Curve registration for mechanistic models

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Résumé. Nous nous intéressons au problème d'alignement de courbes dans une population de n sujets ; c'est à dire à l'estimation de fonctions $\{h_i\}_{i=1,\dots,n}$ quantifiant des déformations temporelles altérant la dynamique des fonctions de regression $\{X_i\}_{i=1,\dots,n}$ à partir d'observations discrètes et bruitées des fonctions perturbées $\{X_i \circ h_i\}_{i=1,\dots,n}$. Dans notre cas, nous avons aussi accès à des informations a priori sur la dynamique des fonctions de regression originales représentées par des équations différentielles ordinaires (EDOs): $\dot{X}_i = f_{\xi_i}(X_i, t)$. Par ce mélange d'approche descriptive/non-paramétrique et causale/paramétrique, nous voulons inférer aussi précisément et exhaustivement que possible l'ensemble des effets d'un traitement sur une population donnée. Via le modèle causal, nous quantifions l'effet du traitement sur des mécanismes déjà identifiés et intégrés dans l'EDO sous la forme de covariables à estimer. A partir du modèle descriptif, nous inférons les effets plus généraux du traitement dus à des mécanismes ignorés par l'EDO mais pris en compte par les fonctions $\{h_i\}_{i=1,\dots,n}$. Le problème est formulé comme un modèle de régression non-linéaire dans un cadre mixte pour incorporer la variabilité inter-sujets. Nous confirmons ensuite sur données simulées la capacité de notre méthode à estimer l'effet d'un traitement à la fois sur l'évolution globale de certaines variables d'intérêt mais aussi sur des mécanismes spécifiques déjà identifiés. Nous concluons ce travail par l'analyse de données pré-cliniques et cliniques d'essais proposant des traitements contre le VIH.

Mots-clés. Alignement de courbes, modèles non linéaires à effets mixtes, modélisation mécaniste, essais cliniques.

Abstract. We tackle the curve registration problem in which we learn time-warping functions $\{h_i\}_{i=1,\dots,n}$ from noisy observations of registered curves $\{X_i \circ h_i\}_{i=1,\dots,n}$. Still, in our case a priori knowledge regarding the unregistered curve dynamics is available under the form of a parametric ordinary differential equations (ODE)s $\dot{X}_i = f_i(X_i, t)$. From this combination of descriptive non-parametric model and causal parametric one, we aim to locate as accurately and exhaustively as possible the effect of a given therapy on a treated population. From the causal representation, we quantify treatment effects on well identified mechanisms, specified as ODE parameter covariates. From the descriptive one, we infer global action of treatment due to other mechanisms missed by the ODE but accounted for by time-warping functions, leading to distorted dynamics for treated subjects compared to the control group. The joint estimation of time-warping functions and ODE parameters is then cast as a non-linear regression problem in a mixed effect setting to account for inter-subject variability. We then confirm on simulated data the capacity of our method to estimate treatment effects on the general evolution of some variables of interests as well as on specific mechanisms acting on the patient dynamic. We conclude this work by analyzing pre-clinical and clinical data from trials testing HIV cures.

Keywords. Curve registration, nonlinear mixed effect models, mechanistic modeling, clinical trials.

1 General Framing of the problem

In this work, we focus on the curve registration problem in the specific case where the dynamic of the unregistered curves are ruled by differential equations. We start by framing this problem within the classic curve registration setting: for a population of n subjects, we aim to infer the time-warping functions $\{h_i\}_{i=1,...,n}$ distorting the original (or unregistered) regression functions $\{X_i\}_{i=1,...,n}$. For this, we have access for the i-th subject to n_i noisy measurements of the distorted (registered) function $X_i \circ h_i$ given by:

$$y(t_{i,j}) = C\left(X_i(h_i(t_{i,j}))\right) + \epsilon_{i,j} \text{ with } \epsilon_{i,j} \sim N(0, \Sigma) \tag{1}$$

