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CURVE REGISTRATION USING FRACTIONAL POLYNOMIALS WITH APPLICATION TO ELECTROENCEPHALOGRAMS ANALYSIS

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Curve registration using fractional polynomials

with application to electroencephalograms analysis

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Abstract

An important issue in functional data analysis consists in deciding whether there is any significant difference between 2 sets of curves. When monitoring some continuous process on similar units (like patients in a clinical study), one often notices a typical pattern common to all curves but with variation both in amplitude and dynamics between curves. Our goal consists in synchronizing the individual curves before any further statistical treatment. In this paper, we propose a new registration technique based on fractional polynomials. We compare this method with two alignment methods: the nonparametric method of Ramsay and Silverman (1997) and the landmark registration technique with markers detected using wavelets proposed by Bigot (2005). The methodology is illustrated on a real biomedical study with the registration of electroencephalograms (EEG). We shall show how this can be used to detect a treatment effect.

Key words : EEG, ERP, P300, registration, fractional polynomials.

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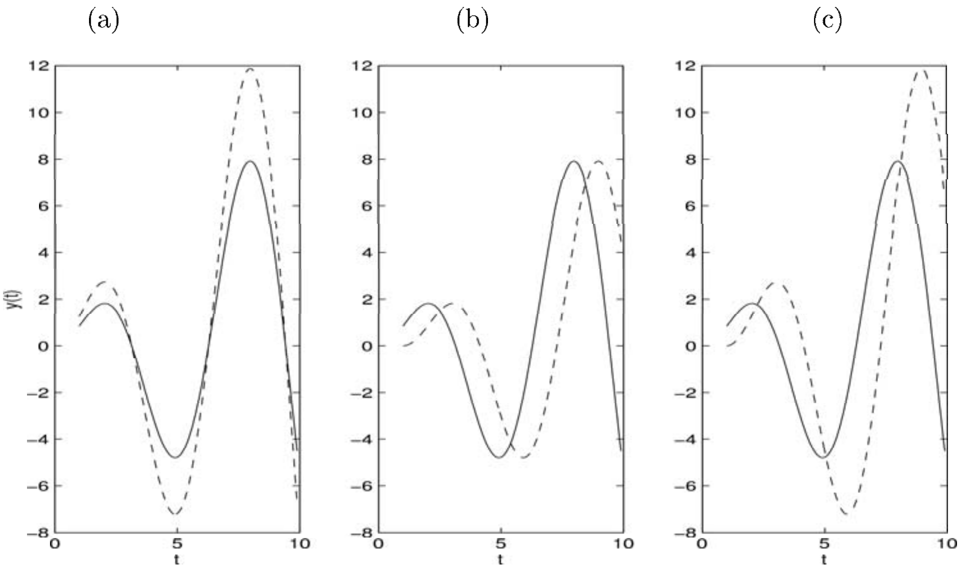

Figure 1: (a) Variation in amplitude between curves. (b) Variation in dynamics between curves. (c) Variation in amplitude and in dynamics between curves.

1 Introduction

When monitoring some continuous process on similar units (like patients in a clinical study), one often notices a typical pattern common to all curves but with variation both in amplitude and dynamics between curves (see Figure 1). In particular, typical peaks are shifted from unit to unit (see Figure 2(a)). This complicates the statistical analysis of sample of curves. For example, the cross-sectional average usually does not reflect a typical curve pattern. Due to shifts, the signal structure is smeared or might even disappear (see dashed line in Figure 2(c)). Our approach consists in synchronizing the individual curves (see Figure 2(b)) before determining the average (see solid line in Figure 2(c)) or any further statistics.

There are two classical procedures of registration. One suggests to align characteristics curve features (named landmarks). Landmark registration involves identifying the timing of pre specified features in the curves, and then transforming time so that these markers events occur at the same time (Kneip and Gasser, 1992). This method is sensitive to errors in feature location that can even be missing in some curves. In this paper, landmarks will be detected using wavelets (Bigot, 2005).

The other classical procedure does not require the identification of markers. It was first proposed by Silverman (1995) and extended by Ramsay and Li (1998) using a flexible smooth monotone transformation family (Ramsay, 1998; Ramsay and Silverman, 1997).

Here, we proposed a new strategy involving a parametric estimation of the warping function using fractional polynomials. This method keeps working when some curve features are missing or difficult to identify (contrary to landmark registration) without distortion of the aligned curve (contrary to nonparametric registration).

