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A coherent framework for learning spatiotemporal piecewise-geodesic trajectories from longitudinal manifold-valued data

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Summary. This paper provides a coherent framework for studying longitudinal manifold-valued data. We introduce a Bayesian mixed-effects model which allows to estimate both a group-representative piecewise-geodesic trajectory in the Riemannian space of shape and inter-individual variability. We prove the existence of the maximum a posteriori estimate and its asymptotic consistency under reasonable assumptions. Due to the non-linearity of the proposed model, we use a stochastic version of Expectation-Maximization algorithm to estimate the model parameters. Our simulations show that our model is not noise-sensitive and succeed in explaining various paths of progression.

Keywords: Bayesian estimation, EM like algorithm, Longitudinal data, MCMC methods, Nonlinear mixed-effects model, Spatio-temporal analysis

1. Introduction

Longitudinal studies are powerful tools to achieve a better understanding of temporal progressions of biological or natural phenomena. For instance, longitudinal psychometric data are often used to explore differences in the progression of Alzheimer's and more generally neurodegenerative diseases. Other important applications such as pattern recognition, chemotherapy monitoring, study of face expression dynamics, *etc.* come also from longitudinal studies. Moreover, efforts in medicine and medical follow-up rely more and more on the understanding of a global disease progression and not only on punctual states of health, often with the help of medical images.

Anatomical data – and most of structured data – are naturally modelled as points on a Riemannian manifold, called shape space. Geometrical properties of shape manifolds have been properly defined over the last decades. Moreover, according to the Whitney embedding theorem (Gallot et al., 2004), as the shape spaces are second-countable, they

will always be embedded in a real d -dimensional Euclidean space, the space of measurements, which leads us to consider the shape manifold as a submanifold of this Euclidean space. Therefore, the temporal evolution of empirical data may be modelled as a parametric curve in the space of measurements and more precisely as a noisy version of an underlying parametric curve living on the Riemannian shape submanifold. Given a cohort of individuals followed over a time period, we thus observe discreet samples of such a curve for each subject. We call this set of observations a longitudinal dataset.

Mixed-effects models have proved their efficiency in the study of longitudinal datasets (Laird and Ware, 1982), especially for medical purposes (Milliken and Edland, 2000; Ribba et al., 2014). Indeed, mixed-effects models provide a general and flexible framework to study correlated data. They consist of two parts: fixed effects which describe the data at the population level and random effects which are associated with individual experimental units drawn at random from a population. Given a longitudinal dataset, our model aims at estimating a representative trajectory of the whole population progression and its variability. Then, we can define subject-specific trajectories in view of the global progression.

The recent generic approach of Schiratti et al. (2015) to align patients is even more suitable. This model was built with the aim of granting temporal and spatial inter-subject variability through individual variations of a common time-line grant and parallel shifting of a representative trajectory. Each individual trajectory has its own intrinsic geometric pattern through spacial variability and its own time parametrization through time variability. In term of modelling, the time variability allows some individuals to follow the same progression path but at a different age and with possibly a different pace. However, Schiratti et al. (2015) have made a strong hypothesis to build their model as they assume the characteristic evolution to be geodesic. Such an assumption significantly reduces the effective framework of their model. In this paper, we will relax this assumption to make the model applicable to a wider variety of situations and datasets: we address each situation in which the evolution can fluctuate several times.

We propose in this paper a coherent and generic statistical framework which includes the model of Schiratti et al. (2015). Following their approach, we define a nonlinear mixed-effects model for the definition and estimation of spatio-temporal piecewise-geodesic trajectories from longitudinal manifold-valued data. We estimate a representative piecewise-geodesic trajectory of the global progression and together with spacial and temporal inter-individual variabilities. Particular attention is paid to estimation of the correlation between the different phases of the evolution.

Estimation is formulated as a well-defined *Maximum A Posteriori* (MAP) problem which we prove to be consistent under mild considerations. Numerically, the MAP estimation of the parameters is performed through a stochastic version of the the Expectation-Maximization (EM) algorithm (Dempster et al., 1977), namely the Monte-Carlo Markov-Chain Stochastic-Approximation Expectation-Maximization (MCMC-SAEM) algorithm (Lavielle, 2014). Theoretical results regarding its convergence have been proved in Delyon et al. (1999) and Allasonnière et al. (2010) and its numerical efficiency has been demonstrated for these types of models (Schiratti et al. (2015), MONOLIX – <http://lixoft.com/>).

The paper is organized as follows: in section 2 we define a generic nonlinear mixed-effects

model for piecewise-geodesically distributed data. Riemannian geometry allows us to derive a method that makes light assumptions about the data and applications we are able to deal with. We then make the generic formulation explicit for one-dimension manifolds and piecewise-logistically distributed data in section 4. This particular case is built in the target of chemotherapy monitoring. In section 3, we explain how to use the MCMC-SAEM algorithm to produce MAP estimates of the parameters. We also prove a consistency theorem, whose proof is postponed in appendix A. In section 5, some experiments are performed for the piecewise-logistic model: both on synthetic and on real data from the Hôpital Européen Georges Pompidou (HEGP). These experiments highlight the robustness of our model to noise and its performance in understanding individual paths of progression.

2. Generic mixed-effects model for piecewise-geodesically distributed data

In the following, we describe a *generic* method to build mixed-effect models for piecewise-geodesically distributed data. This leads us to a large variety of possible situations that we will be able to deal with within the same framework.

We consider a longitudinal dataset \mathbf{y} obtained by repeating multivariate measurements of $n \in \mathbb{N}^*$ individuals, where each individual $i \in \llbracket 1, n \rrbracket$ is observed $k_i \in \mathbb{N}^*$ times, at the time points $\mathbf{t}_i = (t_{i,j})_{j \in \llbracket 1, k_i \rrbracket}$ and where $\mathbf{y}_i = (y_{i,j})_{j \in \llbracket 1, k_i \rrbracket}$ denotes the sequence of observations for this individual. We also denote $k = \sum_{i=1}^n k_i$ the total numbers of observations and assume that each observation $y_{i,j}$ is a point of \mathbb{R}^d where $d \in \mathbb{N}$. Thus, the observed data consist in a sequence $\mathbf{y} = (y_{i,j})_{(i,j) \in \llbracket 1, n \rrbracket \times \llbracket 1, k_i \rrbracket}$ of \mathbb{R}^{kd} .

We generalize the idea of Schiratti et al. (2015) and build our model in a hierarchical way. Our data points are seen as noisy samples along trajectories and we suppose that each individual trajectory derives from a group-representative scenario through spatiotemporal transformations. Key to our model is that the group-representative trajectory is no longer assumed to be geodesic but piecewise-geodesic.

2.1. The group-representative trajectory

Let $m \in \mathbb{N}^*$ and $\mathbf{t}_R = (-\infty < t_R^1 < \dots < t_R^{m-1} < +\infty)$ a subdivision of \mathbb{R} , called the *breaking-up times* sequence. In order the representative trajectory γ_0 to be geodesic on each of the m sub-intervals of \mathbf{t}_R , we build γ_0 component by component.

A piecewise-geodesic curve. In this context, let M_0 be a geodesically complete submanifold of \mathbb{R}^d , $(\bar{\gamma}_0^\ell)_{\ell \in \llbracket 1, m \rrbracket}$ a family of geodesics on M_0 and $(\phi_0^\ell)_{\ell \in \llbracket 1, m \rrbracket}$ a family of isometries defined on M_0 . For all $\ell \in \llbracket 1, m \rrbracket$, we set $M_0^\ell = \phi_0^\ell(M_0)$ and $\gamma_0^\ell = \phi_0^\ell \circ \bar{\gamma}_0^\ell$. The isometric nature of the mapping ϕ_0^ℓ ensures that the manifolds M_0^ℓ remain Riemannian and that the curves $\gamma_0^\ell: \mathbb{R} \rightarrow M_0^\ell$ remain geodesic. In particular, each γ_0^ℓ remains parametrizable (Gallot et al., 2004). We define the representative trajectory γ_0 by

$$\forall t \in \mathbb{R}, \quad \gamma_0(t) = \gamma_0^1(t) \mathbb{1}_{]-\infty, t_R^1]}(t) + \sum_{\ell=2}^{m-1} \gamma_0^\ell(t) \mathbb{1}_{]t_R^{\ell-1}, t_R^\ell]}(t) + \gamma_0^m(t) \mathbb{1}_{]t_R^{m-1}, +\infty[}(t).$$

In other words, given a *manifold-template* of the geodesic components M_0 , we build γ_0 so that the restriction of γ_0 to each sub-interval of \mathbf{t}_R is the deformation of a geodesic curve $\bar{\gamma}_0^\ell$ living on M_0 by the corresponding isometry ϕ_0^ℓ . In practice, M_0 is chosen in order to catch the geometric nature of the observed data : if we are studying a score as in section 4, M_0 will be the standard finite segment $]0, 1[$ for instance. The choice of the isometries ϕ_0^ℓ and the geodesics $\bar{\gamma}_0^\ell$ have to be done with the aim of having an "as regular as possible" (at least continuous) curve γ_0 at the breaking-up time points t_R^ℓ . In the following section, we propose a way to meet this criterion in one dimension. Moreover, the freedoms in the choice of ϕ_0^ℓ and $\bar{\gamma}_0^\ell$ induce a wide panel of models.

Boundary conditions. Because of the piecewise nature of our average-trajectory γ_0 , constraints have to be formulated on each interval of the subdivision \mathbf{t}_R . Following the formulation of the *local existence and uniqueness theorem* (Gallot et al., 2004), constraints on geodesics are generally formulated by forcing a value and a tangent vector at a given time-point. However, as soon as there is more than one geodesic component, *i.e.* $m > 1$, such an approach cannot ensure the curve γ_0 to be at least continuous. That is why we re-formulate these constraints in our model as boundary conditions. Let $\bar{\mathbf{A}} = (\bar{A}^0, \dots, \bar{A}^m) \in (M_0)^{m+1}$. Let $t_0 \in \mathbb{R}$ be a real value representing an initial time and $t_1 \in \mathbb{R}$ representing a final one. We impose that for all $\ell \in \llbracket 1, m - 1 \rrbracket$,

$$\bar{\gamma}_0^1(t_0) = \bar{A}^0, \quad \bar{\gamma}_0^\ell(t_R^\ell) = \bar{A}^\ell, \quad \bar{\gamma}_0^{\ell+1}(t_R^\ell) = \bar{A}^\ell \quad \text{and} \quad \bar{\gamma}_0^m(t_1) = \bar{A}^m.$$

Notably, the $2m$ constraints are defined step by step. In the case where the geodesics could be written explicitly, such constraints do not complicate the model. In more complicated case, we use shooting or matching methods to enforce this constraints.

From this representative curve, we derive a modelling of the individual trajectories that mimics the individual evolution of subjects and best fits the individual observations.

2.2. Individual trajectories: Space and time warping

We want the individual trajectories to represent a wide variety of behaviours and to derive from the group characteristic path by spatiotemporal transformations. To do that, we define for each component of the piecewise-geodesic curve γ_0 a couple of transformations: The *diffeomorphic component deformations* and the *time component reparametrizations* which characterize respectively the spatial and the temporal variability of propagation among the population. Moreover, we decree the less constraints possible in the construction: at least continuity and control of the slopes at the (individual) breaking-up points.

Time component reparametrizations. For compactness, we denote t_0 by t_R^0 from now on.

To allow different paces in the progression and different rupture times for each individual, we introduce some temporal transformations ψ_i^ℓ , called *time-warp*, that are defined for the subject $i \in \llbracket 1, n \rrbracket$ and for the geodesic component $\ell \in \llbracket 1, m \rrbracket$ by

$$\psi_i^\ell(t) = \psi_{i(\alpha_i^\ell, \tau_i^\ell)}^\ell(t) = \alpha_i^\ell(t - t_R^{\ell-1} - \tau_i^\ell) + t_R^{\ell-1} \quad \text{where} \quad (\alpha_i^\ell, \tau_i^\ell) \in \mathbb{R}^+ \times \mathbb{R}.$$

The parameters τ_i^ℓ correspond to the time-shifts between the representative and the individual progression onset ; the α_i^ℓ are the acceleration factors that describe the pace of individuals, being faster or slower than the population characteristic. For all individual $i \in \llbracket 1, n \rrbracket$, let $\mathbf{t}_{R,i} = (t_{R,i}^\ell)_{\ell \in \llbracket 1, m-1 \rrbracket}$ denote the individual sequence of rupture times which is the subdivision of \mathbb{R} such that for all $\ell \in \llbracket 1, m-1 \rrbracket$, $\psi_i^\ell(t_{R,i}^\ell) = t_R^\ell$ i.e. such that

$$t_{R,i}^\ell = t_{R,i}^\ell(\alpha_i^\ell, \tau_i^\ell) = t_R^{\ell-1} + \tau_i^\ell + \frac{t_R^\ell - t_R^{\ell-1}}{\alpha_i^\ell}.$$

To ensure good adjunction at the rupture times, we demand that for all $\ell \in \llbracket 1, m \rrbracket$, $\psi_i^\ell(t_{R,i}^{\ell-1}) = t_R^{\ell-1}$. Hence the time reparametrizations are constrained and only the acceleration factors α_i^ℓ and the first time shift τ_i^1 are free: all other time shift, $\ell \in \llbracket 2, m \rrbracket$, are defined by $\tau_i^\ell = t_{R,i}^{\ell-1} - t_R^{\ell-1}$.

In the following, we will sometimes refer to the individual initial and final times which are defined, for all $i \in \llbracket 1, n \rrbracket$, by $t_0^i = t_0 + \tau_1$ and $t_1^i = t_R^{m-1} + \tau_i^m + \frac{t_1 - t_R^{m-1}}{\alpha_i^m}$.

Diffeomorphic component deformations. Concerning the space variability, we introduce m diffeomorphisms ϕ_i^ℓ to enable the different components of the individual trajectories to vary more irrespectively of each other. We just enforce the adjunctions to be at least continuous and therefore the mappings ϕ_i^ℓ to satisfy $\phi_i^\ell \circ \gamma_0^\ell(t_R^\ell) = \phi_i^{\ell+1} \circ \gamma_0^{\ell+1}(t_R^\ell)$ for all $\ell \in \llbracket 1, m-1 \rrbracket$. Note that, as the individual paths are no longer required to be geodesic, the mappings ϕ_i^ℓ do not need to be isometric.

For all individual $i \in \llbracket 1, n \rrbracket$ and all component $\ell \in \llbracket 1, m \rrbracket$, we set $\gamma_i^\ell = \phi_i^\ell \circ \gamma_0^\ell \circ \psi_i^\ell$ and define the corresponding individual curve γ_i by

$$\forall t \in \mathbb{R}, \quad \gamma_i(t) = \gamma_i^1(t) \mathbb{1}_{]-\infty, t_{R,i}^1]}(t) + \sum_{\ell=2}^{m-1} \gamma_i^\ell(t) \mathbb{1}_{]t_{R,i}^{\ell-1}, t_{R,i}^\ell]}(t) + \gamma_i^m(t) \mathbb{1}_{]t_{R,i}^{m-1}, +\infty[}(t).$$

Finally, the observations $\mathbf{y}_i = (y_{i,j})_{j \in \llbracket 1, k_i \rrbracket}$ are assumed to be distributed along the curve γ_i and perturbed by an additive Gaussian noise $\varepsilon_i \sim \mathcal{N}(0, \sigma^2 I_{k_i, d})$, $\sigma \in \mathbb{R}$:

$$\forall (i, j) \in \llbracket 1, n \rrbracket \times \llbracket 1, k_i \rrbracket, \quad y_{i,j} = \gamma_i(t_{i,j}) + \varepsilon_{i,j} \quad \text{where} \quad \varepsilon_{i,j} \sim \mathcal{N}(0, \sigma^2 I_d).$$

By construction, for each $(i, j) \in \llbracket 1, n \rrbracket \times \llbracket 1, k_i \rrbracket$, there exist $\ell \in \llbracket 1, m \rrbracket$ such that $\gamma_i(t_{i,j})$ lies on the submanifold $\phi_i^\ell(M_0^\ell)$ of \mathbb{R}^d . Thus, the previous sum is well-defined. In particular, we do not assume that the noisy-observation remain on the manifold.

The choice of the isometries ϕ_0^ℓ and the diffeomorphisms ϕ_i^ℓ induces a large range of piecewise-geodesic models. For example, if $m = 1$, $\phi_0^1 = Id$ and if ϕ_i^1 denotes the application that maps a curve onto its parallel curve for a given non-zero tangent vector \mathbf{w}_i , we feature the model proposed by Schiratti et al. (2015). In section 4.1, we propose another specific model which can be used for chemotherapy monitoring for instance.