where $t_i := \{t_{i,j}\}_{j=1,...,n_i}$ and $\epsilon_{i,j} = \{\epsilon_{i,j}\}_{j=1,...,n_i}$ are respectively the n_i measurement timepoints and the i.i.d centered measurement noise corrupting the observations. But here, we move a bit further from this classic framework by assuming that 1/the X_i are d-dimensional state-variables and 2/possibly partially observed where $C : \mathbb{R}^d \longmapsto \mathbb{R}^{d_{obs}}$ is the observation function, with $d_{obs} \leq d$. That is, we consider that a relevant representation of each subject evolution requires a multiple outcome process even though some of its component cannot be directly measured. In order to learn the evolution of the unobserved variables, we assume that we have access to a priori knowledge regarding the interactions between the observed and unobserved part of X_i given by an ordinary differential equation model (ODE)s:

$$\begin{cases} \dot{X}_{\xi_i} = f_{\xi_i}(X_{\xi_i}, t) \\ X_{\xi_i}(0) = x_{i,0}(\xi_i) \end{cases} \tag{2}$$

depending on the $d_\xi-$dimensional parameter ξ_i and ruling the evolution of the unregistered function $X_i := X_{\xi_i}$.

Regarding ξ_i parametrization, we adopt a nonlinear mixed effect (NLME) setting leading to the so-called NLME-ODE models:

$$\xi_{i,l} = \overline{\xi_l} + \sum_{m=1}^{M} \pi_{Gp_m}^{\xi_l} 1_{i \in Gp_m} + b_i^{\xi_l} \text{ for } l = 1, ..., d_\xi \tag{3}$$

with:

1. $\overline{\xi_l}$: the mean value for $\xi_{i,l}$ common to the whole population,
2. $\pi_{Gp_m}^{\xi_l}$: the corrective term applied to the mean value $\overline{\xi_l}$ for subjects belonging to the group Gp_m (with possibly $\pi_{Gp_m}^{\xi_l} = 0$),
3. $b_i^{\xi_l} \sim N(0, \sigma_{\xi_l}^2)$: the subject-specific variations (with possibly $\sigma_{\xi_l}^2 = 0$).

The parametrization (3) makes it possible to aggregate information from the whole population to estimate $\overline{\xi} := \left(\overline{\xi_1}, ..., \overline{\xi_{d_\xi}}\right)$ as well as the regressors $\pi^\xi := \left(\pi_{Gp_m}^{\xi_1}, ...\pi_{Gp_m}^{\xi_{d_\xi}}\right)_{m=1,..,M}$ in a sparse data setting while allowing for inter-subject variability thanks to $b_i^\xi := \left(b_i^{\xi_1}, ...b_i^{\xi_{d_\xi}}\right) \sim N(0, \Sigma_{b^\xi} := diag(\sigma_{\xi_l}^2))$. We use a similar decomposition for the functions $\{h_i\}_{i=1,...,n}$ with a mean value $\overline{h}$ common to everyone, group specific distortion $\pi^h := \left(\pi_{Gp_1}^h, ...\pi_{Gp_M}^h\right)$ and random variations b_i^h. For inference purpose, we rely on the differential equation representation of h_i proposed by Ramsay & Li [9]

to construct a global NLME-ODE model embedding both $\{\xi_i\}_{i=1,\dots,n}$ and $\{h_i\}_{i=1,\dots,n}$ as parameters. We then use the finite basis approximations $(\overline{h}(t,\beta_h), \pi^h(t,\beta_{\pi^h}), b_i^h(t,\beta_{b_i^h}))) \simeq \left(\overline{h}(t), \pi^h(t), b_i^h(t)\right)$ to consider the inference of (ξ_i, h_i) as a classic estimation problem in a mixed effect framework.

