve, 37% of

the patients) than for the other (orange curve, 63% of the patients). As for the clustering, we see indeed that the subjects whose RECIST score do not increase after the rupture time are pooled together (green, red, orange and blue curves). Hence, we are able to separate the patients whose tumor becomes resistant to the treatment from the others. It can also be remarked that we have fewer time points for patients whose tumor becomes resistant because the clinicians change the treatment when this resistance is remarked and so the record of score for this patient stops.

#### 4.3 3D faces

We now obtain shapes of subjects expressing different facial expressions from the Birmingham University 3D dynamic facial expression database (Yin et al.). This database contains short videos from 101 subjects expressing happiness or surprise. We uniformly extract 8 frames, from the first to the 36-th one, which correspond to a subsampling of the first 1.4 seconds of each video. We do not work directly with the texture video, but with a set of 75 semi-automatically extracted landmarks, which were readily available along with this data set. Every set of 3D landmarks is registered to a reference one by Procrustes alignment.

We first apply our algorithm to find two classes, with only one component geodesic for each template. As we can see Fig. 7 and 8, the faces are well reconstructed and we can recognize the two expressions of surprise and happiness on the two templates. In particular, for the surprise class, the mouth is more widely open, while the eyes are wide open and the eyebrows higher. Moreover, 68.5% of the subjects are well classified. However, we can remark that the subjects who are badly classified often have a non neutral expression at the first image. For example, some subjects expressing surprise smile at the beginning of the experience, causing the algorithm to class them in the "happiness" class.

# 4.4 Hippocampi dataset

We finally test the algorithm on 100 subjects obtained from the Alzheimer's Disease Neuroimaging Initiative database (adni.loni.usc.edu). 50 of those subjects are control patients (CN) and 50 are Mild Cognitive Impairment subjects eventually diagnosed with Alzheimer's disease (MCIc). Meshes of the right hippocampus is segmented from the rigidly registered MRI. We first run our algorithm with a forking model as presented in the synthetic experiment. As there is no reason for the control subjects to have two different dynamics, we also ask one of the cluster (i.e. one of the evolution scenario) to follow the same geodesic before and after the rupture time. Our algorithm splits the patients in two clusters, one of them presenting a quicker and different pattern of atrophy (Fig. 11 and left side of Fig. 9 where the hippocampi volume is plotted along time). Moreover, 72%of the subjects are classified as expected: the CN in the cluster with a single dynamic showing a slower atrophy and the MCIc in the cluster with a faster atrophy after the rupture time. We have also studied the relation between our rupture time and the age of diagnosis. The individual rupture times are strongly correlated to the diagnostic age, indicating that we have been able to detect a change of behaviour correlated with the date of diagnosis (Fig. 10).

We run again the algorithm, this time looking for two clusters with separate trajectories, one of them with only one dynamic. The results are presented Fig. 12 and on the right side of Fig. 9 for the hippocampi volumes evolution. It is interesting to remark that the cluster with only one dynamic also presents a slower atrophy, as expected with a normal ageing. We can also detect different pattern of atrophy before and after the rupture time for the cluster with two dynamics. This time, 70% of the subjects are classified as expected: CN in the cluster with one dynamic and MCIc in the cluster with two dynamics and a quicker rate of atrophy.

As we are given two possible evolution scenarii, it is natural to try to quantify the goodness of fit of each of them, allowing for a choice of a better explanation of the disease. As for synthetic data, we use the Bayesian Information Criterion. We find a difference of 2.92% between the two BIC values leading to choose the branching model. Hence, this suggests that the MCI subjects first follow a normal aging scenario but deviate from it at the rupture time. It must however be remarked that our model is quite complex with a lot of high dimensional variables, making model selection quite difficult.

#### **5** Conclusion

We proposed a mixture model for longitudinal shape data sets where representative trajectories take the form of piecewise geodesic curves. Our model can be applied in a wide variety of situations to test whether subpopulations are independent from each other or fork or merge at different time-points. We showed on simulated examples that our tempered optimization scheme is key to achieve convergence of such a mixed effect model



Fig. 6 At the top, the results given with two different templates, at the bottom, with two templates whose first component is the same. To the left, our templates. To the right, 6 subjects and their reconstructed trajectories. In dotted lines, subjects in the cluster of the orange template. In plain lines subjects in the cluster of the blue template.



Fig. 7 Results of the algorithm when applied to a dataset of surprised or happy visages. At the top, the evolution of the template of the happiness class, at the bottom, the evolution of the template of the surprised class, one component for each template.

combining discrete variables with continuous variables of high dimension. We have shown the versatility of our model by applying it to a lot of different cases: trajectories with one or several dynamics, branching or not after a rupture time, with one part of the population still following the same dynamic or not after the rupture time. Its application on 1D data allowed us to present results of the same model in another setting while the



Fig. 8 Reconstitution of a subject expressing surprise. In red, the exact data, in black the reconstitution.

application with 3D faces showed that we can highlight different meaningful dynamics in a same population. Finally, the hippocampi data set allowed us to investigate the relationship between normal and pathological ageing.

Different questions still have to be answered. In particular, our scheme of temperature depends of the current state of the algorithm and a proof of convergence should be provided in this situation. Moreover, specific model selection criterion should be devised in this complex longitudinal setting. Those criterion should in particular help us to detect the optimal number of clusters and rupture times.



Fig. 9 Left: volume evolution for two branching clusters. Right: volume evolution for two clusters with separate trajectories.



Fig. 10 Comparison of the age at diagnosis with the individual rupture time for the MCIc patients in the case of the branching model,  $R^2 = 0.91$ 

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Fig. 11 Representative shape evolution at the ages 63.4y, 68.8y, 74.2y (i.e. rupture time), 75.5y, 80.9y and 86.3y. Bottom shapes: cluster with one dynamic. Top shapes : cluster with change of dynamic after rupture time. The color map gives the norm of the velocity field  $||v_0||$  on the meshes.



Fig. 12 Model with two separate clusters, one of them following only one dynamic. Representative shape evolution at the ages 64.7y, 68.3y, 74.3y (i.e. rupture time for the class with two dynamics), 77.5y, 80.9y and 86.3y. Top shapes : cluster with change of dynamic after rupture time. Bottom shapes: cluster with one dynamic. The color map gives the norm of the velocity field  $||v_0||$  on the meshes.

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