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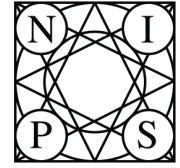
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Learning spatiotemporal piecewise-geodesic trajectories from longitudinal manifold-valued data

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Overview

We introduce a **hierarchical model** which allows to estimate both a group-representative piecewise-geodesic trajectory in the **Riemannian** space of shape and inter-individual variability. Following the approach of [3], we estimate a **representative piecewise-geodesic trajectory** of the global progression and together with **spacial and temporal inter-individual variabilities**. We first introduce our model in its most generic formulation and then make it explicit for RECIST [4] score monitoring, *i.e.* for one-dimension manifolds and piecewise-logistically distributed data.

Medical context – RECIST score

- **New anti-angiogenic therapies.** Patients suffering from the metastatic kidney cancer take a drug each day [1];
- **Tumoral growth.** The RECIST score (Response Evaluation Criteria In Solid Tumors) is a set of published rules that measures the tumoral growth;
- **Patient's response.** The response to a given treatment has generally two distinct phases: first, tumor's size reduces; then, the tumor grows again;
- Moreover, a practical question is to quantify the correlation between both phases and to accurately determine when the patient's response escape to treatment.

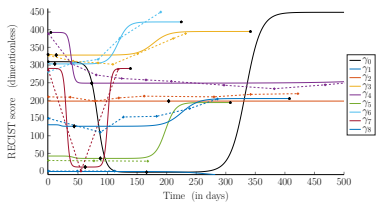


Figure 1: After 600 iterations. First 8 patients among the 176

Longitudinal dataset: Given $n \in \mathbb{N}^*$ individuals and $(k_i)_{i \in [1, n]}$, we observe the sequences $t = (t_{i,j})_{\substack{i \in [1, n] \\ j \in [1, k_i]}} \in \mathbb{R}^k$ and $y = (y_{i,j})_{\substack{i \in [1, n] \\ j \in [1, k_i]}} \in \mathbb{R}^{kd}$ where $k = \sum_{i=1}^n k_i$. Data points are seen as noisy samples along trajectories.

Real data consists of RECIST scores of a drove of 176 patients of the HEGP, with an average of 7 visits per subjects (min:3, max:22).

Mixed-effects model for piecewise-geodesically distributed data

Group-representative trajectory γ_0 . Given $m \in \mathbb{N}^*$ and $t_R = (-\infty < t_R^1 < \dots < t_R^{m-1} < +\infty)$, we build γ_0 in order it to be geodesic on each $]t_R^{\ell-1}, t_R^\ell[$.

① Let $M_0 \subset \mathbb{R}^d$ a geodesically complete manifold, $(\bar{\gamma}_0^\ell)_{\ell \in [1, m]}$ a family of geodesics on M_0 and $(\phi_0^\ell)_{\ell \in [1, m]}$ a family of isometries defined on M_0 ;

② $\forall \ell \in [1, m]$ we set $M_0^\ell = \phi_0^\ell(M_0)$ and $\gamma_0^\ell = \phi_0^\ell \circ \bar{\gamma}_0^\ell$;

③ **A piecewise-geodesic curve.** We define γ_0 as

$$\gamma_0 = \gamma_0^1 \mathbb{1}_{]-\infty, t_R^1]} + \sum_{\ell=2}^{m-1} \gamma_0^\ell \mathbb{1}_{]t_R^{\ell-1}, t_R^\ell]} + \gamma_0^m \mathbb{1}_{]t_R^{m-1}, +\infty[};$$

④ **Boundary conditions.** We impose boundary conditions on the rupture times to ensure continuity.

Individual trajectories $(\gamma_i)_{i \in [1, m]}$. Let $i \in [1, n]$. We build γ_i to derive from γ_0 through spatiotemporal transformations.

① **Time warps $(\psi_i^\ell)_{\ell \in [1, m]}$.** We choose affine time warps constrains by the continuity of each individual paths;

② **Space warps $(\phi_i^\ell)_{\ell \in [1, m]}$** have to be defined in view of applications. We require $\phi_i^\ell \circ \gamma_0^\ell(t_R^\ell) = \phi_i^{\ell+1} \circ \gamma_0^{\ell+1}(t_R^{\ell+1})$;

③ Last, $\forall \ell \in [1, m]$ we set $\gamma_i^\ell = \phi_i^\ell \circ \gamma_0^\ell \circ \psi_i^\ell$ and

$$\gamma_i = \gamma_i^1 \mathbb{1}_{]-\infty, t_{R,i}^1]} + \sum_{\ell=2}^{m-1} \gamma_i^\ell \mathbb{1}_{]t_{R,i}^{\ell-1}, t_{R,i}^\ell]} + \gamma_i^m \mathbb{1}_{]t_{R,i}^{m-1}, +\infty[};$$

④ **Gaussian noise.** $\forall j \in [1, k_i]$, $y_{i,j} = \gamma_i(t_{i,j}) + \varepsilon_{i,j}$ where $\varepsilon_{i,j} \sim \mathcal{N}(0, \sigma^2)$, $\sigma \in \mathbb{R}^+$.

Chemotherapy monitoring: Piecewise-logistic curve model

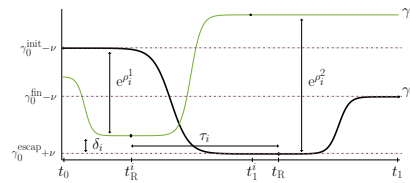


Figure 2: From average to individual path. Boundary conditions and transition from γ_0 to γ_i through spacial and temporal warps.