2 Time-distorted-NLME-ODE models

As in Ramsay & Li [9], we assume that the time transformation functions can be represented as the solution of the second order ODEs $\ddot{h}_i = w_i\dot{h}_i$, equivalently reformulated as a first order one by:

$$\begin{cases} \dot{g}_i = w_i g_i \\ \dot{h}_i = g_i. \end{cases} \tag{4}$$

As required in curve registration setting, this parametrization is enough to ensure h_i is monotonous on $[0, T]$ and strictly increasing if $\dot{h}_i(0) > 0$ without any conditions on w_i. This allows to turn to constrained inference problem of h_i into the unconstrained one of w_i. From the original ODE (2), we can derive the equation followed by the warped function: $X_{h_i,\xi_i}(t) := X_{\xi_i}(h_i(t))$ by differentiation of a composed function:

$$\begin{cases} \dot{X}_{h_i,\xi_i}(t) = \dot{h}_i(t) f_{\xi_i}(X_{h_i,\xi_i}(t), h_i(t)) \\ X_{h_i,\xi_i}(0) = x_i(h_i(0)). \end{cases}$$

We add the constraint $h_i(0) = 0$ to enforce the absence of instantaneous temporal shift for all subjects. We then gather all equations into one to describe the evolution of the time-distorted NLME-ODE:

$$\begin{cases} \dot{X}_{h_i,\xi_i} = g_i f_{\xi_i}(X_{h_i\xi_i}, h_i) \\ \dot{g}_i = w_i g_i \\ \dot{h}_i = g_i \\ (X_{h_i,\xi_i}(0), g_i(0), h_i(0)) = (x_i(0), \dot{h}_i(0), 0). \end{cases} \tag{5}$$

The null function $w_i = 0$ leads to $h_i(t) = \dot{h}_i(0)t$ and so, setting $\dot{h}_i(0) = 1$ corresponds to an absence of instantaneous temporal distortion. So, the original ODE (2) is embedded into the time-distorted NLME-ODE models (5) as a particular case.

We are left with the choice of w_i and $\dot{h}_i(0)$. For w_i, we choose the piecewise linear function:

$$w_i(t) = 2\sum_{k=0}^{K} \beta_{ik} \frac{t - t_k}{(t_{k+1} - t_k)^2} 1_{[t_k, t_{k+1}]}(t) \tag{6}$$

with uniformly reparted anchor points $\{t_k\}_{k=1,\dots K}$. We get $\beta_{ik} = \int_{t_k}^{t_{k+1}} w_i(s)ds$, so the parameters $\beta_i = (\beta_{i0,\dots}\beta_{iK})$ quantify the temporal distortion on each interval $[t_k, t_{k+1}]$. In particular, having $\beta_{ik} < 0$ indicates that the evolution speed of the i-th subject on $[t_k, t_{k+1}]$ is slowed down comparing to the dynamic implied by the original model (2).

Now, we account for group and subject specific variations with parametrization:

$$\begin{cases} \log \dot{h}_i(0) = \overline{\beta_0} + \sum_{m=1}^{M} \log \pi_{Gp_m}^{\beta_0} 1_{i \in Gp_m} + b_i^{\beta_0} \\ \beta_{ik} = \overline{\beta_k} + \sum_{m=1}^{M} \pi_{Gp_m}^{\beta_k} 1_{i \in Gp_m} + b_i^{\beta_k} \text{ for } k = 1, \dots K \end{cases} \tag{7}$$

where

1. $\overline{\beta_k}$: the distortion common to the whole population,
2. $\pi_{Gp_m}^{\beta_k}$: the additional ones applied to subjects belonging to Gp_m,
3. $b_i^{\beta_k} \sim N(0, \sigma_{\beta_k}^2)$: the subject-specific variations.

We can reconstruct the mean function $\overline{w}$ or the group-specific one $\overline{w}_{Gp_m}$ for parametrization (7):

$$\begin{cases} \overline{w}(t) = 2\sum_{k=0}^{K} \overline{\beta_k} \frac{t-t_k}{(t_{k+1}-t_k)^2} 1_{[t_k,t_{k+1}]}(t) \\ \overline{w}_{Gp_m}(t) = 2\sum_{k=0}^{K} \left(\overline{\beta_k} + \pi_{Gp_m}^{\beta_k}\right) \frac{t-t_k}{(t_{k+1}-t_k)^2} 1_{[t_k,t_{k+1}]}(t) \end{cases}$$

and we can subsequently solve the ODE (4) for $w = \overline{w}$ (resp. $w = \overline{w}_{Gp_m}$) with initial conditions $\dot{\overline{h}}(0) = e^{\overline{\beta_0}}$ (resp. $\dot{\overline{h}}_{Gp_m}(0) = \pi_{Gp_m}^{\beta_0} e^{\overline{\beta_0}}$) to derive the corresponding time-warping function $\overline{h}$ (resp. $\overline{h}_{Gp_m}$).