2.3. Toward a coherent and tractable statistical generative model

We first introduce some notations in order to clearly state our statistical generative model. Let $\mathbf{z}_i^\psi = (\alpha_i^\ell, \tau_i^\ell)_{\ell \in \llbracket 1, m \rrbracket}$ denote the individual temporal variables and similarly \mathbf{z}_i^ϕ denote the individual spatial variables, *i.e.* the variables associated to the variation of the m diffeomorphic deformations ϕ_i^ℓ . Likewise, let \mathbf{z}_{pop} denote the population variable, *i.e.* the variable associated to the variation of the m isometric mappings ϕ_0^ℓ .

Let $p_{\text{ind}} \in \mathbb{N}$ be the dimension of each vector $\mathbf{z}_i = (\mathbf{z}_i^\psi, \mathbf{z}_i^\phi)$ such that $\forall i \in \llbracket 1, n \rrbracket$, $\mathcal{Z}_i \subset \mathbb{R}^{p_{\text{ind}}}$ denotes the space of random effects. Similarly, let $p_{\text{pop}} \in \mathbb{N}$ be the dimension of \mathbf{z}_{pop} and $\mathcal{Z}_{\text{pop}} \subset \mathbb{R}^{p_{\text{pop}}}$ denotes the space of fixed effects.

Modelling constraints... In a modelling perspective, we are interested in understanding the individual behaviours with respect to the characteristic one. Thus, we focus on the variance of the random effects $\mathbf{z}_i = (\mathbf{z}_i^\psi, \mathbf{z}_i^\phi)$ rather than their marginal distributions. Moreover, as we want the representative path to characterize the pattern of behaviour of the individual trajectories, we have to slightly modify the individual parameters \mathbf{z}_i in such a way that for all i , $\mathbb{E}(\mathbf{z}_i) = 0$. In particular, if our model were linear, this would have ensured the representative trajectory to be the mean (in the statistical meaning) of the individual ones. Concerning the individual temporal variables for instance, the acceleration parameters $(\alpha_i^\ell)_{\ell \in \llbracket 1, m \rrbracket}$ have to be positive and equal to one on average while the time shifts $(\tau_i^\ell)_{\ell \in \llbracket 1, m \rrbracket}$ are of any signs and must be zero on average. For these reasons, we set $\alpha_i^\ell = e^{\xi_i^\ell}$ and consider the "new" temporal variable, still denoted \mathbf{z}_i^ψ for compactness, $\mathbf{z}_i^\psi = (\xi_i^\ell, \tau_i^\ell)_{\ell \in \llbracket 1, m \rrbracket}$. We proceed in the same way for the individual spatial variables.

To sum up, we assume that it exists a symmetric positive-definite matrix $\Sigma \in \mathcal{S}_{p_{\text{ind}}}^+(\mathbb{R})$ such that $\mathbf{z}_i \sim \mathcal{N}(0, \Sigma)$, and now want to estimate Σ . Hence, the parameters we are interested in are $\theta = (\mathbf{z}_{\text{pop}}, \Sigma, \sigma) \in \mathcal{Z}_{\text{pop}} \times \mathcal{S}_{p_{\text{ind}}}^+(\mathbb{R}) \times \mathbb{R}^+$.

...and computational feasibility. Given a n -sample, we target $\hat{\theta}_n$ an estimation of our parameters. Following the classical approach for maximum likelihood estimation in nonlinear mixed-effects models, we use the MCMC-SAEM algorithm. However, the theoretical convergence of this algorithm is proved only if the model belongs to the curved exponential family. This framework is also important for numerical performances. Without further hypothesis, our model does not satisfy this constraint. Therefore, we proceed as in Kuhn and Lavielle (2005): we assume that \mathbf{z}_{pop} is the realization of independent Gaussian random variables with fixed small variances and estimate the means of those variables. So, the parameters we want to estimate are $\theta = (\overline{\mathbf{z}_{\text{pop}}}, \Sigma, \sigma)$ and we define by $\Theta = \mathbb{R}^{p_{\text{pop}}} \times \mathcal{S}_{p_{\text{ind}}}^+(\mathbb{R}) \times \mathbb{R}^+$ the space of admissible parameters.

The fixed and random effects $\mathbf{z} = (\mathbf{z}_{\text{pop}}, \mathbf{z}_i)_{i \in \llbracket 1, n \rrbracket}$ are considered as latent variables. Our model writes in a hierarchical way as

$$\mathbf{y} | \mathbf{z}, \theta \sim \bigotimes_{i=1}^n \bigotimes_{j=1}^{k_i} \mathcal{N}(\gamma_i(t_{i,j}), \sigma^2) \quad \text{and} \quad \mathbf{z} | \theta \sim \mathcal{N}(\overline{\mathbf{z}_{\text{pop}}}, \mathcal{D}_{\text{pop}}^{-1}) \bigotimes_{i=1}^n \mathcal{N}(0, \Sigma)$$

where $\sigma_{\text{pop}} \in \mathbb{R}_+^{p_{\text{pop}}}$ is an hyperparameter of the model and $\mathcal{D}_{\text{pop}} = \sigma_{\text{pop}}^2 I_{p_{\text{pop}}} \in \mathcal{M}_{p_{\text{pop}}}(\mathbb{R})$. The products \otimes mean that the corresponding entries are considered to be independent. In other words, we assume that each of the measurement noises is independent of all the others. Of course, it may not be the case in practise. But, as all the observations for a given subject come from a single curve, this assumption is reasonable in our context. Moreover, this assumption leads us to a more computationally tractable algorithm.

3. Parameters estimation

As said just above, we want to estimate $\theta = (\overline{\mathbf{z}}_{\text{pop}}, \Sigma, \sigma) \in \mathbb{R}^{p_{\text{pop}}} \times \mathcal{S}_{p_{\text{ind}}}^+(\mathbb{R}) \times \mathbb{R}^+$. As we want our model to be consistent with high-dimensional data analysis, we consider a Bayesian framework, *i.e.* we assume the following priors

$$(\Sigma, \sigma) \sim \mathcal{W}^{-1}(V, m_{\Sigma}) \otimes \mathcal{W}^{-1}(v, m_{\sigma}) \quad \text{where } V \in \mathcal{S}_{p_{\text{ind}}}^+(\mathbb{R}), \quad v, m_{\Sigma}, m_{\sigma} \in \mathbb{R}$$

and $\mathcal{W}^{-1}(V, m_{\Sigma})$ denotes the inverse Wishart distribution with scale matrix V and degrees of freedom m_{Σ} . Regularization has indeed proven its fruitful in this context (Giraud, 2014). In order for the inverse Wishart to be non-degenerate, the degrees m_{Σ} and m_{σ} must satisfy $m_{\Sigma} > 2p_{\text{ind}}$ and $m_{\sigma} > 2$. In practice, we yet use degenerate priors but with well-defined posteriors. To be consistent with the one-dimension inverse Wishart distribution, we define the density function distribution of higher dimension as

$$f_{\mathcal{W}^{-1}(V, m_{\Sigma})}(\Sigma) = \frac{1}{\Gamma_{p_{\text{ind}}}\left(\frac{m_{\Sigma}}{2}\right)} \left(\frac{\sqrt{|V|}}{2^{\frac{p_{\text{ind}}}{2}} \sqrt{|\Sigma|}} \exp\left(-\frac{1}{2} \text{tr}(V\Sigma^{-1})\right) \right)^{m_{\Sigma}}$$

where $\Gamma_{p_{\text{ind}}}$ is the multivariate gamma function.

The estimates are obtained by maximizing the posterior density on θ conditionally on the observations $\mathbf{y} = (y_{i,j})_{(i,j) \in \llbracket 1, n \rrbracket \times \llbracket 1, k_i \rrbracket}$.

In the following paragraphs, we first show that the model is well-posed *i.e.* that for any finite sample the *maximum* we are looking for exists. We then prove a consistency theorem which ensures that the set of parameters which well-explain the observations is non-empty and that the MAP estimator converges to this set. Last, we explain how to use the MCMC-SAEM algorithm to produce MAP estimates.

3.1. Existence of the maximum a posteriori estimator

The inverse Wishart priors on the variances not only regularize the log-likelihood of the model, they also ensure the existence of the MAP estimator.

THEOREM 1 (EXISTENCE OF THE MAP ESTIMATOR). *Given a piecewise-geodesic model and the choice of probability distributions for the parameters and latent variables of the model, for any dataset $(t_{i,j}, y_{i,j})_{(i,j) \in \llbracket 1, n \rrbracket \times \llbracket 1, k_i \rrbracket}$, there exists $\hat{\theta}_{\text{MAP}} \in \underset{\theta \in \Theta}{\text{argmax}} q(\theta | \mathbf{y})$.*

The demonstration of the theorem uses the following lemma.

LEMMA 1. *Given a piecewise-geodesic model and the choice of a probability distribution for the parameters and latent variables of the model, the posterior $\theta \mapsto q(\theta|\mathbf{y})$ is continuous on the parameter space Θ .*

PROOF. Let $\mathcal{Z} = \mathcal{Z}_{\text{pop}} \times \prod_{i=1}^n \mathcal{Z}_i$ the space of latent variables. Using Bayes rule, for all $\theta \in \Theta$,

$$q(\theta|\mathbf{y}) = \frac{1}{q(\mathbf{y})} \left(\int_{\mathcal{Z}} q(\mathbf{y}|z, \theta) q(z|\theta) dz \right) q_{\text{prior}}(\theta).$$

The density functions $\theta \mapsto q_{\text{prior}}(\theta)$ and $\theta \mapsto q(\mathbf{y}|z, \theta) q(z|\theta)$ is continuous on Θ for all $z \in \mathcal{Z}$. Moreover, for all $\theta \in \Theta$ and all $z \in \mathcal{Z}$,

$$q(\mathbf{y}|z, \theta) = \frac{1}{(\sigma\sqrt{2\pi})^k} \exp\left(-\frac{1}{2\sigma^2} \sum_{i=1}^n \sum_{j=1}^{k_i} (y_{i,j} - \gamma_i(t_{i,j}))^2\right)$$

and so, for all $\theta \in \Theta$ and $z \in \mathcal{Z}$, $q(\mathbf{y}|z, \theta) q(z|\theta) \leq \frac{1}{(\sigma\sqrt{2\pi})^k} q(z|\theta)$ which is positive and integrable as a probability distribution. As a consequence, $z \mapsto q(\mathbf{y}|z, \theta) q(z|\theta)$ is integrable – and positive – on \mathcal{Z} for all $\theta \in \Theta$ and $\theta \mapsto q(\mathbf{y}|\theta)$ is continuous.

PROOF (THEOREM 1 – EXISTENCE OF THE MAP). Given the result of the lemma 1 and considering the Alexandrov one-point compactification $\bar{\Theta} = \Theta \cup \{\infty\}$ of the parameters space Θ , it suffices to prove that $\lim_{\theta \rightarrow \infty} \log q(\theta|\mathbf{y}) = -\infty$. We keep the notation of the previous proof and proceed similarly. In particular, for all $\theta \in \Theta$,

$$\log q(\theta|\mathbf{y}) \leq -\log q(\mathbf{y}) - k \log(\sqrt{2\pi}) - k \log(\sigma) + \log q_{\text{prior}}(\theta).$$

By computing the prior distribution q_{prior} , we remark that there exists C which does not depend on the parameter θ such as

$$\log q(\theta|\mathbf{y}) \leq C(\mathbf{y}) - (k + m_\sigma) \log(\sigma) - \frac{m_\Sigma}{2} \log(|\Sigma|) - \frac{m_\Sigma}{2} \text{tr}(V\Sigma^{-1}) - \frac{m_\sigma}{2} \left(\frac{v}{\sigma}\right)^2$$

Let $\mu(V)$ denote the smallest eigenvalue of V and $\rho(\Sigma^{-1})$ the largest eigenvalue of Σ^{-1} , which is also its operator norm. We know that $\langle \Sigma | V \rangle_F \geq \mu(V) \rho(\Sigma^{-1})$ and $\log(|\Sigma^{-1}|) \leq p_{\text{ind}} \log(\|\Sigma^{-1}\|)$ so that

$$-\frac{m_\Sigma}{2} \text{tr}(V\Sigma^{-1}) + \frac{m_\Sigma}{2} \log(|\Sigma^{-1}|) \leq \frac{m_\Sigma}{2} [-\mu(V) \|\Sigma^{-1}\| + p_{\text{ind}} \log(\|\Sigma^{-1}\|)]$$

and

$$\lim_{\|\Sigma\| + \|\Sigma^{-1}\| \rightarrow +\infty} \left\{ -\frac{m_\Sigma}{2} \text{tr}(V\Sigma^{-1}) + \frac{m_\Sigma}{2} \log(|\Sigma^{-1}|) \right\} = -\infty.$$

Likewise,

$$\lim_{\sigma + \sigma^{-1} \rightarrow +\infty} \left\{ -(k + m_\sigma) \log(\sigma) - \frac{m_\sigma}{2} \left(\frac{v}{\sigma}\right)^2 \right\} = -\infty$$

hence the result.

We have detailed the previous proof in order to emphasize the necessity of prior distribution on the variances Σ and σ to ensure the existence of the *maximum a posteriori*.

3.2. Consistency of the maximum a posteriori estimator

We are interested in the consistency of the MAP estimator without making strong assumptions on the distribution of the observations \mathbf{y} . In particular, we do not assume that the observations are generated by the model.

We denote $P(d\mathbf{y})$ the distribution governing the observations and Θ_* the set of admissible parameters inducing a model distribution close to $P(d\mathbf{y})$:

$$\Theta_* = \left\{ \theta_* \in \Theta \mid \mathbb{E}_{P(d\mathbf{y})} [\log q(\mathbf{y}|\theta_*)] = \sup_{\theta \in \Theta^\omega} \mathbb{E}_{P(d\mathbf{y})} [\log q(\mathbf{y}|\theta)] \right\}.$$

The MAP estimator is said consistent if it converges to the set Θ_* (on every compact of Θ possibly). Classical results of consistency assume that the space Θ_* is non-empty (see the Wald's consistency theorem (van der Vaart, 2000)). However, such an hypothesis is not entirely satisfactory: we have no guarantee that Θ_* is actually non-empty. We propose below a reasonable framework in which the convergence of the MAP estimator toward the corresponding non-empty set Θ_* is guaranteed.

Two kinds of latent variables. To this end and for any $\omega \in \mathbb{R}$, we define the space Θ^ω of admissible parameters such that on average, the fixed effects are bounded by ω :

$$\Theta^\omega = \{ \theta = (\overline{\mathbf{z}}_{\text{pop}}, \Sigma, \sigma) \in \Theta \mid \|\overline{\mathbf{z}}_{\text{pop}}\|_2 \leq \omega \} \quad \text{where} \quad \Theta = \mathbb{R}^{p_{\text{pop}}} \times \mathcal{S}_{p_{\text{ind}}}^+(\mathbb{R}) \times \mathbb{R}^+.$$

As the assumption only concern the average behaviour of the population variable \mathbf{z}_{pop} , it is not restrictive. Moreover, fixed effects are most of the time bounded (but potentially with high bounds) in applications. In this new framework, for all $\omega \in \mathbb{R}$,

$$\Theta_*^\omega = \{ \theta \in \Theta^\omega \mid \mathbb{E}_{P(d\mathbf{y})} [\log q(\mathbf{y}|\theta)] = \mathbb{E}^*(\omega) \} \quad \text{where} \quad \mathbb{E}^*(\omega) = \sup_{\theta \in \Theta^\omega} \mathbb{E}_{P(d\mathbf{y})} [\log q(\mathbf{y}|\theta)].$$

To state the consistency of the MAP estimator, we first have to give some notations. For all $i \in \llbracket 1, n \rrbracket$, we assume the existence of two subsets of \mathcal{Z}_i – $\mathcal{Z}_i^{\text{reg}}$ and $\mathcal{Z}_i^{\text{crit}}$ – such that $\mathcal{Z}_i = \mathcal{Z}_i^{\text{reg}} \times \mathcal{Z}_i^{\text{crit}}$. In other words, we assume that each component of each individual latent variable \mathbf{z}_i is of two sorts: *regular* or *critical*. We will respectively denote $\mathbf{z}_i^{\text{reg}}$ and $\mathbf{z}_i^{\text{crit}}$ this sub-variables leading to write, up to permutations, $\mathbf{z}_i = (\mathbf{z}_i^{\text{reg}}, \mathbf{z}_i^{\text{crit}})$. Likewise, we assume that the components of the population latent variables can be regular or critical, *i.e.* that it exists $\mathcal{Z}_{\text{pop}}^{\text{reg}}, \mathcal{Z}_{\text{pop}}^{\text{crit}} \subset \mathcal{Z}_{\text{pop}}$ such that $\mathbf{z}_{\text{pop}} = (\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_{\text{pop}}^{\text{crit}}) \in \mathcal{Z}_{\text{pop}}^{\text{reg}} \times \mathcal{Z}_{\text{pop}}^{\text{crit}}$. To stay consistent with the previous notations, we denote $p_{\text{ind}}^{\text{reg}}, p_{\text{ind}}^{\text{crit}}, p_{\text{pop}}^{\text{reg}}$ and $p_{\text{pop}}^{\text{crit}}$ the dimension of the ambient space of the matching sets: $\mathcal{Z}_i^{\text{reg}} \subset \mathbb{R}^{p_{\text{ind}}^{\text{reg}}}$ and so on.