$z_{\text{pop}} = (\gamma_0^{\text{init}}, \gamma_0^{\text{escap}}, \gamma_0^{\text{fin}}, t_R, t_1)$ and $z_i = (\xi_i^1, \xi_i^2, \tau_i, \rho_i^1, \rho_i^2, \delta_i)$.

Parameters estimation with the MCMC-SAEM algorithm

Existence of the MAP

Given the piecewise-geodesic model and the choice of probability distributions for the parameters and latent variables of the model, for any dataset (t, y) , there exists $\hat{\theta}_{\text{MAP}} \in \arg\max_{\theta \in \Theta} q(\theta|y)$.

- **Parameters.** We assume that $z_{\text{pop}} \sim \mathcal{N}(\bar{z}_{\text{pop}}, \Sigma_{\text{pop}})$ where Σ_{pop} is a diagonal matrix with small fixed entries [2] and that $z_i \sim \mathcal{N}(0, \Sigma)$ where $\Sigma \in \mathcal{S}_6(\mathbb{R})$. Let $\theta = (\gamma_0^{\text{init}}, \gamma_0^{\text{escap}}, \gamma_0^{\text{fin}}, \bar{t}_R, \bar{t}_1, \Sigma, \sigma)$;

Our observations consist of patient's RECIST score over time. So, we set $m = 2$, $d = 1$ and $M_0 =]0, 1[$ equipped with the logistic metric. Let $\nu \in \mathbb{R}$ and $i \in [1, n]$.

- **Representative trajectory γ_0 .** Let $\gamma_0^{\text{init}}, \gamma_0^{\text{escap}}, \gamma_0^{\text{fin}} \in \mathbb{R}$. We map M_0 onto $]\gamma_0^{\text{escap}}, \gamma_0^{\text{init}}[$ and $]\gamma_0^{\text{escap}}, \gamma_0^{\text{fin}}[$ through affine transformations and require that $\gamma_0^1(t_0) = \gamma_0^{\text{init}} - \nu$, $\gamma_0^1(t_R) = \gamma_0^{\text{escap}} + \nu$ and $\gamma_0^2(t_1) = \gamma_0^{\text{fin}} - \nu$;

- **Time warps (ψ_i^1, ψ_i^2) .** We set $\alpha_i^\ell = e^{\xi_i^\ell}$, $\ell \in \{1, 2\}$;

- **Space warps (ϕ_i^1, ϕ_i^2) .** Given $(\rho_i^1, \rho_i^2, \delta_i) \in \mathbb{R}^3$, we set $\phi_i^\ell: x \mapsto e^{\rho_i^\ell} (x - \gamma_0(t_R)) + \gamma_0(t_R) + \delta_i$, $\ell \in \{1, 2\}$.

- **Hierarchical model.** Let $z = (z_{\text{pop}}, z_i)_{i \in [1, n]}$. We have

$$\begin{cases} y | z, \theta \sim \bigotimes_{i=1}^n \bigotimes_{j=1}^{k_i} \mathcal{N}(\gamma_i(t_{i,j}), \sigma^2) \\ z | \theta \sim \mathcal{N}(\bar{z}_{\text{pop}}, \Sigma_{\text{pop}}) \bigotimes_{i=1}^n \mathcal{N}(0, \Sigma) \\ (\Sigma, \sigma) \sim \mathcal{W}^{-1}(V, m_\Sigma) \otimes \mathcal{W}^{-1}(v, m_\sigma) \end{cases}$$

where $V \in \mathcal{S}_6(\mathbb{R})$ and $v, m_\Sigma, m_\sigma \in \mathbb{R}$;

- **Estimation.** We use a symmetric Random walk Hastings-Metropolis sampler in a stochastic version of the EM algorithm.

Experimental results

Synthetic data. Experiments are performed for the piecewise-logistic model.

Table 1: Mean (standard deviation) of relative error (expressed as a percentage) for the population parameters \bar{z}_{pop} and the residual standard deviation σ for 50 runs according to the sample size n .

n	50	100	150
$\bar{\gamma}_0^{\text{init}}$	1.63 (1.46)	2.42 (1.50)	2.14 (1.17)
$\bar{\gamma}_0^{\text{escap}}$	9.45 (5.40)	9.07 (5.19)	11.40 (5.72)
$\bar{\gamma}_0^{\text{fin}}$	6.23 (2.25)	7.82 (2.43)	5.82 (2.55)
\bar{t}_R	11.58 (1.64)	13.62 (1.31)	9.24 (1.63)
\bar{t}_1	4.41 (0.75)	5.27 (0.60)	3.42 (0.71)
σ	25.24 (12.84)	10.35 (3.96)	2.83 (2.31)

Real data. Figure 1 illustrates the qualitative performance of the model on the first 8 patients.

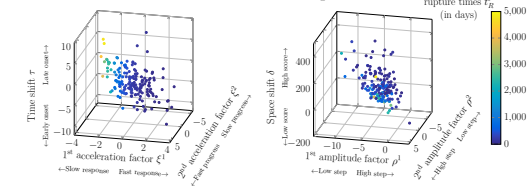


Figure 3: Individual random effects. Figure 3a: ξ_1^1 and ξ_2^2 against τ_i . Figure 3b: ρ_i^1 and ρ_i^2 against δ_i . In both figure, the color corresponds to the individual rupture time t_R^i .

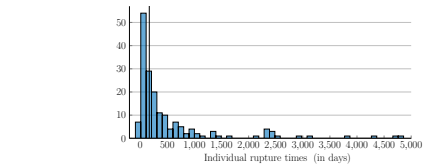


Figure 4: Distribution of the individual rupture times t_R^i . In black bold line, the estimated average rupture time t_R .

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