The estimation of the time-distorted NLME-ODE (5) can be done in a same manner as the original model (2) with the addition of parameters $\overline{\beta} = (\overline{\beta_0}, ...\overline{\beta_K})$, $\pi^{\beta} = \left(\pi_{Gp_m}^{\beta_0}, ..., \pi_{Gp_m}^{\beta_K}\right)_{m=1,....M}$. Nonetheless, we aim to ensure that fidelity to the data is preferably explained by structural parameter variations internal to the assumed model rather than by external adjustment. For this, we add the prior distributions $\overline{\beta} \sim N(0, I_{K+1})$ and $\pi^{\beta} \sim N(0, I_{M(K+1)})$, this is equivalent to start with the null hypothesis that there is no time-warping. We estimate the population parameters $\left(\overline{\xi}, \pi^{\xi}, \Sigma_{b^{\xi}}, \overline{\beta}, \pi^{\beta}\right)$ with maximum a posteriori, the estimation uncertainty being quantified by Fisher Information matrix; all of the required numerical methods being implemented in Monolix [5].

3 Illustration

3.1 Numerical Experiment

We test on simulated data our ability to estimate the parameters of a time distorted NLME-ODE model, both the time-warping functions and the structural parameters. As tested model, we consider a time-warped and structurally identifiable version of the ODE proposed by [6] describing the evolution of target/infected CD4+T cells and HIV viral load:

$$\begin{aligned} \dot{T} &= 1 - \phi TV - d_T T \\ \dot{I} &= \phi TV - d_I I \\ \dot{V} &= \Lambda \overline{I} - cV. \end{aligned} \tag{8}$$

In this ODE, T and I respectively represent rescaled concentrations of target and infected cell populations and V, the viral load. The parameter ϕ is the viral infection rate of target cells, Λ the viral production rate and the remaining terms d_T, d_I and c are respectively the death rate of T , I and the viral clearance rate. The model is used to predict viral load rebound just after the interruption of a long antiretroviral therapy (ART) exposure, so we assume at $t = 0$ there is no infection ($\phi \simeq 0$) and the system is near its steady state $(T(0), I(0), V(0)) = (1/d_T, I_0, 0)$ but with $I_0 \neq 0$ to mimic the existence of viral reservoir in long-lived lymphocytes [10].

We use the mean parameter value given in Prague et al. [8, 7], $\phi = 7.7e^{-7}$, $d_T = 0.05$, $d_I = 0.4$, $c = 23$ as well as $\Lambda = 2.5e^6$ and $I(0) = 2e^{-6}$. Regarding the applied temporal distortion to ODE (8),

Parameter	Target Value	Mean Estimates	Relative Bias	Empirical Std	Estimated Std	MSE	Coverage Rate
$\overline{\Lambda}$	$2.5e^6$	$2.6e^6$	0.02	$1.3e^5$	$1.8e^5$	$1.6e^{10}$	0.93
$\pi^{\overline{\Lambda}}_{Gp_1}$	0.8	0.8	0.01	$5.3e^{-2}$	$4.0e^{-2}$	$2.9e^{-3}$	0.91
$\pi^{\overline{\Lambda}}_{Gp_2}$	1.0	1.0	0.01	$6.6e^{-2}$	$4.9e^{-2}$	$4.5e^{-3}$	0.90
$\overline{I}(0)$	$2.0e^{-6}$	$1.9e^{-6}$	<0.01	$1.8e^{-7}$	$1.7e^{-7}$	$2.5e^{-14}$	0.95
$\pi^{\beta_1}_{Gp_1}$	-0.7	-0.7	0.02	$8.2e^{-2}$	$7.5e^{-2}$	$6.8e^{-3}$	0.93
$\pi^{\beta_2}_{Gp_1}$	-1.9	-1.9	<0.01	$7.6e^{-2}$	$7.5e^{-2}$	$5.8e^{-3}$	0.93
$\pi^{\beta_1}_{Gp_2}$	-1.5	-1.5	<0.01	0.1	0.1	$9.0e^{-3}$	0.97
$\pi^{\beta_2}_{Gp_2}$	-2.3	-2.3	0.01	0.2	0.2	$3.3e^{-2}$	0.91

