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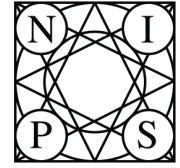
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# Learning spatiotemporal piecewise-geodesic trajectories from longitudinal manifold-valued data

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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.

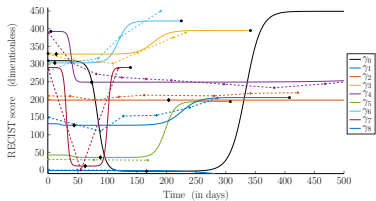


Figure 1: After 600 iterations. First 8 patients among the 176

**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  $\gamma_0$ .** Given  $m \in \mathbb{N}^*$  and  $t_R = (-\infty < t_R^1 < \dots < t_R^{m-1} < +\infty)$ , we build  $\gamma_0$  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  $\gamma_0$  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  $\gamma_i$  to derive from  $\gamma_0$  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

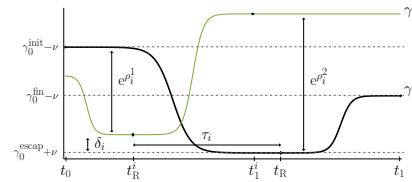


Figure 2: From average to individual path. Boundary conditions and transition from  $\gamma_0$  to  $\gamma_i$  through spacial and temporal warps.

$z_{\text{pop}} = (\gamma_0^{\text{init}}, \gamma_0^{\text{escap}}, \gamma_0^{\text{fin}}, t_R, t_1)$  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  $\Sigma_{\text{pop}}$  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  $\gamma_0$ .** 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  $(\psi_i^1, \psi_i^2)$ .** We set  $\alpha_i^\ell = e^{\xi_i^\ell}$ ,  $\ell \in \{1, 2\}$ ;

- **Space warps  $(\phi_i^1, \phi_i^2)$ .** 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  $\bar{z}_{\text{pop}}$  and the residual standard deviation  $\sigma$  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)
$\sigma$	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.

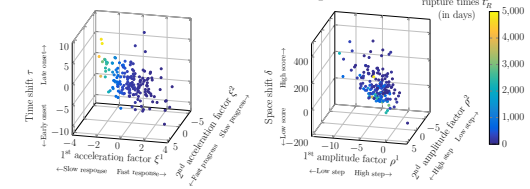


Figure 3: Individual random effects. Figure 3a:  $\xi_1^1$  and  $\xi_2^2$  against  $\tau_i$ . Figure 3b:  $\rho_i^1$  and  $\rho_i^2$  against  $\delta_i$ . In both figure, the color corresponds to the individual rupture time  $t_R^i$ .

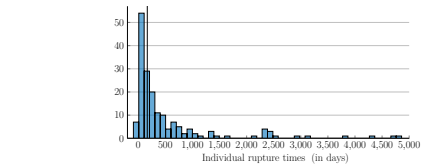


Figure 4: Distribution of the individual rupture times  $t_R^i$ . In black bold line, the estimated average rupture time  $t_R$ .

## References

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