Consistency of the maximum a posteriori estimator. In the following, we want to study the effect of the variables $(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)$ on the trajectories. To this end, we introduce for all i the notation $\vec{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i) = (\gamma_i(t_{i,j}))_{j \in \llbracket 1, k_i \rrbracket} \in \mathbb{R}^{k_i}$ and more generally the functions $\vec{\gamma}_i: \mathcal{Z}_{\text{pop}} \times \mathcal{Z}_i \rightarrow \mathbb{R}^{k_i}$. Let $\ell \in \llbracket 1, n \rrbracket$, consider a ℓ -tuple of individuals and denote by $k^\ell = \sum_{i=1}^\ell k_i$ the total number of measures for this ℓ -tuple. Let $\mathbf{y}^\ell = (y_i)_{i \in \llbracket 1, \ell \rrbracket} \in \mathbb{R}^{k^\ell}$ and $\mathbf{z}^\ell = (\mathbf{z}_{\text{pop}}, \mathbf{z}_i)_{i \in \llbracket 1, \ell \rrbracket} \in \mathbb{R}^{p_{\text{pop}} + \ell p_{\text{ind}}}$ be the vectors made up of the ℓ corresponding vectors. As in the one-by-one case, we define by $\vec{\gamma}^\ell: \mathcal{Z}_{\text{pop}} \times \mathcal{Z}_i^\ell \rightarrow \mathbb{R}^{k^\ell}$ the function which maps the vector \mathbf{z}^ℓ to the one $(\vec{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i))_{i \in \llbracket 1, \ell \rrbracket}$.

For all vector of the form $(\mathbf{a}, \mathbf{b}) \in \mathbb{R}^{p_a} \times \mathbb{R}^{p_b}$ where p_a and p_b are any integer number and for all index $v \in \llbracket 1, p_a + p_b \rrbracket$, $(\mathbf{a}, \mathbf{b})_v$ and $(\mathbf{a}, \mathbf{b})_{-v}$ refer respectively to

$$\begin{aligned} (\mathbf{a}, \mathbf{b})_v &= ((a_1, \dots, a_{p_a}), (b_1, \dots, b_{p_b}))_v = \begin{cases} a_v & \text{if } v \leq p_a \\ b_{v-p_a} & \text{else} \end{cases} \\ (\mathbf{a}, \mathbf{b})_{-v} &= \begin{cases} ((a_1, \dots, a_{v-1}, a_{v+1}, \dots, a_{p_a}), (b_1, \dots, b_{p_b})) & \text{if } v \leq p_a \\ ((a_1, \dots, a_{p_a}), (b_1, \dots, b_{v-p_a-1}, b_{v-p_a+1}, \dots, b_{p_b})) & \text{else} \end{cases}. \end{aligned}$$

Last, for all $k \in \mathbb{N}$, \mathcal{L}_k refers to the Lebesgue measure on \mathbb{R}^k .

THEOREM 2 (CONSISTENCY OF THE MAP ESTIMATOR). *Assume that*

- (H1) *The number of observations is bigger than the one of latent variables. This writes: it exists $\ell \in \llbracket 1, n \rrbracket$ such that $p^\ell < k^\ell$ where $k^\ell = \sum_{i=1}^\ell k_i$ and $p^\ell = p_{\text{pop}} + \ell p_{\text{ind}}$;*
- (H2) *The density $P(d\mathbf{y}^\ell)$ is continuous with polynomial tail decay of degree bigger than the dimension of the truncated space of latent variables, i.e. bigger than $p^\ell + 1$, apart from a subset compact K of \mathbb{R}^{k^ℓ} ;*
- (H3) *The observation noise is negligible regarding the individual trajectories: for all subjects $i \in \llbracket 1, n \rrbracket$, $\|\varepsilon_i\|_2 \leq \|\vec{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)\|_2$;*
- (H4) *The individual trajectories grow over-linearly with respect to the regular variables: for all individuals $i \in \llbracket 1, n \rrbracket$ and for all $v \in \llbracket 1, p_{\text{pop}}^{\text{reg}} + p_{\text{ind}}^{\text{reg}} \rrbracket$, there exists two functions $a_{i,v}, b_{i,v}: \mathbb{R}^{p_{\text{pop}}^{\text{reg}} + p_{\text{ind}}^{\text{reg}} - 1} \rightarrow \mathbb{R}$ which depend only of $(\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_{-v}$ and such that for all $(\mathbf{z}_{\text{pop}}, \mathbf{z}_i) \in \mathcal{Z}_{\text{pop}} \times \mathcal{Z}_i$,*

$$a_{i,v} \left((\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_{-v} \right) \geq 0 \quad \text{where} \quad a_{i,v} \left((\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_{-v} \right) = 0 \quad \text{iff} \quad (\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_{-v} = 0$$

$$\text{and} \quad \|\vec{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)\|_\infty \geq a_{i,v} \left((\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_{-v} \right) \left| (\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_v \right| + b_{i,v} \left((\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_{-v} \right);$$

- (H5) *Critical variables induce critical trajectories: for all individuals $i \in \llbracket 1, n \rrbracket$ and for all $v \in \llbracket 1, p_{\text{pop}}^{\text{crit}} + p_{\text{ind}}^{\text{crit}} \rrbracket$, there exists a critical trajectory $\gamma_{i,v}^{\text{crit}}$*

$$\lim_{(\mathbf{z}_{\text{pop}}^{\text{crit}}, \mathbf{z}_i^{\text{crit}})_v \rightarrow +\infty} \vec{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i) = \gamma_{i,v}^{\text{crit}} \quad \text{and} \quad \mathcal{L}_{k_i}(\{y_i = \gamma_{i,v}^{\text{crit}}\}) = 0.$$

Let $(\hat{\theta}_m)_{m \in \mathbb{N}}$ denote any MAP estimator. Then $\Theta_*^\omega \neq \emptyset$ and for any $\varepsilon \in \mathbb{R}_+^*$,

$$\lim_{m \rightarrow \infty} \mathbb{P} \left[\delta(\hat{\theta}_m, \Theta_*^\omega) \geq \varepsilon \right] = 0$$

where δ in any metric compatible with the topology on Θ^ω .

See appendix A for the proof.

The condition $p^\ell \leq k^\ell$ means that without enough observations, we cannot build a consistent model. Such an assumption is quite reasonable as we have no chance to catch the trajectories behaviour with certitude with less observations than the constraints over them. Assumptions on the distribution $P(d\mathbf{y})$ and the observation noise are really weak and always fulfilled in practice. Moreover, as the theorem holds for all $\omega \in \mathbb{R}$, the boundary over the average of the population latent variable $\overline{z_{\text{pop}}}$ is not really restrictive.

For compactness, we have stated the theorem by considering that a latent variable may be of only one kind: regular or critical. Actually, a single latent variable can be of two kinds: critical in the neighbourhood of $+\infty$ and regular around $-\infty$, and *vice-versa* (see the proof for details). This remark is all the more important in view of some applications and the section 4 but can be treated by our proof.

3.3. Estimation with the MCMC-SAEM algorithm

As explain at the paragraph 2.3, a stochastic version of the EM algorithm is adopted, namely the SAEM algorithm. As the conditional distribution $q(\mathbf{z}|\mathbf{y}, \theta)$ is unknown, the simulation step is replaced using a sampling algorithm, leading to consider the MCMC-SAEM algorithm. It alternates between simulation, stochastic approximation and maximization steps until convergence. The simulation step is achieved using a symmetric random walk Hasting-Metropolis within Gibbs sampler (Robert and Casella, 1999).

The complete log-likelihood of our model writes

$$\begin{aligned} \log q(\mathbf{y}, \mathbf{z}, \theta) = & -\frac{1}{2\sigma^2} \sum_{i=1}^n \sum_{j=1}^{k_i} (y_{i,j} - \gamma_i(t_{i,j}))^2 - k \log(\sigma) - \frac{1}{2} \sum_{i=1}^n ({}^t \mathbf{z}_i \Sigma^{-1} \mathbf{z}_i) - \frac{n}{2} \log(|\Sigma|) \\ & - \frac{1}{2} {}^t (\mathbf{z}_{\text{pop}} - \overline{\mathbf{z}_{\text{pop}}}) D^{-1} (\mathbf{z}_{\text{pop}} - \overline{\mathbf{z}_{\text{pop}}}) - \frac{1}{2} \log(|D|) - \frac{1}{2} \text{tr}(V \Sigma^{-1}) \\ & + \frac{m_\Sigma}{2} (\log(|V|) - \log(|\Sigma|)) + m_\sigma \log\left(\frac{v}{\sigma}\right) - \frac{m_\sigma}{2} \left(\frac{v}{\sigma}\right)^2 + \text{csts}. \end{aligned}$$

It is clear to see that this model belongs to the curved exponential family : the sufficient statistics may for instance be defined as

$$\mathbf{S}_1(\mathbf{y}, \mathbf{z}) = \mathbf{z}_{\text{pop}} \quad ; \quad \mathbf{S}_2(\mathbf{y}, \mathbf{z}) = \frac{1}{n} \sum_{i=1}^n {}^t \mathbf{z}_i \mathbf{z}_i \quad ; \quad \mathbf{S}_3(\mathbf{y}, \mathbf{z}) = \frac{1}{k} \sum_{i=1}^n \sum_{j=1}^{k_i} (y_{i,j} - \gamma_i(t_{i,j}))^2$$

where $\mathbf{S}_1(\mathbf{y}, \mathbf{z}) \in \mathbb{R}^{p_{\text{pop}}}$, $\mathbf{S}_2(\mathbf{y}, \mathbf{z}) \in \mathcal{M}_{\text{pind}}(\mathbb{R})$ and $\mathbf{S}_3(\mathbf{y}, \mathbf{z}) \in \mathbb{R}$.

Algorithm 1: Overview of the SAEM for the generic piecewise-geodesic model.

Input: $\theta^* = (\overline{\mathbf{z}}_{\text{pop}}^*, \Sigma^*, \sigma^*)$, (V, m_Σ) , (v, m_σ) , maxIter , Nburnin .

Output: $\theta = (\overline{\mathbf{z}}_{\text{pop}}, \Sigma, \sigma)$.

- 1 # Initialization: $\theta \leftarrow \theta^*$; $S \leftarrow 0$; $(\varepsilon_{\text{iter}})_{\text{iter}>0}$; $z_{\text{pop}} \leftarrow \overline{\mathbf{z}}_{\text{pop}}$; $(\mathbf{z}_i)_i \leftarrow 0$;
- 2 **for** $\text{iter} = 1$ **to** maxIter **do**
- 3 | # Simulation: $(\mathbf{z}_{\text{pop}}, (\mathbf{z}_i)_i) \leftarrow \text{sampler}(\mathbf{z}_{\text{pop}}, (\mathbf{z}_i)_i)$;
- 4 | # Stochastic Approximation: $\mathbf{S}_1 \leftarrow \mathbf{S}_1 + \varepsilon_{\text{iter}} (\mathbf{z}_{\text{pop}} - \mathbf{S}_1)$;
- 5 | $S_2 \leftarrow S_2 + \varepsilon_{\text{iter}} \left(\frac{1}{n} \sum_i^t \mathbf{z}_i \mathbf{z}_i - S_2 \right)$;
- 6 | $S_3 \leftarrow S_3 + \varepsilon_{\text{iter}} \left(\frac{1}{k} \sum_{i=1}^n \sum_{j=1}^{k_i} (y_{i,j} - \gamma_i(t_{i,j}))^2 - S_3 \right)$;
- 7 | # Maximization: $\overline{\mathbf{z}}_{\text{pop}} \leftarrow \mathbf{S}_1$; $\Sigma \leftarrow \frac{nS_2 + m_\Sigma V}{n + m_\Sigma}$; $\sigma \leftarrow \sqrt{\frac{kS_3 + m_\sigma v^2}{k + m_\sigma}}$;
- 8 **end**

The maximization step is straightforward given the sufficient statistics of our exponential model: we update the parameters by taking a barycenter between the corresponding sufficient statistic and the prior (when it exists). In other words, by denoting iter the increment: $\overline{\mathbf{z}}_{\text{pop}}^{(\text{iter}+1)} = \mathbf{S}_1(\mathbf{y}, \mathbf{z}^{(\text{iter})})$,

$$\Sigma^{(\text{iter}+1)} = \frac{nS_2(\mathbf{y}, \mathbf{z}^{(\text{iter})}) + m_\Sigma V}{n + m_\Sigma} \quad \text{and} \quad \sigma^{2(\text{iter}+1)} = \frac{kS_3(\mathbf{y}, \mathbf{z}^{(\text{iter})}) + m_\sigma v^2}{k + m_\sigma}.$$

Finally, given an adapted sampler and the sequence $(\varepsilon_{\text{iter}})_{\text{iter}>0}$ defined by

$$\forall \text{iter} \geq 1, \quad \varepsilon_{\text{iter}} = \mathbb{1}_{\text{iter} \leq \text{Nburnin}} + (\text{iter} - \text{Nburnin})^{-0.65} \mathbb{1}_{\text{iter} > \text{Nburnin}}$$

our algorithm writes as above. Some experimental results are presented in section 5.

4. Example of the piecewise-logistic curve model

In this section, we explicit the generic model with logistic geodesics and $M =]0, 1[$. This is motivated by the study of the RECIST score monitoring, which leads to consider one-dimension manifold, with one rupture point. As this explicit model is designed in view of our target application, we first give a short description of RECIST score.

4.1. Motivation: Chemotherapy monitoring through RECIST score

Patients suffering from the metastatic kidney cancer, take a drug each day and regularly have to check their tumor evolution. Indeed, during the past few years, the way we treat renal metastatic cancer was profoundly changed: a new class of anti-angiogenic therapies targeting the tumor vessels instead of the tumor cells has emerged and drastically improved survival by a factor of three (Escudier et al., 2016). These new drugs, however, do not cure

the cancer, and only succeed in delaying the tumor growth, requiring the use of successive therapies which must be continued or interrupted at the appropriate moment according to the patient's response. So, the new medicine process has also created a new scientific challenge: how to choose the more efficient drug therapy.

The RECIST (Response Evaluation Criteria In Solid Tumors) score (Therasse et al., 2000) is a set of published rules that measures the tumoral growth. Physicians select at most five lesions, with a sufficient diameter, and sum the longest diameter for all target lesions. This leads them to determine if the tumours in cancer patients respond (completely or partially), stabilize or progress during treatment.

The response to a given treatment has generally two distinct phases: first, tumour's size reduces; then, the tumour grows again. So, we have to build a model which allow to us to catch this behaviours. Moreover, a practical question is to quantify the correlation between both phases and to determine as accurately as possible the individual rupture times t_R^i which are related to an escape of the patient's response to treatment.

4.2. The piecewise-logistic curve model

Our observations consist of patient's RECIST score over time, *i.e.* of sequences of bounded one-dimension measures. As explained above, we could make out two phases in the evolution of RECIST scores: a decreasing and a growing one. So, we set $m = 2$ and $d = 1$, which leads us to propose a way to build models for chemotherapy monitoring. This model has been designed after discussions with oncologists of the HEGP.