The paper is organized as follows. We shall first explain the curve registration problem (Section 2). In Section 3, we shall present different registration tech-

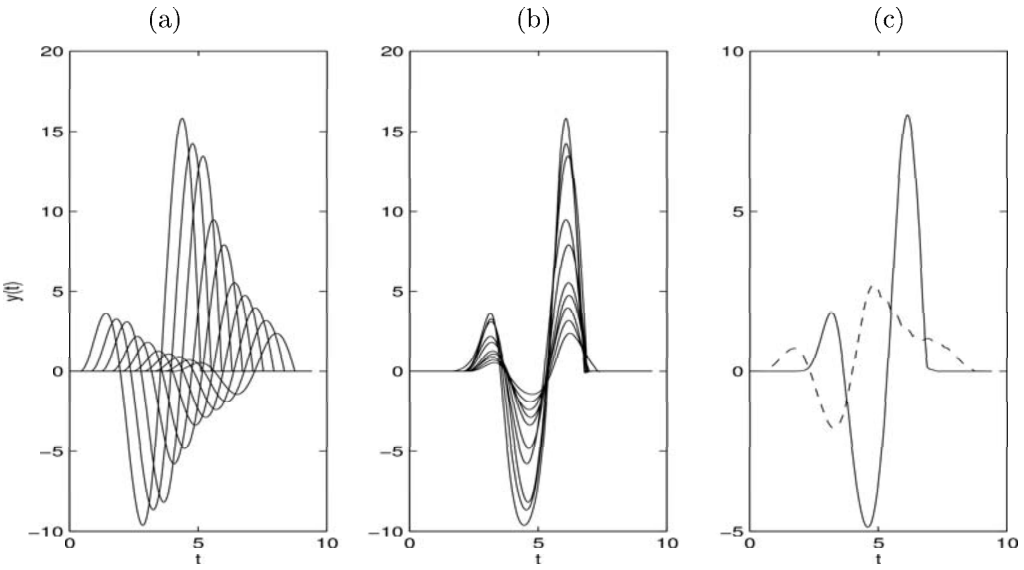

Figure 2: (a) Sample of curves with variation both in amplitude and dynamics. (b) Registered curves. (c) Mean of the curves (dashed line) and of the aligned curves (solid line).

niques: the nonparametric method of Ramsay and Silverman (1997) and marker registration using landmark detection with wavelet. In Section 4, we propose a new registration method based on the parametric estimation of the warping function using fractional polynomials. We shall illustrate these 3 methods on human growth acceleration curves in Section 5. In Section 6, we shall apply the registration using fractional polynomials on electroencephalograms (EEG) analysis. First, we present the clinical study where one is interested in comparing an interesting characteristic of the signals (an event-related potential (ERP) named P300 over EEG records. The classical registration techniques and our method are compared in the context of ERPs registration.

2 Curve registration problem

Suppose that we have a sample of I curves evaluated at N time points t_n ($n = 1, \ldots, N$). Each observation $y_i(t_n)$ ($i = 1, \ldots, I$) is the realization of an unknown process f_i:

$$y_i(t_n) = f_i(t_n) + \epsilon_{in}, \tag{1}$$

for $i = 1, \ldots, I$ and $n = 1, \ldots, N$. Dynamic time warping has been designed for aligning one curve with respect to another. Suppose that one wishes to align all the curves $y_i(t_n)$ ($i = 1, \ldots, I$ and $n = 1, \ldots, N$) on a template curve $\hat{y}(t_n)$. The problem is to find the warping functions $h_i(t_n)$ such as :

$$\hat{y}(t_n) = y_i(h_i(t_n)), \forall i, \forall n. \tag{2}$$

Warping function $h(t) > t$ corresponds to the alignment of a curve y_i delayed with respect to the template curve (see dashed curves of Figure 3), and $h(t) < t$

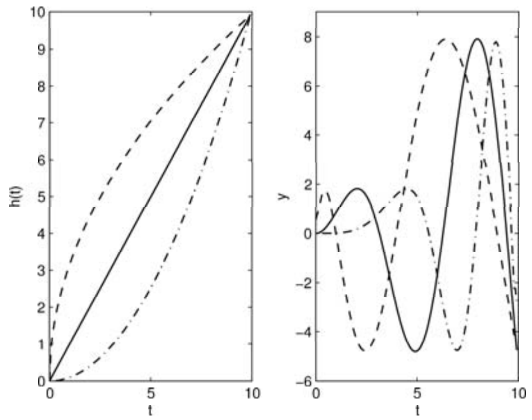

Figure 3: Left panel: 2 warping functions. Right panel: The dashed and dot-dashed curves correspond to the warping functions in the left panel applied on the template curve (solid line).

to the alignment of a curve y_i in advance with respect to the template curve (see dot-dashed curves of Figure 3).