Table 1: Estimation results for time-distorted ODE (8)

we resume the finite basis decomposition (6) for w_i with $K = 2$ elements and $t_{k+1} - t_k = 30$ days between anchor points but we do not add mean temporal distortion by setting $\overline{\beta_0} = \overline{\beta_1} = \overline{\beta_2} = 0$.

We consider $M = 2$ treatment groups in addition to a placebo one. To account for both group and patient specific variations, we use the following parametrization:

$$\begin{cases} \ln \Lambda_i &= \ln \overline{\Lambda} + \ln \pi^{\overline{\Lambda}}_{Gp_1} 1_{i \in Gp_1} + \ln \pi^{\overline{\Lambda}}_{Gp_2} 1_{i \in Gp_2} + b_i^{\Lambda} \\ \ln I_i(0) &= \ln \overline{I}(0) + b_i^{I(0)} \\ \beta_{i0} &= b_i^{\beta_0} \\ \beta_{i1} &= \pi^{\beta_1}_{Gp_1} 1_{i \in Gp_1} + \pi^{\beta_1}_{Gp_2} 1_{i \in Gp_2} + b_i^{\beta_1} \\ \beta_{i2} &= \pi^{\beta_2}_{Gp_1} 1_{i \in Gp_1} + \pi^{\beta_2}_{Gp_2} 1_{i \in Gp_2} + b_i^{\beta_2} \end{cases}$$

with $\sigma^2_{\Lambda} = 0.3$ and $\sigma^2_{I(0)} = 1.0$, $\sigma^2_{\beta_0} = \sigma^2_{\beta_1} = \sigma^2_{\beta_2} = 0.2$ as well as regressors $\left(\pi^{\overline{\Lambda}}_{Gp_1}, \pi^{\beta_1}_{Gp_1} \pi^{\beta_2}_{Gp_1}\right) = (0.8, -0.7, -1.9)$ and $\left(\pi^{\overline{\Lambda}}_{Gp_2}, \pi^{\beta_1}_{Gp_2}, \pi^{\beta_2}_{Gp_2}\right) = (1.0, -1.5, -2.3)$.

We simulate a population of $n = 150$ subjects uniformly reparted within each group $m = 0, ..., M$ ($m = 0$ representing the placebo one). We generate for each subject $n_i = 21$ viral load measurements given by $Y_{i,j} = \log_{10}(V(t_{i,j})) + \varepsilon_{i,j}$ where $\varepsilon_{i,j} \sim N(0, 0.2^2)$ with two measurements a week for the first four weeks followed by one measurement each week afterward up to 40 weeks. From this synthetic dataset, we estimate the mean parameter value $\left(\overline{\Lambda}, \overline{I}(0)\right)$ as well as the regressors $\left(\pi^{\overline{\Lambda}}_{Gp_1}, \pi^{\beta_1}_{Gp_1} \pi^{\beta_2}_{Gp_1}\right)$ and $\left(\pi^{\overline{\Lambda}}_{Gp_2}, \pi^{\beta_1}_{Gp_2}, \pi^{\beta_2}_{Gp_2}\right)$.

We proceed to $N_{MC} = 10^3$ trials of such data simulation and subsequent parameter estimation. From these trials, we estimate the mean, the bias, the empirical standard deviation as well as the mean square error of our estimator to quantify its practical accuracy. We also estimate the standard deviation derived from the Fisher Information Matrix as well as the coverage rate of the corresponding 95% confidence intervals. The estimation results are given in table 1. We can see that both empirical and estimated standard deviation globally coincides and the actual coverage rate is generally close to the expected rate of 0.95, thus indicating a well-conditioned estimation problem. Still, we denote a slight under-estimation of variance for regressors linked to Λ consistent with the small drop in coverage rate for $\pi^{\overline{\Lambda}}_{Gp_1}$ and $\pi^{\overline{\Lambda}}_{Gp_2}$.