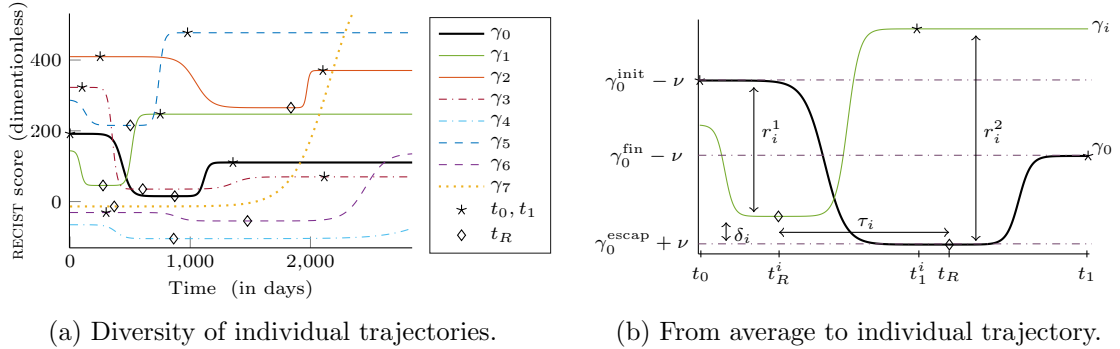
The group-average trajectory. Let M_0 be the open interval $]0, 1[$, equipped with the logistic metric. Given three real numbers γ_0^{init} , γ_0^{escap} and γ_0^{fin} we define two affine functions by setting down $\phi_0^1: x \mapsto (\gamma_0^{\text{init}} - \gamma_0^{\text{escap}})x + \gamma_0^{\text{escap}}$ and $\phi_0^2: x \mapsto (\gamma_0^{\text{fin}} - \gamma_0^{\text{escap}})x + \gamma_0^{\text{escap}}$. This allows us to map M_0 onto the intervals $] \gamma_0^{\text{escap}}, \gamma_0^{\text{init}} [$ and $] \gamma_0^{\text{escap}}, \gamma_0^{\text{fin}} [$ respectively: if $\bar{\gamma}_0$ refers to the sigmoid function, $\phi_0^1 \circ \bar{\gamma}_0$ will be a logistic curve, growing from γ_0^{escap} to γ_0^{init} . For compactness, we note t_R the single breaking-up time at the population level and t_R^i at the individual one. Moreover, due to our target application, we force the first logistic to be decreasing and the second one increasing (this condition may be easily relaxed for other framework).

Logistics are defined on open intervals, with asymptotic constraints. We want to formulate our constraints on some non-infinite time-points, as explained in paragraph 2.1. So, we set a positive threshold ν , close to zero, and demand the logistics γ_0^1 and γ_0^2 to be ν -near from their corresponding asymptotes. More precisely, we impose the trajectory γ_0 to be of the form $\gamma_0 = \gamma_0^1 \mathbb{1}_{]-\infty, t_R]} + \gamma_0^2 \mathbb{1}_{]t_R, +\infty[}$ where, for all time $t \in \mathbb{R}$,

$$\gamma_0^1(t) = \frac{\gamma_0^{\text{init}} + \gamma_0^{\text{escap}} e^{(at+b)}}{1 + e^{(at+b)}} \in] \gamma_0^{\text{escap}}, \gamma_0^{\text{init}} [, \quad \gamma_0^2(t) = \frac{\gamma_0^{\text{fin}} + \gamma_0^{\text{escap}} e^{-(ct+d)}}{1 + e^{-(ct+d)}} \in] \gamma_0^{\text{escap}}, \gamma_0^{\text{fin}} [$$

and a , b , c and d are some positive numbers given by the following constraints

$$\gamma_0^1(t_0) = \gamma_0^{\text{init}} - \nu , \quad \gamma_0^1(t_R) = \gamma_0^2(t_R) = \gamma_0^{\text{escap}} + \nu \quad \text{and} \quad \gamma_0^2(t_1) = \gamma_0^{\text{fin}} - \nu .$$



(a) Diversity of individual trajectories.

(b) From average to individual trajectory.

Fig. 1. Model description. Figure 1a represents a typical average trajectory and several individual ones, for different vectors z_i . The rupture times are represented by diamonds and the initial/final times by stars. Figure 1b illustrates the non-standard constraints for γ_0 and the transition from the average trajectory to an individual one: the trajectory γ_i is subject to a temporal and a spacial warp. In other "words", $\gamma_i = \phi_i^1 \circ \gamma_0^1 \circ \psi_i^1 \mathbb{1}_{]-\infty, t_R^i]} + \phi_i^2 \circ \gamma_0^2 \circ \psi_i^2 \mathbb{1}_{]t_R^i, +\infty[}$.

In order the previous logistics to be well-defined, we also have to enforce $\gamma_0^{\text{escap}} + 2\nu \leq \gamma_0^{\text{init}}$ and $\gamma_0^{\text{escap}} + 2\nu \leq \gamma_0^{\text{fin}}$. Thus, $p_{\text{pop}} = 5$ and

$$\mathcal{Z}_{\text{pop}} = \left\{ \left(\gamma_0^{\text{init}}, \gamma_0^{\text{escap}}, \gamma_0^{\text{fin}}, t_R, t_1 \right) \in \mathbb{R}^5 \mid \gamma_0^{\text{escap}} + 2\nu \leq \gamma_0^{\text{init}} \wedge \gamma_0^{\text{escap}} + 2\nu \leq \gamma_0^{\text{fin}} \right\}.$$

In our context, the initial time of the process is known: it is the beginning of the treatment. So, we assume that the average initial time t_0 is equal to zero.

Individual trajectories. For each subject $i \in \llbracket 1, n \rrbracket$, given $(\alpha_i^1, \alpha_i^2, \tau_i) \in \mathbb{R}_+^2 \times \mathbb{R}$, the time-warps (cf. 2.2) write $\psi_i^1(t) = \alpha_i^1(t - t_0 - \tau_i) + t_0$ and $\psi_i^2(t) = \alpha_i^2(t - t_R - \tau_i^2) + t_R$ where $\tau_i^2 = \tau_i^1 + \left(\frac{1 - \alpha_i^1}{\alpha_i^1} \right) (t_R - t_0)$.

In the same way as the time-warp, the diffeomorphisms ϕ_i^1 and ϕ_i^2 (cf. 2.2) are chosen to allow different amplitudes and rupture values: for each $i \in \llbracket 1, n \rrbracket$, given the two scaling factors r_i^1 and r_i^2 and the space-shift δ_i , we define $\phi_i^\ell(x) = r_i^\ell(x - \gamma_0(t_R)) + \gamma_0(t_R) + \delta_i$, $\ell \in \{1, 2\}$. Other choices are conceivable but in the context of our target applications, this one is the more appropriate: as we want to study the correlation between growth and decrease phase, none of the portions of the curves have to be favoured and affine functions allow us to put the same weight on the whole curves. Mathematically, any regular and injective function defined on $] \gamma_0^{\text{escap}}, \gamma_0^{\text{init}} [$ (respectively $] \gamma_0^{\text{escap}}, \gamma_0^{\text{fin}} [$) is suited.

To sum up, each individual trajectory γ_i depends on the characteristic curve γ_0 through fixed $\mathbf{z}_{\text{pop}} = (\gamma_0^{\text{init}}, \gamma_0^{\text{escap}}, \gamma_0^{\text{fin}}, t_R, t_1)$ and random $\mathbf{z}_i = (\alpha_i^1, \alpha_i^2, \tau_i, r_i^1, r_i^2, \delta_i)$ effects. This leads to a non-linear mixed-effects model. More precisely, we set for all individual $i \in \llbracket 1, n \rrbracket$ $\gamma_i^1 = \phi_i^1 \circ \gamma_0^1 \circ \psi_i^1$, $\gamma_i^2 = \phi_i^2 \circ \gamma_0^2 \circ \psi_i^2$ and $t_R^i = t_0 + \tau_i^1 + \frac{t_R - t_0}{\alpha_i^1}$, which leads us to write for

all "time" $j \in \llbracket 1, k_i \rrbracket$,

$$y_{i,j} = \left[r_i^1 (\gamma_i^1(t_{i,j}) - \gamma_0(t_R)) + \gamma_0(t_R) + \delta_i \right] \mathbb{1}_{]-\infty, t_R]}(t_{i,j}) \\ + \left[r_i^2 (\gamma_i^2(t_{i,j}) - \gamma_0(t_R)) + \gamma_0(t_R) + \delta_i \right] \mathbb{1}_{]t_R, +\infty[}(t_{i,j}) + \varepsilon_{i,j}.$$

Figure 1 provides an illustration of the model. On each subfigure, the bold black curve represents the average trajectory γ_0 and the colour curves several individual trajectories.

We proceed as in the paragraph 2.3 and set $\alpha_i^\ell = e^{\xi_i^\ell}$ for $\ell \in \{1, 2\}$. Likewise, the scaling parameters r_i^ℓ have to be positive and equal to one on average while the space shifts δ_i can be of any signs and must be zero on average. So, we set $r_i^\ell = e^{\rho_i^\ell}$ for $\ell \in \{1, 2\}$ leading to $\mathbf{z}_i = (\xi_i^1, \xi_i^2, \tau_i, \rho_i^1, \rho_i^2, \delta_i)$. In particular, $p_{\text{ind}} = 6$ and we assume that it exists $\Sigma \in \mathcal{S}_{p_{\text{ind}}}^+(\mathbb{R})$ such that $\mathbf{z}_i \sim \mathcal{N}(0, \Sigma)$ for all $i \in \llbracket 1, n \rrbracket$. This assumption is really important: usually, the random effects are studied independently. Here, we are interested in correlations between the two phases of patient's response to treatment.

4.3. Theoretical analysis of the piecewise-logistic curve model

Theorem 1 applies as is and the MAP estimator for the piecewise-logistic is well-defined. Moreover, at the risk of assuming some restriction concerning the distribution of our observations, the piecewise-logistic model is consistent.

More precisely, let Θ^{PL} be the space of the admissible parameters for the piecewise-logistic model, *i.e.* $\Theta^{\text{PL}} = \{(\overline{\gamma_0^{\text{init}}}, \overline{\gamma_0^{\text{escap}}}, \overline{\gamma_0^{\text{fin}}}, \overline{t_R}, \overline{t_1}, \Sigma, \sigma) \in \mathbb{R}^{p_{\text{pop}}} \times \mathcal{S}_{p_{\text{ind}}}^+(\mathbb{R}) \times \mathbb{R}^+\}$. We define $\Theta^{\omega, \text{PL}} = \{\theta \in \Theta^{\text{PL}} \mid \|(\overline{\gamma_0^{\text{init}}}, \overline{\gamma_0^{\text{escap}}}, \overline{\gamma_0^{\text{fin}}}, \overline{t_R}, \overline{t_1})\| \leq \omega\}$ the space of the parameters associated to bounded on average fixed effects, for the piecewise-logistic model and, as in the generic framework, the space $\Theta_*^{\omega, \text{PL}} = \{\theta \in \Theta^{\omega, \text{PL}} \mid \mathbb{E}_{P(\mathbf{d}\mathbf{y}^\ell)} [\log q(\mathbf{y}^\ell | \theta)] = \mathbb{E}^*(\omega)\}$ where $\mathbb{E}^*(\omega) = \sup_{\theta \in \Theta^{\omega, \text{PL}}} \mathbb{E}_{P(\mathbf{d}\mathbf{y}^\ell)} [\log q(\mathbf{y}^\ell | \theta)]$.

THEOREM 3 (CONSISTENCY OF THE MAP, PIECEWISE-LOGISTIC MODEL). *Assume that*

- (H1) *The number of observations is bigger than the one of latent variables: It exists $\ell \in \llbracket 1, n \rrbracket$ such that $p^\ell < k^\ell$ where $k^\ell = \sum_{i=1}^\ell k_i$ and $p^\ell = p_{\text{pop}} + \ell p_{\text{ind}}$;*
- (H2) *The density $P(\mathbf{d}\mathbf{y}^\ell)$ is continuous with polynomial tail decay of degree bigger $p^\ell + 1$ apart from a subset compact K of \mathbb{R}^{k^ℓ} ;*
- (H3) *The observation noise is negligible regarding the individual trajectories: for all subjects $i \in \llbracket 1, n \rrbracket$, $\|\varepsilon_i\|_2 \leq \|\vec{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)\|_2$;*

Then, the piecewise-logistic model satisfy the hypothesis of the theorem 2. In particular, if $(\hat{\theta}_m)_{m \in \mathbb{N}}$ denote any MAP estimator, $\Theta_^{\omega, \text{PL}} \neq \emptyset$ and for any $\varepsilon \in \mathbb{R}_+^*$,*

$$\lim_{m \rightarrow \infty} \mathbb{P} \left[\delta(\hat{\theta}_m, \Theta_*^{\omega, \text{PL}}) \geq \varepsilon \right] = 0$$

where δ in any metric compatible with the topology on $\Theta^{\omega, \text{PL}}$.

PROOF. We demonstrate that, for all $i \in \llbracket 1, n \rrbracket$, the variables $(t_R, t_1, \xi_i^1, \xi_i^2, \tau_i)$ are critical, that $(\gamma_0^{\text{init}}, \gamma_0^{\text{escap}}, \gamma_0^{\text{fin}}, \rho_i^1, \rho_i^2, \delta_i)$ are regular and that (ρ_i^1, ρ_i^2) are regular in the neighbourhood of $+\infty$ and critical near $-\infty$. See the remark after the theorem 2.

(H 4) Let $i \in \llbracket 1, n \rrbracket$. By definition of $\vec{\gamma}_i$,

$$\|\vec{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)\|_\infty = \max \left\{ \begin{array}{l} |\gamma_0^{\text{escap}} + \nu + \delta_i| \\ |\gamma_0^{\text{escap}} + \nu + \delta_i + e^{\rho_i^1}(\gamma_0^{\text{init}} - \gamma_0^{\text{escap}} - 2\nu)| \\ |\gamma_0^{\text{escap}} + \nu + \delta_i + e^{\rho_i^2}(\gamma_0^{\text{fin}} - \gamma_0^{\text{escap}} - 2\nu)| \end{array} \right\}.$$

And we can check that for $\gamma_0^{\text{init}}, \gamma_0^{\text{escap}}, \gamma_0^{\text{fin}}, \rho_i^1, \rho_i^2$ and δ_i and that for ρ_i^1 and ρ_i^2 as soon as $|\rho_i^1|, |\rho_i^2| \geq 1$ there exists two functions a_i and b_i as in [Theorem 2(H 4)].

(H 5) Let $i \in \llbracket 1, n \rrbracket$ and $j \in \llbracket 1, k_i \rrbracket$. By definition of $\vec{\gamma}_i$,

$$\lim_{t_R \rightarrow +\infty} \vec{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)_j = \left[e^{\rho_i^1}(\gamma_0^{\text{init}} - \gamma_0^{\text{escap}} - 2\nu) + \gamma_0^{\text{escap}} + \nu + \delta_i \right] \mathbb{1}_{[t_0, +\infty[}(t_{i,j})$$

where $\vec{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)_j$ denotes the j^{th} coordinate of the vector $\vec{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i) \in \mathbb{R}^{k_i}$. However, by construction, $\gamma_0^{\text{init}} - \gamma_0^{\text{escap}}$ and γ_0^{escap} follow a normal distribution so

$$\mathcal{L}_{k_i} \left(\left\{ y_{i,j} = e^{\rho_i^1}(\gamma_0^{\text{init}} - \gamma_0^{\text{escap}} - 2\nu) + \gamma_0^{\text{escap}} + \nu + \delta_i \right\} \right) = 0.$$

Likewise for $t_R \rightarrow -\infty$. The same argument holds when t_1, ξ_i^1, ξ_i^2 or τ_i become infinite and when ρ_i^1 or ρ_i^2 go to $-\infty$.

5. Experimental results

Experimentations are performed for the piecewise-logistic curve model introduced above. In order to validate our model and numerical scheme, we first run experiments on synthetic data. We then test our estimation algorithm on real data from the HEGP.

5.1. Synthetic data

We generate four types of dataset, to put our algorithm in different situations. More precisely, we want to quantify its sensitivity to initialisation, sample size and noise.

Influence of the initialization. The estimation is performed through the SAEM algorithm (Algorithm 1). This iterative algorithm is proven to converge toward a critical point of the observed likelihood. Therefore, as our model does not imply a convex likelihood, one may end up with a local *maximum* depending on the initialization point and the dynamic of our iterations. This choice of initialization appears crucial. In particular the choice of the initial mean population parameters $\mathbf{z}_{\text{pop}}^{\text{init}}$ as illustrated below.

If our model were linear, the representative curve γ_0 would exactly be the one induced by the mean of the individual trajectories γ_i , *i.e.* the one where $\mathbf{z}_{\text{pop}} = \text{mean}_{i \in \llbracket 1, n \rrbracket} \mathbf{z}_i$. Following this idea, we set in our experiments

$$\begin{aligned} \overline{\gamma_0^{\text{init}}} &= \text{mean}_{i \in \llbracket 1, n \rrbracket} y_{i,1} \quad ; \quad \overline{\gamma_0^{\text{escap}}} &= \text{mean}_{i \in \llbracket 1, n \rrbracket} \min_{j \in \llbracket 1, k_i \rrbracket} y_{i,j} \quad ; \quad \overline{\gamma_0^{\text{fin}}} &= \text{mean}_{i \in \llbracket 1, n \rrbracket} y_{i,k_i} \quad ; \\ \overline{t_R^{\text{init}}} &= \frac{1}{2} \text{mean}_{i \in \llbracket 1, n \rrbracket} t_{k_i} \quad \text{and} \quad \overline{t_1^{\text{init}}} &= \text{mean}_{i \in \llbracket 1, n \rrbracket} t_{k_i} . \end{aligned}$$

Note that the choice of the initial covariance matrix Σ^{init} and the residual noise σ^{init} does not seem to be very influential. We just demand Σ^{init} to be definite positive.

Influence of the proposal variances. The SAEM algorithm is very sensitive to the choice of the proposal variances in the sampling step. Thus, we have to carefully tune these variances in order the mean acceptance ratio to stay around the optimal rate – 24% as we are using a symmetric random walk sampler. To decrease the influence of a bad calibration, we adapt the proposal variances over the iterations in the way of Roberts and Rosenthal (2007, 2009): every m^{th} batch of 50 iterations, we increase or decrease the logarithm of the proposal variances by $\delta(m) = \min\left(0.001, \frac{1}{\sqrt{m}}\right)$ depending on whether the mean associated variable acceptance rate is bigger or smaller than the optimal one. Note that we have also tried to adapt the proposal variances as in Atchadé (2006) but the results we obtained were not satisfactory. Actually, it appears numerically that if we want the adaptive procedure to increase the efficiency of our algorithm, we must modify the proposal variance neither too often nor with a too big amplitude of change.

Construction of the datasets. For each type of dataset, given the corresponding ground truth parameters θ^{true} , we generate three datasets of respective size 50, 100 and 250. Last, to put our algorithm on a more realistic situation, the synthetic individual times are non-periodically spaced and individual sizes vary between 12 and 18.

The first type – A – is said quasilinear in the sense that, for these datasets, the representative trajectory γ_0 is "close" to the mean trajectory described above. Hence, we put our algorithm in a favourable situation where the optimal representative trajectory is close to the initial one. The second type – A* – is a noisy version of A.

On the contrary, the third type – B – is built in order to be "truly non-linear": the representative trajectory γ_0 is "far" from the curve built by $\overline{\mathbf{z}_{\text{pop}}^{\text{init}}}$. Likewise, the fourth type – B* – is a noisy version of B. To measure this degree of non-linearity, we introduce the ratio $\Delta_{\mathcal{L}}(\overline{\mathbf{z}_{\text{pop}}})$ which is the relative error of $\overline{\mathbf{z}_{\text{pop}}^{\text{init}}}$: $\Delta_{\mathcal{L}}(\overline{\mathbf{z}_{\text{pop}}}) = \frac{\|\overline{\mathbf{z}_{\text{pop}}^{\text{init}}} - \overline{\mathbf{z}_{\text{pop}}^{\text{true}}}\|}{\|\overline{\mathbf{z}_{\text{pop}}^{\text{init}}}\|}$. Table 1 compiles this ratio for every dataset, and for every parameter in $\overline{\mathbf{z}_{\text{pop}}}$.

Estimation of the fixed effects. Table 2 displays the relative errors for the estimated population parameters. In most case, these errors decrease with the size of the dataset. More specific to our model, we observe that these errors are correlated to the subjective linearity

Table 1. Degree of non-linearity: Relative errors (expressed as a percentage) for the initial population parameters $\overline{z_{\text{pop}}^{\text{init}}}$ and residual noise σ^{true} used to generate the dataset, according to the type of dataset and the sample size n .

	n	$\Delta_{\mathcal{L}}(\overline{\gamma_0^{\text{init}}})$	$\Delta_{\mathcal{L}}(\overline{\gamma_0^{\text{escap}}})$	$\Delta_{\mathcal{L}}(\overline{\gamma_0^{\text{fin}}})$	$\Delta_{\mathcal{L}}(\overline{t_R})$	$\Delta_{\mathcal{L}}(\overline{t_1})$	σ
A	50	7.08	17.01	5.94	1.97	1.98	1.99
	100	2.93	22.33	3.66	2.40	2.42	1.99
	250	2.16	24.06	2.12	3.52	3.54	1.99
A*	50	5.63	283.14	1.51	1.03	1.01	20.09
	100	3.38	259.25	0.07	4.75	4.76	20.09
	250	3.67	269.42	0.41	3.94	3.95	20.09
B	50	80.47	2.77	39.78	35.04	35.09	0.29
	100	88.17	4.39	51.83	36.14	36.19	0.29
	250	83.52	12.91	47.90	33.23	33.27	0.29
B*	50	59.25	201.98	33.46	28.85	28.89	20.86
	100	74.94	213.96	43.50	30.74	30.78	20.86
	250	79.14	229.40	47.30	34.39	34.44	20.86

of the model. With the exception of $\overline{\gamma_0^{\text{escap}}}$, the errors for estimating population parameters grow linearly with the non-linearity of the model. We suppose that the difference of scale between $\overline{\gamma_0^{\text{escap}}}$ and the others can, at least partly, explain this phenomena: $\overline{\gamma_0^{\text{escap}}}$ is about a few tens of units ; $\overline{\gamma_0^{\text{init}}}$, $\overline{\gamma_0^{\text{fin}}}$ and $\overline{t_R}$ about a few hundreds and $\overline{t_1}$ about one thousand. Thus, a same absolute error will lead to markedly different relative error.

The degree of non-linearity in the dataset seems to play a significant role in the estimation of the population parameters. To be certain that the poor estimation of $\overline{z_{\text{pop}}}$ when the ratio $\Delta_{\mathcal{L}}(\overline{z_{\text{pop}}})$ is too big is due to the non-linearity of the dataset and not to a bad initialization, we have also performed estimations by assigning $\theta^{\text{init}} = \theta^{\text{true}}$. The results were better but not so significantly. Despite this limitation, the algorithm we propose is not noise-sensitive: errors for non-noisy and noisy version of a same type of dataset are notably the same. Moreover, the population parameters are well-learned in quasilinear cases and in particular in large dataset ($n = 250$) and the mean rupture time $\overline{t_R}$ seems to be well-estimated, no matter the subjective linearity of the dataset.

Estimation of the inter-individual variability. In the target of our application, the covariance matrix Σ gives a lot of information on the health status of a patient: pace and amplitude of tumour progression, individual rupture times, *etc.* Therefore, we have to pay special attention to the estimation of Σ .

Much as the representative trajectory is not always good-estimated, our algorithm always allows a well-understanding of the inter-individual variability. We present at Table 3 the Kullback-Leibler divergence from Σ^{estim} to Σ^{true} , the relative error of the individual rupture times and the estimated residual noise. As for the estimation of the population parameters, errors decrease with the sample size n and are not significantly different between noisy and non-noisy versions of a same type of dataset. Moreover, in that case, the errors seem to not rely on the subjective linearity of the dataset.

Table 2. *Fixed effects:* Mean (standard deviation) relative errors (expressed as a percentage) over 50 runs, for the estimated parameters $\bar{z}_{\text{pop}}^{\text{estim}}$, according to the dataset and the sample size n .

	n	$\bar{\gamma}_0^{\text{init}}$	$\bar{\gamma}_0^{\text{escap}}$	$\bar{\gamma}_0^{\text{fin}}$	\bar{t}_R	\bar{t}_1
A	50	6.03 (0.32)	10.25 (0.50)	3.69 (0.25)	1.95 (0.13)	2.43 (0.18)
	100	2.19 (0.17)	3.28 (0.22)	2.07 (0.18)	1.69 (0.11)	1.86 (0.17)
	250	1.30 (0.10)	1.96 (0.13)	1.53 (0.08)	0.78 (0.06)	1.67 (0.09)
A*	50	3.74 (0.26)	25.73 (1.64)	6.84 (0.40)	3.32 (0.26)	3.73 (0.26)
	100	2.35 (0.15)	12.20 (0.64)	1.35 (0.09)	2.98 (0.22)	2.29 (0.18)
	250	1.70 (0.12)	3.94 (0.29)	1.33 (0.09)	1.36 (0.10)	1.51 (0.10)
B	50	71.13 (1.33)	100.24 (8.09)	90.73 (2.54)	7.78 (0.56)	46.39 (1.32)
	100	58.73 (0.98)	58.88 (3.00)	84.99 (1.42)	8.13 (0.57)	42.06 (1.04)
	250	67.49 (0.47)	23.12 (1.54)	57.82 (0.74)	6.01 (0.33)	38.09 (0.36)
B*	50	41.61 (1.26)	29.86 (2.53)	46.38 (1.60)	9.04 (0.58)	29.90 (0.58)
	100	60.39 (0.81)	28.43 (2.06)	58.35 (1.07)	8.11 (0.54)	29.75 (0.50)
	250	55.89 (0.74)	15.56 (0.98)	59.90 (0.58)	3.26 (0.25)	39.28 (0.43)

Reconstruction of the individual trajectories. Figure 2 illustrates the well-understanding of the variance within the population, including for the non-linear dataset. Determining accurate individual rupture time t_R^i is all the most important as, in the aim of chemotherapy monitoring, these times are related to an escape of the patient’s response to treatment.

An important point was to allow a lot of different individual behaviours. In our synthetic example, Figure 1a illustrates this variability. From a single average trajectory (γ_0 in bold plain line), we can generate individuals who are cured at the end (dot-dashed lines: γ_3 and γ_4), some whose response to the treatment is bad (dashed lines: γ_5 and γ_6), some who only escape (no positive response to the treatments – dotted lines: γ_7). Likewise, we can generate ”patients” with only positive responses or no response at all. The case of individual 4 is interesting in practice: the tumour still grows but so slowly that the growth is negligible, at least in the short-run.

Figure 3 illustrates the qualitative performance of the estimation. We are notably able to understand various behaviours and fit subjects which are far from the average path. Moreover, the noise seems to not reduce the quality of the estimation. We represent only five individuals but 250 subjects have been used to perform the estimation.

5.2. Metastatic kidney cancer monitoring

The algorithm is now run on RECIST score of real patients suffering from kidney cancer. The estimation is performed over a drove of 176 patients of the HEGP. There is an average of 7 visits per subjects (min: 3, max: 22), with an average duration of 90 days between consecutive visits. We present here a run with a low residual standard variation in respect to the amplitude of the trajectories and complexity of the dataset: $\sigma = 9.10$.

Figure 4a illustrates the qualitative performance of the model on ten patients. Although we cannot explain all the paths of progression, the algorithm succeeds in fitting various

Table 3. *Variability and residual noise:* Mean (standard deviation) of KullbackLeibler divergences from Σ^{estim} to Σ^{true} , mean (standard deviation) relative errors (expressed as a percentage) for the individual rupture times $t_R^{i, \text{estim}}$ and mean estimated residual noise σ^{estim} according to the dataset and the sample size n . All over 50 runs.

	n	Type A			Type B		
		Σ	t_R^i	σ	Σ	t_R^i	σ
X	50	15.54 (5.17)	0.49 (0.04)	2.03	16.53 (7.72)	5.89 (3.45)	3.07
	100	8.45 (2.26)	0.63 (0.06)	1.97	13.59 (5.42)	4.44 (1.93)	2.14
	250	9.29 (3.13)	0.57 (0.60)	2.06	22.24 (9.77)	4.96 (1.93)	2.49
X*	50	16.52 (19.45)	4.66 (0.45)	19.81	27.62 (17.71)	14.32 (4.06)	19.93
	100	12.86 (4.26)	3.85 (0.32)	19.03	23.98 (18.07)	13.97 (3.71)	20.56
	250	6.72 (2.44)	3.98 (0.32)	20.07	17.70 (5.35)	11.57 (2.42)	21.38

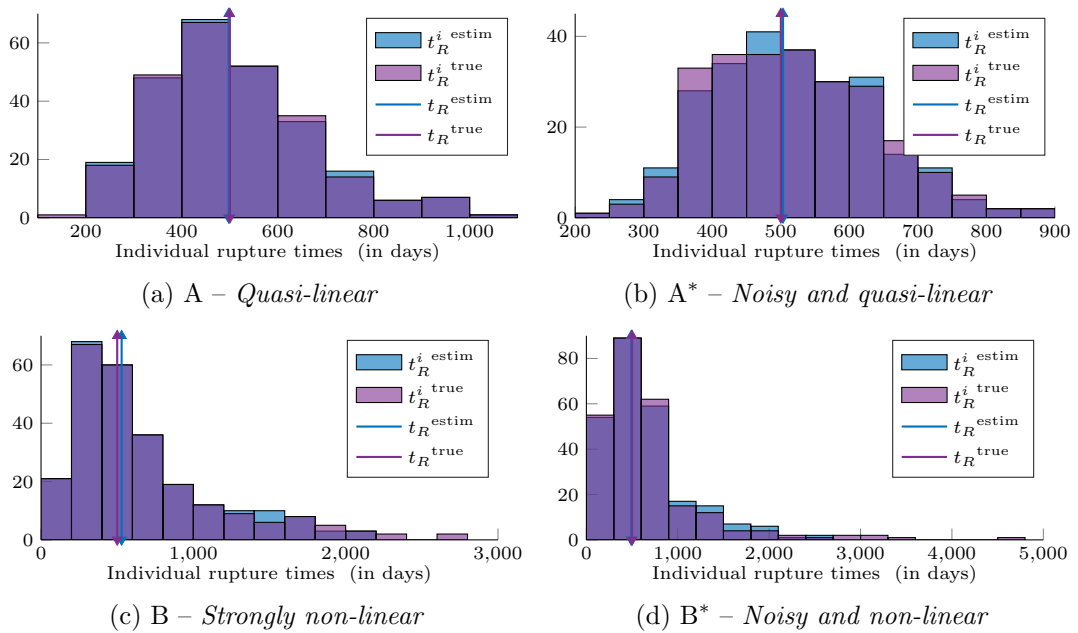


Fig. 2. *Distribution of the individual rupture times.* Each sub-figure compares the distribution of the (mean of the) estimated individual rupture times $t_R^{i, \text{estim}}$ and the distribution of the true individual rupture times $t_R^{i, \text{true}}$. In bold line, the estimated average rupture time t_R^{estim} and the true average rupture time t_R^{true} are relatively close to each other. $n = 250$.

types of curves: from the curve γ_6 which is flat to the curve γ_3 which is spiky. From Figure 4b, it seems that the rupture times occur early in the progression in average.

In Figure 5, we plot the individual estimates of the random effects (obtained from the last iteration) in comparison to the individual rupture times. Even though the parameters which lead the space warp, *i.e.* ρ_i^1 , ρ_i^2 and δ_i are correlated, the correlation with the rupture time is not clear. In other words, the volume of the tumours seems to not be relevant to

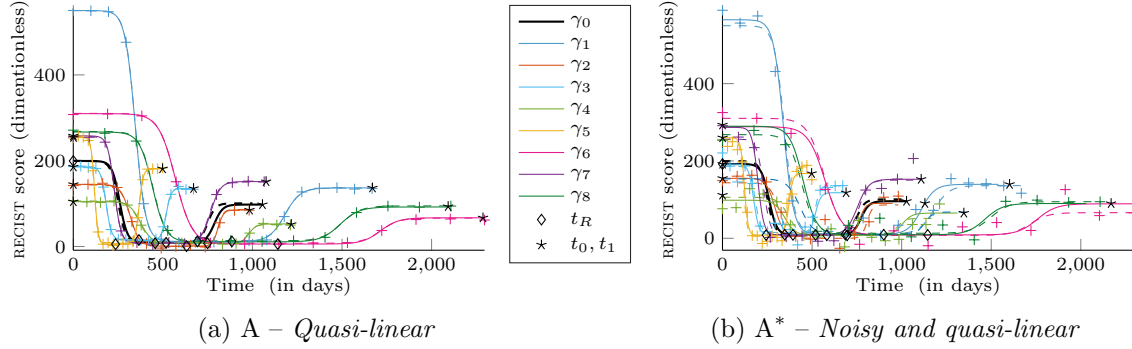


Fig. 3. Qualitative performance of the estimation and robustness to noise of the MAP estimator. On both figures, the estimated trajectories are in plain lines and the target curves in dashed lines. The (noisy) observations are represented by crosses. The representative path is in bold black line, the individuals in colour. $n = 250$.