3.2 Real Data

We will apply this methodology to trials in which HIV cure therapies and vaccines have been tested either in non-human primates [1, 4, 8] and humans [3, 2]. The dataset consists in Antiretroviral treatment interruption (ATI) trials, which are pivotal in the landscape of HIV cure research, offering a structured framework to evaluate the efficacy of cure strategies by temporarily halting antiretroviral therapy (ART) under stringent medical oversight. These trials aim to elucidate the immune system's capacity to control HIV in the absence of medication, thereby shedding light on potential pathways to achieve viral remission or cure. In situations where effective or functional cures are not available (as for nowadays), the impact of any intervention is likely to result from a combination of intrinsic alterations in the virus system's mechanistic capabilities, along with a delayed response that occurs at varying rates across individuals. The issue of this variability, particularly the delayed response that differs from one person to another, is addressed through the technique of curve registration.

Bibliographie

References

[1] Erica N Borducchi, Crystal Cabral, Kathryn E Stephenson, Jinyan Liu, Peter Abbink, David Nganga, Joseph P Nkolola, Amanda L Brinkman, Lauren Peter, Benjamin C Lee, et al. Ad26/mva therapeutic vaccination with tlr7 stimulation in siv-infected rhesus monkeys. *Nature*, 540(7632):284–287, 2016.

[2] Amanda Cobb, Lee K Roberts, A Karolina Palucka, Holly Mead, Monica Montes, Rajaram Ranganathan, Susan Burkeholder, Jennifer P Finholt, Derek Blankenship, Bryan King, et al. Development of a hiv-1 lipopeptide antigen pulsed therapeutic dendritic cell vaccine. *Journal of immunological methods*, 365(1-2):27–37, 2011.

[3] Y Lévy, C Lacabaratz, Edouard Lhomme, A Wiedemann, Claire Bauduin, C Fenwick, E Foucat, M Surenaud, L Guillaumat, Valerie Boilet, et al. A randomized placebo-controlled efficacy study of a prime boost therapeutic vaccination strategy in hiv-1-infected individuals: Vri02 anrs 149 light phase ii trial. *Journal of Virology*, 95(9):10–1128, 2021.

[4] So-Yon Lim, Christa E Osuna, Peter T Hraber, Joe Hesselgesser, Jeffrey M Gerold, Tiffany L Barnes, Srisowmya Sanisetty, Michael S Seaman, Mark G Lewis, Romas Geleziunas, et al. Tlr7 agonists induce transient viremia and reduce the viral reservoir in siv-infected rhesus macaques on antiretroviral therapy. *Science translational medicine*, 10(439):eaao4521, 2018.

[5] Lixoft. Monolix version 2023r1. *Antony, France*, 2023.

[6] Alan S Perelson and Ruy M Ribeiro. Modeling the within-host dynamics of hiv infection. *BMC biology*, 11:1–10, 2013.

[7] Mélanie Prague, Daniel Commenges, Julia Drylewicz, and Rodolphe Thiébaut. Treatment monitoring of hiv-infected patients based on mechanistic models. *Biometrics*, 68(3):902–911, 2012.

[8] Mélanie Prague, Jeffrey M Gerold, Irene Balelli, Chloé Pasin, Jonathan Z Li, Dan H Barouch, James B Whitney, and Alison L Hill. Viral rebound kinetics following single and combination immunotherapy for hiv/siv. *BioRxiv*, page 700401, 2019.

[9] James O Ramsay and Xiaochun Li. Curve registration. *Journal of the Royal Statistical Society Series B: Statistical Methodology*, 60(2):351–363, 1998.

[10] Janet D Siliciano and Robert F Siliciano. The latent reservoir for hiv-1 in resting cd4+ t cells: a barrier to cure. *Current Opinion in HIV and AIDS*, 1(2):121–128, 2006.