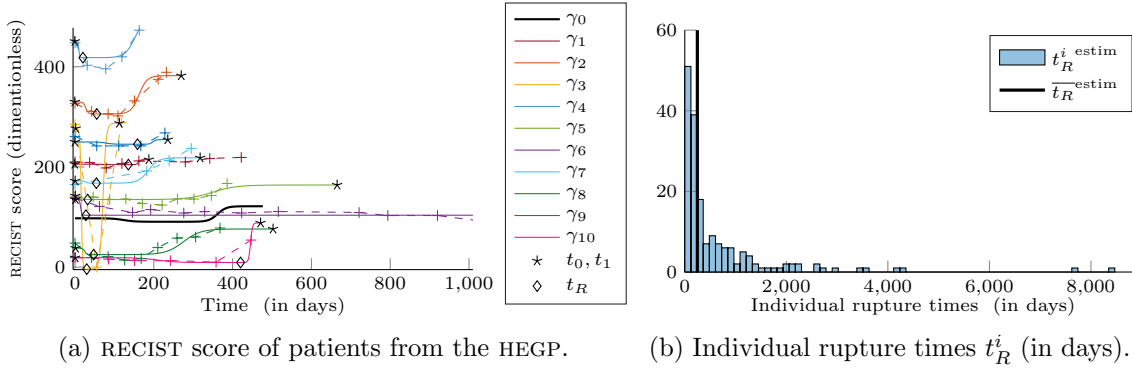


Fig. 4. RECIST score. We keep conventions of the previous figures. We represent at Fig. 4a only 10 patients among the 176. Fig. 4b is the histogram of the rupture times t_R^i for this run. In black bold line, the estimated average rupture time \bar{t}_R^{estim} is a good estimate of the average of the individual rupture times although there exists a large range of escape.

evaluate the escapement of a patient. On the contrary, which is logical, the time warp strongly impacts the rupture time.

6. Discussion and perspective

We have proposed a coherent statistical framework for the spatio-temporal analysis of piecewise-geodesic manifold-valued measurements. This model allows each individual to have his own intrinsic geometry and his own time-parametrization. The model is built in a hierarchical way as a non-linear mixed-effects model whose fixed effects define a representative trajectory of the global evolution in the space of measurements and random effects

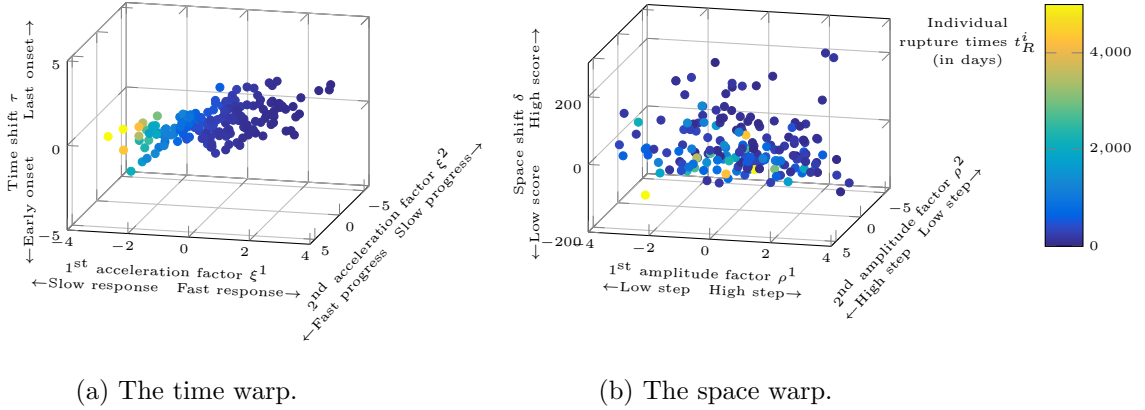


Fig. 5. Individual random effects. Fig. 5a: log-acceleration factors ξ_i^1 and ξ_i^2 against times shifts τ_i . Fig. 5b: log-amplitude factors ρ_i^1 and ρ_i^2 against space shifts δ_i . In both figure, the colour corresponds to the individual rupture time t_R^i . These estimates hold for the same run as Fig. 4.

account for the spatio-temporal variability of the trajectories at the individual level.

Estimation was formulated as a well-defined MAP problem and numerically performed through the MCMC-SAEM algorithm. Experimentations have highlighted the robustness of our model to noise and its performance in catching individual behaviours. We believe that the complexity of our model ensures its practical identifiability, even if it is not structurally identifiable (Lavielle and Aarons, 2016). Besides, as the posterior-likelihood is not convex, the MAP could be difficult to determine numerically. Future work focuses on exploring some possible improvement of the numerical scheme.

Our model can be applied to a wide variety of situations and datasets. In particular, we can address medical follow-up such as neurodegenerative diseases or chemotherapy monitoring. The example of chemotherapy monitoring is especially interesting in a modelling perspective as the patients are treated and tumours may respond, stabilize or progress during the treatment, with different conducts for each phase. At the age of personalized medicine, to give physicians decision support systems is really important. Therefore learning correlations between phases is crucial. This has been taken into account in our experimentations. More generally, the inter-individual variability allows us to personalize the model to new patient and thus perform predictive medicine.

A. Proof of the consistency theorem for bounded population variable

The proof of the theorem relies on several lemmas. Lemma 4 is the heart of the proof: we control here the behaviour of the log-likelihood at the boundary points of the parameters space Θ_*^ω and prove that this set is non-empty. It is based on Lemma 3 which states the integrability of the supremum over the parameter space of the positive part of the log-likelihood. Lemma 2 is derived from Allasonnière et al. (2007). We transpose the proof

of the cited article here (with few more details) as this lemma is critical in the proof of Lemma 3 and not such classical.

In the following, we freely (and without reminder) use the notations introduced in the section 3.2. Moreover, (H1), (H2), (H3), (H4) and (H5) refer to the hypothesis of the consistency theorem (Theorem 2, page 10).

A.1. Lemmas

We first recall that the minimal number of balls of radius $r \in \mathbb{R}_+^*$ required to cover a compact set $K \in \mathbb{R}^p$ is upper bounded by $\left(\frac{\text{Diam}(K)}{r}\right)^p$.

LEMMA 2 (PRELIMINARY OF MEASURE THEORY). *Let $p < q$ be two integers. Then, for any differentiable map $f: \mathbb{R}^p \rightarrow \mathbb{R}^q$ and any compact subset K of \mathbb{R}^p , it exists a constant λ which depends only on p and q such that*

$$\int_{\mathbb{R}^q} \log^+ \frac{1}{d(\mathbf{y}, f(K))} d\mathbf{y} < \lambda \left(\sup_K \|\mathcal{D}f\| + 2 \right)^q \text{Diam}(K)^p$$

where d is the euclidean distance on \mathbb{R}^q , $\mathcal{D}f$ the differential of f and $\text{Diam}(K)$ the diameter of the compact K . Especially, $\int_{\mathbb{R}^q} \log^+ \frac{1}{d(\mathbf{y}, f(K))} d\mathbf{y} < +\infty$.

PROOF. For all $\rho, \rho_1, \rho_2 \in \mathbb{R}_+^*$, $\rho_1 < \rho_2$, let $M_{\rho_1, \rho_2} = \{\mathbf{y} \in \mathbb{R}^q \mid \rho_1 \leq d(\mathbf{y}, f(K)) \leq \rho_2\}$ and $M_\rho = M_{0, \rho}$. For all $\rho \in \mathbb{R}_+^*$, due to the compactness of K , there exists a finite set $\Lambda_\rho \subset K$ such that $K \subset \bigcup_{\mathbf{x} \in \Lambda_\rho} \mathcal{B}(\mathbf{x}, \rho)$ and $|\Lambda_\rho| \leq \left(\frac{\text{Diam}(K)}{\rho}\right)^p$. Let $\tau = \sup_K \|\mathcal{D}f\|$. According to the mean value theorem, $M_{0, \rho} \subset \mathcal{B}(f(\mathbf{x}), (\tau + 2)\rho)$ and

$$\mathcal{L}_q(M_\rho) \leq \sum_{\mathbf{x} \in \Lambda_\rho} \mathcal{L}_q(\mathcal{B}(f(\mathbf{x}), (\tau + 2)\rho)) \leq \frac{\sqrt{\pi}^p (\tau + 2)^p}{\Gamma\left(\frac{p}{2} + 1\right)} \times (\text{Diam}(K))^p \times \rho^{q-p}.$$

Let $s \in]0, 1[$. Then, from the Abel transformation,

$$\begin{aligned} \int_{\mathbb{R}^q} \log^+ \frac{1}{d(\mathbf{y}, f(K))} d\mathbf{y} &= \sum_{n=0}^{+\infty} \int_{M_{s^{n+1}, s^n}} \log^+ \frac{1}{d(\mathbf{y}, f(K))} d\mathbf{y} \\ &\leq \sum_{n=0}^{+\infty} \log \frac{1}{s^{n+1}} [\mathcal{L}_q(M_{s^n}) - \mathcal{L}_q(M_{s^{n+1}})] \leq -\log(s) \sum_{n=0}^{+\infty} \mathcal{L}_q(M_{s^n}). \end{aligned}$$

Hence the result as $s \in]0, 1[$.

LEMMA 3. *Assume (H1), (H2), (H4) and*

(H'5) *Bounded regular variables implies bounded trajectories: For all individuals $i \in \llbracket 1, n \rrbracket$, if there exists $b \in \mathbb{R}$ such that $\|(\mathbf{z}_{pop}^{reg}, \mathbf{z}_i^{reg})\|_\infty < b$ then it exists $R \in \mathbb{R}_+^*$ such that $\|\vec{\gamma}_i(\mathbf{z}_{pop}, \mathbf{z}_i)\|_\infty < R$.*

Then, for any such ℓ ,

$$\mathbb{E}_{P(d\mathbf{y}^\ell)} \left[\sup_{\theta \in \Theta} \left(\sum_{i=1}^{\ell} \log q(\mathbf{y}_i | \theta) \right)^+ \right] < +\infty.$$

PROOF. Let $i \in \llbracket 1, \ell \rrbracket$, $\Gamma_i = \mathcal{I}m(\tilde{\gamma}_i)$ and $\Gamma^\ell = \prod_{i=1}^{\ell} \Gamma_i$. For all $\theta \in \Theta^\omega$,

$$\begin{aligned} q(\mathbf{y}_i | \theta) &= \frac{1}{(\sigma\sqrt{2\pi})^{k_i}} \int_{\bar{\mathcal{Z}}_i} \exp \left(-\frac{1}{2\sigma^2} \|\mathbf{y}_i - \tilde{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)\|_2^2 \right) q(\mathbf{z}_{\text{pop}}, \mathbf{z}_i | \theta) d(\mathbf{z}_{\text{pop}}, \mathbf{z}_i) \\ &\leq \frac{1}{(\sigma\sqrt{2\pi})^{k_i}} \exp \left(-\frac{1}{2\sigma^2} d(\mathbf{y}_i, \Gamma_i)^2 \right). \end{aligned}$$

where d denotes the Euclidean distance on \mathbb{R}^{k_i} . Thus for all $\theta \in \Theta^\omega$,

$$\sum_{i=1}^{\ell} \log q(\mathbf{y}_i | \theta) \leq -\frac{k^\ell}{2} \log(2\pi\sigma^2) - \frac{1}{2\sigma^2} d(\mathbf{y}^\ell, \Gamma^\ell)^2$$

where d denotes now the Euclidean distance on \mathbb{R}^{k^ℓ} , $k^\ell = \sum_{i=1}^{\ell} k_i$. As the right hand side is maximized for $\sigma^2 = \frac{1}{k^\ell} d(\mathbf{y}^\ell, \Gamma^\ell)^2$, it exists a constant $\lambda \in \mathbb{R}_+^*$ such that

$$\sup_{\theta \in \Theta} \left(\sum_{i=1}^{\ell} \log q(\mathbf{y}_i | \theta) \right)^+ \leq \lambda + k^\ell \log^+ \frac{1}{d(\mathbf{y}^\ell, \Gamma^\ell)}.$$

(a) Assume there exists $i_0 \in \llbracket 1, n \rrbracket$ such that that for all $b \in \mathbb{R}$, $\|(\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_{i_0}^{\text{reg}})\|_\infty \geq b$.

For all $r_1, r_2 \in \mathbb{R}$ we define a compact subset Γ_{r_1, r_2}^ℓ of Γ^ℓ by setting

$$\begin{aligned} \bar{A}(r_1, r_2) &= \{\mathbf{z}^\ell \in \mathbb{R}^{p^\ell} \mid r_1 \leq \|(\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_{i \in \llbracket 1, \ell \rrbracket}\|_\infty, \|(\mathbf{z}_{\text{pop}}^{\text{crit}}, \mathbf{z}_i^{\text{crit}})_{i \in \llbracket 1, \ell \rrbracket}\|_\infty \leq r_2\} \\ \text{and } \Gamma_{r_1, r_2}^\ell &= \{\tilde{\gamma}^\ell(\mathbf{z}^\ell) \mid \mathbf{z}^\ell \in \bar{A}(r_1, r_2)\}. \end{aligned}$$

Especially, $\lim_{r_2 \rightarrow \infty} \Gamma_{r_1, r_2}^\ell = \Gamma^\ell$. Moreover, $\tilde{\gamma}^\ell$ is differentiable *a.e.*, at least one-side differentiable everywhere and it exists $\tau \in \mathbb{R}$ such that $\sup_{\mathbb{R}^{p^\ell}} \|\mathcal{D}_{\mathbf{z}^\ell} \tilde{\gamma}^\ell\| < \tau$. So, according to the lemma 2, for all $r_1, r_2 \in \mathbb{R}$, it exists $\mu \in \mathbb{R}$ which depends only on p^ℓ and k^ℓ such that $\mathbb{E} \left[\log^+ \frac{1}{d(\mathbf{y}^\ell, \Gamma_{r_1, r_2}^\ell)} \right] < \mu (\tau + 2)^{k^\ell} r_2^{p^\ell}$. As in the proof of the lemma 2, we set $\bar{\Gamma}_{r_1, r_2}^\ell = \{\mathbf{y}^\ell \in \mathbb{R}^{k^\ell} \mid d(\mathbf{y}^\ell, \Gamma_{r_1, r_2}^\ell) \leq 1\}$ and we have for all $r_1, r_2 \in \mathbb{R}$,

$$\int_{\mathbb{R}^{k^\ell}} \log^+ \frac{1}{d(\mathbf{y}^\ell, \Gamma_{r_1, r_2}^\ell)} P(d\mathbf{y}^\ell) = \int_{\bar{\Gamma}_{r_1, r_2}^\ell} \log^+ \frac{1}{d(\mathbf{y}^\ell, \Gamma_{r_1, r_2}^\ell)} P(d\mathbf{y}^\ell) \leq \bar{\mu} r_2^{p^\ell} \sup_{\bar{\Gamma}_{r_1, r_2}^\ell} P(\mathbf{y}^\ell)$$

where $\bar{\mu} = \mu (\tau + 2)^{k^\ell} \in \mathbb{R}$. Let $R_1, R_2 \in \mathbb{N}$ such that $K \subset \bar{\mathcal{B}}(0, R_1)$ and $R_1 < R_2$. By definition of the distance to a subset, it comes that

$$\mathbb{E}_{P(d\mathbf{y}^\ell)} \left[\log^+ \frac{1}{d(\mathbf{y}^\ell, \Gamma_{0, R_2}^\ell)} \right] \leq \bar{\mu} R_1^{p^\ell} \sup_{\bar{\Gamma}_{0, R_1}^\ell} P(\mathbf{y}^\ell) + \bar{\mu} \sum_{r=R_1}^{R_2-1} (r+1)^{p^\ell} \sup_{\bar{\Gamma}_{r, r+1}^\ell} P(\mathbf{y}^\ell).$$

The first term is finite as $P(d\mathbf{y})$ is continuous. Besides, if $\mathbf{y}^\ell \in \overline{\Gamma_{r,r+1}^\ell}$, there exists $\mathbf{z}^\ell \in \bar{\mathcal{A}}(r, r+1)$ such that $\|\tilde{\gamma}^\ell(\mathbf{z}^\ell) - \mathbf{y}^\ell\|_\infty \leq 1$. Let $i \in \llbracket 1, n \rrbracket$ and $v \in \llbracket 1, p_{\text{pop}}^{\text{reg}} + p_{\text{ind}}^{\text{reg}} \rrbracket$ so that $\|(\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_{i \in \llbracket 1, n \rrbracket}\|_\infty = |(\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_v|$. Such a couple exists due to the existence of i_0 . Moreover, there exists $a_{i,v}((\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_{-v})$ and $b_{i,v}((\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_{-v})$ as in (H 4) and by definition of \mathbf{z}^ℓ and the infinite norm,

$$\begin{aligned} \|\mathbf{y}^\ell\|_\infty &\geq \|\tilde{\gamma}^\ell(\mathbf{z}^\ell)\|_\infty - 1 \geq \|\tilde{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)\|_\infty - 1 \\ &\geq a_{i,v} |(\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_v| + b_{i,v} - 1 \geq a_{i,v} \times r + b_{i,v} - 1. \end{aligned}$$

Consequently, $\sup_{\overline{\Gamma_{r,r+1}^\ell}} P(\mathbf{y}^\ell) \leq \sup\{P(\mathbf{y}^\ell) \mid \|\mathbf{y}^\ell\|_\infty \geq a_{i,v} \times r + b_{i,v} - 1\}$ and the series $\sum (r+1)^{p^\ell} \sup_{\overline{\Gamma_{r,r+1}^\ell}} P(\mathbf{y}^\ell)$ converge since $P(d\mathbf{y})$ has a polynomial decay tail of degree bigger than $p^\ell + 1$ apart from K by assumption (H 2).

- (b) Assume that it exists $b \in \mathbb{R}$ such that for all $i \in \llbracket 1, n \rrbracket$, $\|(\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})\|_\infty \leq b$. Then, by assumption (H' 5), it exists $R \in \mathbb{R}_+^*$ such that for all i , $\|\tilde{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)\|_\infty < R$. In particular, $\|\tilde{\gamma}^\ell(\mathbf{z}^\ell)\|_\infty < R$ and $\Gamma^\ell \subset \bar{\mathcal{B}}(0, R)$. Thus,

$$\mathbb{E}_{P(d\mathbf{y}^\ell)} \left[\log^+ \frac{1}{d(\mathbf{y}^\ell, \Gamma^\ell)} \right] \leq \mathbb{E}_{P(d\mathbf{y}^\ell)} \left[\log^+ \frac{1}{d(\mathbf{y}^\ell, \bar{\mathcal{B}}(0, R))} \right].$$

Yet, by still denoting $\overline{\bar{\mathcal{B}}(0, R)} = \{\mathbf{y}^\ell \in \mathbb{R}^{k^\ell} \mid d(\mathbf{y}^\ell, \bar{\mathcal{B}}(0, R)) \leq 1\}$ and applying the lemma 2 to the compact $K = \bar{\mathcal{B}}(0, R)$ and $f = Id$, it exists $\mu \in \mathbb{R}$ such that

$$\begin{aligned} \mathbb{E}_{P(d\mathbf{y}^\ell)} \left[\log^+ \frac{1}{d(\mathbf{y}^\ell, \bar{\mathcal{B}}(0, R))} \right] &= \int_{\bar{\mathcal{B}}(0, R)} \log^+ \frac{1}{d(\mathbf{y}^\ell, \bar{\mathcal{B}}(0, R))} P(d\mathbf{y}^\ell) \\ &\leq \mu 3^{k^\ell} R^{p^\ell} \sup_{\bar{\mathcal{B}}(0, R)} P(\mathbf{y}^\ell) < +\infty. \end{aligned}$$

Finally, in both cases, $\mathbb{E}_{P(d\mathbf{y}^\ell)} \left[\sup_{\theta \in \Theta} \left(\sum_{i=1}^\ell \log q(\mathbf{y}_i | \theta) \right)^+ \right] < +\infty$.

LEMMA 4. Assume (H 1), (H 2), (H 3), (H 4) and (H 5). Let $\overline{\mathcal{S}_{p_{\text{ind}}}^+(\mathbb{R})} = \mathcal{S}_{p_{\text{ind}}}^+(\mathbb{R}) \cup \{\infty\}$ be the one point Alexandrov compactification of $\mathcal{S}_{p_{\text{ind}}}^+(\mathbb{R})$ and consider the compactification of the parameter space Θ^ω

$$\overline{\Theta^\omega} = \left\{ \theta = (\overline{\mathbf{z}_{\text{pop}}}, \Sigma, \sigma) \in \mathbb{R}^{p_{\text{pop}}} \times \overline{\mathcal{S}_{p_{\text{ind}}}^+(\mathbb{R})} \times \overline{\mathbb{R}^+} \mid \|\overline{\mathbf{z}_{\text{pop}}}\| \leq \sigma \right\}$$

where $\overline{\mathbb{R}^+} = [0, +\infty[\cup \{+\infty\}$. Then, we have for all $\omega \in \mathbb{R}$,

- (C 1) $P(d\mathbf{y}^\ell)$ almost surely, for any sequence $\theta_m = (\overline{\mathbf{z}_{\text{pop}}}_m, \Sigma_m, \sigma_m)$ of elements from Θ^ω such that $\lim_{m \rightarrow \infty} \theta_m \in \overline{\Theta^\omega} \setminus \Theta^\omega$,

$$\lim_{m \rightarrow \infty} \sum_{i=1}^\ell \log q(\mathbf{y}_i | \theta_m) = -\infty;$$

(C2) For any sequence $(\theta_m) \in \Theta^{\omega \mathbb{N}}$ such that $\lim_{m \rightarrow \infty} \theta_m \in \overline{\Theta^\omega} \setminus \Theta^\omega$,

$$\lim_{m \rightarrow \infty} \mathbb{E}_{P(d\mathbf{y}^\ell)} [\log q(\mathbf{y}|\theta_m)] = -\infty ;$$

(C3) The mapping $\theta \mapsto \mathbb{E}_{P(d\mathbf{y}^\ell)} [\log q(\mathbf{y}|\theta)]$ is continuous on Θ^ω and $\Theta_*^\omega \neq \emptyset$.

PROOF. We prove the three points in order.

(a) As $\overline{\Theta^\omega} \setminus \Theta^\omega = \left\{ (\Sigma, \sigma) \in \overline{\mathcal{S}_{\text{ind}}^+(\mathbb{R})} \times \overline{\mathbb{R}^+} \mid \|\Sigma\| = +\infty \wedge \sigma \in \{0, +\infty\} \right\}$, we proceed by disjunction. Let, for all $m \in \mathbb{N}$, $\theta_m = (\overline{\mathbf{z}_{\text{pop}}}_m, \Sigma_m, \sigma_m) \in \Theta^\omega$.

(i) Assume that $\|\Sigma_m\| \rightarrow \infty$. Let $M = \|\mathbf{y}^\ell\|_\infty$.

For all individuals $i \in \llbracket 1, n \rrbracket$, the marginal density of \mathbf{y}_i given θ_m is given by :

$$q(\mathbf{y}_i|\theta_m) = \frac{1}{(\sigma_m \sqrt{2\pi})^{k_i}} \int_{\mathcal{Z}_{\text{pop}} \times \mathcal{Z}_i} \exp \left(-\frac{1}{2\sigma_m^2} \|\mathbf{y}_i - \vec{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)\|_2^2 \right) q(\mathbf{z}_{\text{pop}}, \mathbf{z}_i|\theta_m) d(\mathbf{z}_{\text{pop}}, \mathbf{z}_i).$$

Let $x \geq 1$, $\mathcal{Z}_{i,-1}^{\text{reg}} = \left\{ (\mathbf{z}_{i,2}^{\text{reg}}, \dots, \mathbf{z}_{i,p_{\text{ind}}}^{\text{reg}}) \mid \mathbf{z}_i^{\text{reg}} \in \mathcal{Z}_i^{\text{reg}} \right\}$ and likewise $\mathcal{Z}_{\text{pop},-1}^{\text{reg}}$. Let $\bar{\mathcal{B}}_{i,1}^x$ be the closed ball defined by

$$\bar{\mathcal{B}}_{i,1}^x = \bar{\mathcal{B}}_{i,1}^x \left((\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_{-1} \right) = \bar{\mathcal{B}} \left(0, \frac{xM - b_{i,1}((\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_{-1})}{a_{i,1}((\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_{-1})} \right)$$

where $a_{i,1}((\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_{-1})$ and $b_{i,1}((\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}})_{-1})$ are defined as in (H4). Thus, by slicing the integral in half and bounding the exponential on $\bar{\mathcal{B}}_{i,1}^x$ by 1,

$$\begin{aligned} q(\mathbf{y}_i|\theta_m) &\leq \frac{1}{(\sigma_m \sqrt{2\pi})^{k_i}} \int_{\bar{\mathcal{B}}_{i,1}^x \times \mathcal{Z}_{i,-1}} q(\mathbf{z}_{\text{pop}}, \mathbf{z}_i|\theta_m) d(\mathbf{z}_{\text{pop}}, \mathbf{z}_i) \\ &\quad + \frac{1}{(\sigma_m \sqrt{2\pi})^{k_i}} \int_{\bar{\mathcal{B}}_{i,1}^x \complement \times \mathcal{Z}_{i,-1}} \exp \left(-\frac{1}{2\sigma_m^2} \|\mathbf{y}_i - \vec{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)\|_2^2 \right) q(\mathbf{z}_{\text{pop}}, \mathbf{z}_i|\theta_m) d(\mathbf{z}_{\text{pop}}, \mathbf{z}_i). \end{aligned}$$

where $\mathcal{Z}_{i,-1} = \mathcal{Z}_{\text{pop},-1}^{\text{reg}} \times \mathcal{Z}_{\text{pop}}^{\text{crit}} \times \mathcal{Z}_{i,-1}^{\text{reg}} \times \mathcal{Z}_i^{\text{crit}}$. Moreover, by conditioning,

$$\int_{\bar{\mathcal{B}}_{i,1}^x \times \mathcal{Z}_{i,-1}} q(\mathbf{z}_{\text{pop}}, \mathbf{z}_i|\theta_m) d(\mathbf{z}_{\text{pop}}, \mathbf{z}_i) = \int_{\bar{\mathcal{B}}_{i,1}^x} q(\mathbf{z}_{\text{pop},1}^{\text{reg}}, \mathbf{z}_{i,1}^{\text{reg}}|\theta_m) d(\mathbf{z}_{\text{pop},1}^{\text{reg}}, \mathbf{z}_{i,1}^{\text{reg}}).$$

By continuity of $(\mathbf{z}_{\text{pop},1}^{\text{reg}}, \mathbf{z}_{i,1}^{\text{reg}}) \mapsto q(\mathbf{z}_{\text{pop},1}^{\text{reg}}, \mathbf{z}_{i,1}^{\text{reg}}|\theta_m)$ and compactness of $\bar{\mathcal{B}}_{i,1}^x$,

$$\int_{\bar{\mathcal{B}}_{i,1}^x \times \mathcal{Z}_{i,-1}} q(\mathbf{z}_{\text{pop}}, \mathbf{z}_i|\theta_m) d(\mathbf{z}_{\text{pop}}, \mathbf{z}_i) \leq \sup_{\bar{\mathcal{B}}_{i,1}^x} q(\mathbf{z}_{\text{pop},1}^{\text{reg}}, \mathbf{z}_{i,1}^{\text{reg}}|\theta_m) \mathcal{L}_1(\bar{\mathcal{B}}_{i,1}^x).$$

Since the marginal of a multivariate distribution is a multivariate distribution whose mean vector and covariance matrix are obtained by dropping the irrelevant variables, $\lim_{\|\Sigma\|_m \rightarrow \infty} q(\mathbf{z}_{\text{pop},1}^{\text{reg}}, \mathbf{z}_{i,1}^{\text{reg}} | \theta_m) = 0$ and the first integral goes to zero as $\|\Sigma\|_m \rightarrow \infty$.

The second integral is maximized at $\sigma_m^2 = \frac{1}{k_i} \|\mathbf{y}_i - \tilde{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)\|^2$. Due to (H3), the Cauchy-Schwarz inequality gives $\|\mathbf{y}_i - \tilde{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)\|_2^2 \geq (\|\mathbf{y}_i\|_2 - \|\tilde{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)\|_2)^2$. Thus, it exists $c \in \mathbb{R}_+^*$ such that for all $(\mathbf{z}_{\text{pop}}, \mathbf{z}_i) \in \bar{\mathcal{B}}_{i,1}^x \times \mathcal{Z}_{i,-1}$,

$$\|\mathbf{y}_i - \tilde{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)\|_2^2 \geq c \left(a_{i,1} \times \frac{xM - b_{i,1}}{a_{i,1}} + b_{i,1} - \|\mathbf{y}_i\|_\infty \right)^2 \geq c((x-1)M)^2$$

and by bounding the marginal density $q(\mathbf{z}_{\text{pop}}, \mathbf{z}_i | \theta_m)$ on $\bar{\mathcal{B}}_{i,1}^x \times \mathcal{Z}_{i,-1}$ by 1, the second integral is upper-bounded by $\left(\frac{k_i}{2\pi}\right)^{\frac{k_i}{2}} e^{-\frac{k_i}{2}} \frac{1}{(\sqrt{c}(x-1)M)^{k_i}}$. Therefore,

$$\limsup_{m \rightarrow \infty} \sum_{i=1}^{\ell} \log q(\mathbf{y}_i | \theta_m) \leq -\frac{k^\ell}{2} \left[1 + \log(2\pi) + \log(\sqrt{c}(x-1)M) \right] + \frac{1}{2} \sum_{i=1}^{\ell} k_i \log k_i.$$

Since x can be chosen arbitrarily large, we obtain the result for the case $\|\Sigma_m\| \rightarrow +\infty$.

(ii) Assume that $\sigma_m \rightarrow 0$ or $\sigma_m \rightarrow \infty$. Let $M = \|\mathbf{y}^\ell\|_\infty$.

With the same notations as in the proof of the lemma 3,

$$\sum_{i=1}^{\ell} \log q(\mathbf{y}_i | \theta_m) \leq -\frac{k^\ell}{2} \log(2\pi\sigma_m^2) - \frac{1}{2\sigma^2} d(\mathbf{y}^\ell, \Gamma^\ell)^2 \quad \text{where } \Gamma^\ell = \mathcal{I}m(\tilde{\gamma}^\ell)$$

and d denotes the Euclidean distance on \mathbb{R}^{k^ℓ} . Let us prove that $d(\mathbf{y}^\ell, \Gamma^\ell) > 0$ *a.s.* : the result will go along whatever $\sigma_m \rightarrow 0$ or $\sigma_m \rightarrow +\infty$ with the previous inequality. Let $\mathcal{Z}^\ell = \mathcal{Z}_{\text{pop}} \times \prod_{i=1}^{\ell} \mathcal{Z}_i$.

Due to (H4), for all $i \in \llbracket 1, \ell \rrbracket$, $\lim_{\|(\mathbf{z}_{\text{pop}}, \mathbf{z}_i^{\text{reg}})\|_\infty \rightarrow \infty} \|\gamma_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)\|_\infty = +\infty$, and so for all $\varepsilon \in \mathbb{R}_+^*$ non-negative, there exists $R \in \mathbb{R}$ such as for all $\mathbf{z}^\ell \in \mathcal{Z}^\ell$ satisfying $\|\mathbf{z}^\ell\| > R$, $\|\tilde{\gamma}^\ell(\mathbf{z}^\ell)\| > M + \varepsilon$. In particular, by definition of M , $\|\mathbf{y}^\ell - \tilde{\gamma}^\ell(\mathbf{z}^\ell)\|_\infty > 0$ for $\|(\mathbf{z}_{\text{pop}}, \mathbf{z}_i^{\text{reg}})_{i \in \llbracket 1, \ell \rrbracket}\|_\infty$ sufficiently large.

On the other hand, if at least a critical variable blows up, then by (H5) it exists a critical trajectory γ_i^{crit} such that $\lim_{\|(\mathbf{z}_{\text{pop}}, \mathbf{z}_i^{\text{crit}})\|_\infty \rightarrow \infty} \|\tilde{\gamma}_i(\mathbf{z}_{\text{pop}}, \mathbf{z}_i)\|_\infty = \gamma_i^{\text{crit}}$ and as soon as this variable becomes sufficiently large, $\mathbf{y}_i \neq \gamma_i^{\text{crit}}$ *a.s.* Thus, $\|\mathbf{y}^\ell - \tilde{\gamma}^\ell(\mathbf{z}^\ell)\|_\infty > 0$ *a.s.* for $\|(\mathbf{z}_{\text{pop}}, \mathbf{z}_i^{\text{crit}})_{i \in \llbracket 1, \ell \rrbracket}\|_\infty$ sufficiently large.

In other words, there exists $R \in \mathbb{R}_+^*$ such that for all $\mathbf{z}^\ell \in \mathcal{Z}^\ell$, if $\|\mathbf{z}^\ell\|_\infty > R$, then $\|\mathbf{y}^\ell - \tilde{\gamma}^\ell(\mathbf{z}^\ell)\|_\infty > 0$ *a.s.* So, by contraposition, if it exists $\mathbf{z}^\ell \in \mathcal{Z}^\ell$ such that $\|\mathbf{y}^\ell - \tilde{\gamma}^\ell(\mathbf{z}^\ell)\|_\infty = 0$ (at least *a.s.*) then $\|\mathbf{z}^\ell\|_\infty \leq R$. Especially, $\{\mathbf{z}^\ell \in \mathcal{Z}^\ell \mid \mathbf{y}^\ell = \tilde{\gamma}^\ell(\mathbf{z}^\ell) \text{ a.s.}\} \subset \bar{\mathcal{B}}(0, R)$. Since (H2) assumes that $P(d\mathbf{y})$ has a continuous density

and since $\tilde{\gamma}^\ell(\bar{\mathcal{B}}(0, R))$ is a submanifold of dimension $p^\ell < k^\ell$, $P[\mathbf{z}^\ell \in \bar{\mathcal{B}}(0, R)] = 0$. Hence, $\mathcal{L}_{k^\ell}(\{\mathbf{y}^\ell \mid d(\mathbf{y}^\ell, \mathcal{I}m(\tilde{\gamma}^\ell)) = 0\}) = 0$.

- (b) Let $f_m(\mathbf{y}^\ell) = \sum_{i=1}^\ell \log q(\mathbf{y}_i | \theta_m)$. From (C 1), we deduce that the negative part $(f_m(\mathbf{y}^\ell))^-$ is almost surely a non-decreasing and non-negative sequence converging to $+\infty$. From the monotone convergence theorem we then have

$$\liminf_{m \rightarrow +\infty} \mathbb{E}_{P(d\mathbf{y}^\ell)} \left[(f_m(\mathbf{y}^\ell))^- \right] = +\infty \quad \text{and so} \quad \lim_{m \rightarrow +\infty} \mathbb{E}_{P(d\mathbf{y}^\ell)} \left[(f_m(\mathbf{y}^\ell))^- \right] = +\infty.$$

Concerning the positive part $(f_m(\mathbf{y}^\ell))^+$, using the dominated convergence theorem, the Lemma 3 and the point (C 1), we get $\lim_{m \rightarrow +\infty} \mathbb{E}_{P(d\mathbf{y}^\ell)} \left[(f_m(\mathbf{y}^\ell))^+ \right] = 0$. Actually, for all $i \in \llbracket 1, n \rrbracket$ the application $(\mathbf{z}_{\text{pop}}^{\text{reg}}, \mathbf{z}_i^{\text{reg}}) \mapsto \gamma_i^{\text{crit}}$ is continuous by continuity of the function $\tilde{\gamma}_i$ and so (H' 5) holds.

Finally, we have proved that $\lim_{m \rightarrow +\infty} \mathbb{E}_{P(d\mathbf{y}^\ell)} \left[\sum_{i=1}^\ell \log q(\mathbf{y}_i | \theta_m) \right] = -\infty$ and (C 2) follows immediately.

- (c) The continuity statement is straightforward. If Θ_*^ω is empty, any maximizing sequence θ_m of $\mathbb{E}_{P(d\mathbf{y}^\ell)} [\log q(\mathbf{y}^\ell | \theta)]$ satisfies (up to extraction of a subsequence) $\theta_m \in \Theta^\omega$, $\|\Sigma_m\| \rightarrow +\infty$, $\sigma_m \rightarrow 0$ or $\sigma_m \rightarrow +\infty$, which is on contradiction with conclusion (C 2).

A.2. Proof of the consistency theorem

We follow in the following proof the classical approach of van der Vaart (2000).

PROOF. As in the lemma 4, let $\bar{\Theta}^\omega$ denote the one point Alexandrov compactification of the parameter space Θ^ω . We have already proved [Lemma 4 (C 3)] that $\Theta_*^\omega \neq \emptyset$. To achieve the proof, let us first demonstrate that for all $\theta_\infty \in \bar{\Theta}^\omega$ such that $\delta(\theta_\infty, \Theta_*^\omega) \geq \varepsilon$ it exists an open set $\mathcal{U} \subset \Theta^\omega$ such that

$$\frac{1}{\ell} \mathbb{E}_{P(d\mathbf{y}^\ell)} \left[\sup_{\theta \in \mathcal{U} \cap \Theta^\omega} \sum_{i=1}^\ell \log q(\mathbf{y}_i | \theta) \right] < \mathbb{E}^*(\omega). \quad (0)$$

Let $\varepsilon \geq 0$, $(\mathcal{U}_h) \subset \Theta^{\omega^{\mathbb{N}}}$ be a non-increasing sequence of open subsets of Θ^ω for which $\bigcap_{h \geq 0} \mathcal{U}_h = \{\theta_\infty\}$ and f_h be the function defined by $f_h(\mathbf{y}^\ell) = \frac{1}{\ell} \sup_{\theta \in \mathcal{U}_h} \sum_{i=1}^\ell \log q(\mathbf{y}_i | \theta)$.

- (a) If $\theta_\infty \in \Theta^\omega$, through the continuity of the map $\theta \mapsto \sum_{i=1}^\ell \log q(\mathbf{y}_i | \theta)$ and the definition of the sequence (\mathcal{U}_h) , $\lim_{h \rightarrow +\infty} f_h(\mathbf{y}^\ell) = \frac{1}{\ell} \sum_{i=1}^\ell \log q(\mathbf{y}_i | \theta_\infty)$. So, according to the monotone convergence theorem, the lemma 3 and since $\theta_\infty \notin \Theta_*^\omega$,

$$\lim_{h \rightarrow +\infty} \mathbb{E}_{P(d\mathbf{y}^\ell)} [f_h(\mathbf{y}^\ell)] = \frac{1}{\ell} \sum_{i=1}^\ell \mathbb{E}_{P(d\mathbf{y}^\ell)} [\log q(\mathbf{y}_i | \theta_\infty)] < \mathbb{E}^*(\omega).$$

- (b) If $\theta_\infty \notin \Theta^\omega$, we can prove that for all observations $\mathbf{y}^\ell \in \mathbb{R}^{k^\ell}$ $\lim_{h \rightarrow \infty} f_h(\mathbf{y}^\ell) = -\infty$ $P(d\mathbf{y}^\ell)$ a.s. We proceed by contradiction : assume that it exists a measurable set $A \in \mathcal{B}(\mathbb{R}^{k^\ell})$ such that $\mathbb{P}(\mathbf{y}^\ell \in A) > 0$ and for all $\mathbf{y}^\ell \in A$, $\inf_{h \in \mathbb{N}} f_h(\mathbf{y}^\ell) > -\infty$. Then, by definition of the *infimum*, for all $\mathbf{y}^\ell \in A$ it exists a sequence $(h_m) \in \mathbb{R}^{\mathbb{N}}$ such as $\liminf_{m \rightarrow +\infty} f_{h_m}(\mathbf{y}^\ell) > -\infty$. However for all $\mathbf{y}^\ell \in A$, $h \mapsto f_h(\mathbf{y}^\ell)$ is non-increasing and reaches its *infimum* limit for $h = +\infty$ and thus $\lim_{m \rightarrow +\infty} \mathcal{U}_{h_m} = \mathcal{U}_\infty = \{\theta_\infty\}$. Finally, up to considering a sequence $(\theta_{m,n}) \in \mathcal{U}_{h_m}^{\mathbb{N}}$ for all subsets $\mathcal{U}_{h_m} \subset \Theta^\omega$ such that for all $m \in \mathbb{N}$, $\lim_{n \rightarrow +\infty} \sum_{i=1}^\ell \log q(\mathbf{y}_i | \theta_{m,n}) = \sup_{\theta \in \mathcal{U}_m} \sum_{i=1}^\ell \log q(\mathbf{y}_i | \theta)$, concatenating, reindexing those sequences and using the continuity of the map $\theta \mapsto \sum_{i=1}^\ell \log q(\mathbf{y}_i | \theta)$ we know that it exists a sequence $(\theta_m) \in \Theta^{\omega^{\mathbb{N}}}$ such that

$$\lim_{m \rightarrow \infty} \theta_m = \theta_\infty \quad \text{and} \quad \liminf_{m \rightarrow +\infty} \sum_{i=1}^\ell \log q(\mathbf{y}_i | \theta_m) > -\infty.$$

Moreover, $\theta_\infty = (\overline{z_{pop}_\infty}, \Sigma_\infty, \sigma_\infty) \in \overline{\Theta^\omega} \setminus \Theta^\omega$ and thus $\sigma_\infty \in \{0, +\infty\}$ or $\|\Sigma_\infty\| = +\infty$, in contradiction to [lemma 4 (C1)]. So for all \mathbf{y} , $\lim_{h \rightarrow \infty} f_h(\mathbf{y}^\ell) = -\infty$ $P(d\mathbf{y})$ a.s. As in the proof of the lemma 4, the hypothesis (H 5) implies (H' 5) and according the the lemma 3 and the monotone convergence theorem,

$$\lim_{h \rightarrow +\infty} \mathbb{E}_{P(d\mathbf{y}^\ell)} [f_h(\mathbf{y}^\ell)] = -\infty < \mathbb{E}^*(\omega).$$

That is, in both cases $\lim_{h \rightarrow +\infty} \mathbb{E}_{P(d\mathbf{y}^\ell)} [f_h(\mathbf{y}^\ell)] < \mathbb{E}^*(\omega)$ and it exists an open set $\mathcal{U} \subset \Theta^\omega$ such that $\frac{1}{\ell} \mathbb{E}_{P(d\mathbf{y}^\ell)} \left[\sup_{\theta \in \mathcal{U} \cap \Theta^\omega} \sum_{i=1}^\ell \log q(\mathbf{y}_i | \theta) \right] < \mathbb{E}^*(\omega)$ as announced.

Let $K_\varepsilon = \{\theta \in \overline{\Theta^\omega} \mid \delta(\theta, \Theta^*) \geq \varepsilon\}$. Through the compactness of K_ε , it exists an open finite cover $(\mathcal{U}_j)_{j \in [1, J]}$ of K_ε satisfying (0). Thus, denoting $q_n = \lfloor \frac{n}{\ell} \rfloor$ and $r_n = n - q_n \ell$ the quotient and the rest of the euclidean division of n by ℓ , we get for all $\theta \in K_\varepsilon$,

$$\begin{aligned} \sup_{\theta \in K_\varepsilon \cap \Theta^\omega} \sum_{i=1}^n \log q(\mathbf{y}_i | \theta) &\leq \sup_{j \in [1, J]} \left(\sum_{q=0}^{q_n} \sup_{\theta \in \mathcal{U}_j \cap \Theta^\omega} \sum_{r=1}^\ell \log q(\mathbf{y}_{q\ell+r} | \theta) \right. \\ &\quad \left. + \sup_{\theta \in \mathcal{U}_j \cap \Theta^\omega} \sum_{r=\ell+1}^{r_n} \log q(\mathbf{y}_{q_n\ell+r} | \theta) \right). \end{aligned}$$

However, according to the strong law of large numbers and (0),

$$\lim_{q_n \rightarrow \infty} \frac{1}{q_n} \sum_{q=0}^{q_n} \sup_{\theta \in \mathcal{U}_j \cap \Theta^\omega} \sum_{r=1}^\ell \log q(\mathbf{y}_{q\ell+r} | \theta) \leq \ell \mathbb{E}^*(\omega)$$

hence, since $\lim_{n \rightarrow +\infty} q_n = +\infty$ and $r_n < \ell$ for all $n \in \mathbb{N}$,

$$\begin{aligned} \limsup_{n \rightarrow \infty} \left[\frac{q_n}{n} \sup_{j \in \llbracket 1, J \rrbracket} \left(\frac{1}{q_n} \sum_{q=0}^{q_n} \sup_{\theta \in \mathcal{U}_j \cap \Theta^\omega} \sum_{r=1}^{\ell} \log q(\mathbf{y}_{q\ell+r} | \theta) \right) \right] \\ = \frac{1}{\ell} \times \sup_{j \in \llbracket 1, J \rrbracket} \left(\mathbb{E}_{P(\mathrm{d}\mathbf{y}^\ell)} \left[\sup_{\theta \in \mathcal{U}_j \cap \Theta^\omega} \sum_{r=1}^{\ell} \log q(\mathbf{y}_{q_n \ell + r} | \theta) \right] \right) < \mathbb{E}^*(\omega). \end{aligned}$$

Otherwise, for all $r \in \llbracket \ell + 1, \ell_n \rrbracket$, $\log q(\mathbf{y}_{q_n \ell + r} | \theta) \leq -k^\ell \log q(\sigma\sqrt{2\pi})$ so

$$\frac{1}{n} \sup_{j \in \llbracket 1, J \rrbracket} \left(\sup_{\theta \in \mathcal{U}_j \cap \Theta^\omega} \sum_{r=\ell+1}^{r_n} \log q(\mathbf{y}_{q_n \ell + r} | \theta) \right) \leq \frac{k^\ell (r_n - 1)}{n} \log(\sigma\sqrt{2\pi}).$$

Thereafter $\limsup_{n \rightarrow \infty} \left[\frac{1}{n} \sup_{j \in \llbracket 1, J \rrbracket} \left(\sup_{\theta \in \mathcal{U}_j \cap \Theta^\omega} \sum_{r=\ell+1}^{r_n} \log q(\mathbf{y}_{q_n \ell + r} | \theta) \right) \right] \leq 0$ and

$$\limsup_{n \rightarrow \infty} \frac{1}{n} \sup_{\theta \in K_\varepsilon \cap \Theta^\omega} \sum_{i=1}^n \log q(\mathbf{y}_i | \theta) < \mathbb{E}^*(\omega). \quad (1)$$

By definition of Θ_*^ω and according to the strong law of large numbers, for all $\theta^* \in \Theta_*^\omega$ $\lim_{n \rightarrow \infty} \frac{1}{n} \sum_{i=1}^n \log q(\mathbf{y}_i | \theta^*) = \mathbb{E}^*(\omega)$ *a.s.* Moreover for all $i \in \llbracket 1, n \rrbracket$,

$$q(\mathbf{y}_i | \hat{\theta}_n) = \frac{q(\hat{\theta}_n | \mathbf{y}_i) q(\mathbf{y}_i)}{q_{\text{prior}}(\hat{\theta}_n)} \geq \frac{q(\theta_* | \mathbf{y}_i) q(\mathbf{y}_i)}{q_{\text{prior}}(\hat{\theta}_n)} = \frac{q(\mathbf{y}_i | \theta_*) q_{\text{prior}}(\theta_*)}{q_{\text{prior}}(\hat{\theta}_n)}$$

and so $\sum_{i=1}^n \log q(\mathbf{y}_i | \hat{\theta}_n) \geq \sum_{i=1}^n \log q(\mathbf{y}_i | \theta_*) + \left(\log q_{\text{prior}}(\theta_*) - \log q_{\text{prior}}(\hat{\theta}_n) \right)$. Since q_{prior} is upper-bounded on Θ^ω , there exists $M \in \mathbb{R}^+$ such that

$$\frac{1}{n} \left(\log q_{\text{prior}}(\theta_*) - \log q_{\text{prior}}(\hat{\theta}_n) \right) \geq \frac{1}{n} \log \left(\frac{q_{\text{prior}}(\theta_*)}{M} \right)$$

i.e. $\liminf_{n \rightarrow +\infty} \frac{1}{n} \left(\log q_{\text{prior}}(\theta_*) - \log q_{\text{prior}}(\hat{\theta}_n) \right) \geq 0$ and

$$\liminf_{n \rightarrow +\infty} \frac{1}{n} \sum_{i=1}^n \log q(\mathbf{y}_i | \hat{\theta}_n) \geq \mathbb{E}^*(\omega). \quad (2)$$

The result follows from (1) and (2) by contradiction : Assume that for all $n \in \mathbb{N}$, $\hat{\theta}_n \in K_\varepsilon$ *i.e.* that $\delta(\hat{\theta}_n, \Theta_*^\omega) \geq \varepsilon$. Then $\sum_{i=1}^n \log q(\mathbf{y}_i | \hat{\theta}_n) \leq \sup_{\theta \in K_\varepsilon \cap \Theta^\omega} \sum_{i=1}^n \log q(\mathbf{y}_i | \theta)$ and by taking the limit superior, we get

$$\mathbb{E}^*(\omega) \stackrel{(2)}{\leq} \limsup_{n \rightarrow \infty} \frac{1}{n} \sum_{i=1}^n \log q(\mathbf{y}_i | \hat{\theta}_n) \stackrel{(1)}{<} \mathbb{E}^*(\omega)$$

i.e. $\mathbb{E}^*(\omega) < \mathbb{E}^*(\omega)$. Hence $\lim_{n \rightarrow \infty} \mathbb{P} \left[\delta(\hat{\theta}_n, \Theta_*^\omega) \geq \varepsilon \right] = 0$.

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