The fact that the timings of events retain the same order regardless of the time scale implies that the time warping functions h_i must be strictly increasing, so that $h_i(t_n) > h_i(t_{n+1})$ if and only if $t_n > t_{n+1}$. Moreover, we suppose that $h_i(0) = 0$ and $h_i(t_N) = t_N$. Ramsay and Silverman (1997) use nonparametric estimation of these functions. We shall propose in Section 4 a parametric model for the warping functions. In the next section, we shall discuss about the choice of the template curve $\hat{y}(t_n)$ (in Section 3.1).

3 Classical curve registration techniques

3.1 Choice of the template curve

In most applications, the target function $\hat{y}(t)$ is not given. Instead, we have to construct it from the data. Typically, one first computes the sample mean $\bar{y}(t)$ of the functions $y_i(t)$ to have a first guess for $\hat{y}(t)$. Then, one registers the individual curves $y_i(t)$ and update the estimation of $\hat{y}(t)$ by the mean of the registered functions. New estimations of the warping functions are obtained by registering the individual functions to this new estimate of $\hat{y}(t)$. In principle, it is possible to iterate the process of updating $\hat{y}(t)$ then re estimating the warping functions, but this is rarely necessary in practice.

In the example of the ERP curves that we shall discuss in Section 6, one can see in Figure 4 that the target function $\hat{y}(t)$ does not change anymore after 2 updates of the warping functions.

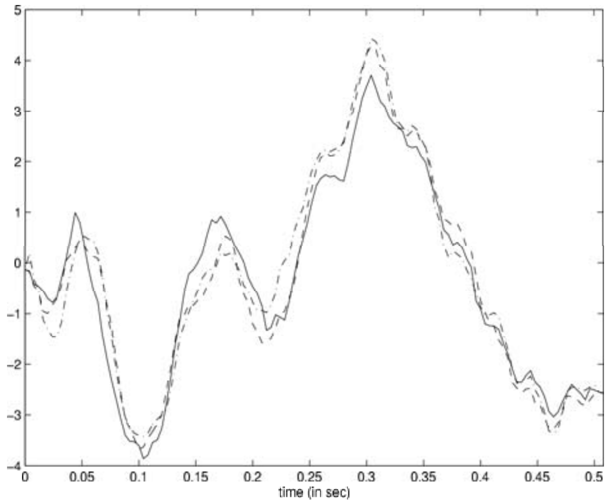

Figure 4: Target function $\hat{y}(t)$ evaluated as the mean of the original curves (solid line) and as the mean of the registered curves (dashed and dot -dashed lines).

3.2 Ramsay and Silverman's nonparametric estimation of warping function

Suppose that the function h has an integrable second derivative in addition to being strictly increasing. D^m will denote the derivative of order m operator ($m > 0$), the identity operator corresponding to $m = 0$, and, the value $m = -1$ yielding the partial integration operator:

$$D^{-1}h(t) = \int_0^t h(s)ds. \tag{3}$$

The class of monotone functions discussed here consists of those function h for which $\log(Dh)$ is differentiable and $D\{\log(h)\} = D^2h/Dh$ is Lebesgue square integrable. These conditions ensure both that the function is strictly monotone increasing ($Dh > 0$) and that its first derivative is smooth and bounded almost everywhere. Ramsay (1998) proved that every such function can be described by the homogenous linear differential equation:

$$D^2h = wDh \tag{4}$$

because a strictly increasing monotone function has a non-zero derivative, and hence the weight function w is simply D^2h/Dh, or the relative curvature of h.

Ramsay showed also that Equation (4), subject to the requirement that $h(t_1) = t_1$ and $h(t_N) = t_N$, has the solution:

$$h(t) = C\{D^{-1}\exp(D^{-1}w)\}(t) \tag{5}$$

where $C = t_N/D^{-1}\exp\{D^{-1}w(t_1)\}$. When w is constant, $h(t) = (C/w)\exp(wt)$, so that an exponential function has constant relative curvature.

The warping function h can be estimated non parametrically by minimizing the penalized squared error criterion:

$$\int \|\hat{y}(t) - y_i(h(t))\|^2 dt + \lambda \int w^2(t)dt, \tag{6}$$

for h in the smooth monotone family defined in Equation (5). Thus h is estimated by estimating its relative curvature w. The function w can be represented by a linear combination of B-spline bases. If $\hat{y}$ is observed discretely, $\int \|.\|^2 dt$ is replaced by the sum of squared errors. Ramsay and Li (1998) showed that small value of λ (say 10^{-4} to 10^{-2}) have worked well over a range of applications. However, we shall show in Section 6.3 that the choice of λ and of the number of knots of the B-spline basis used to represent w can be important (see also Ramsay and Li, 1997). The new method based on a direct approximation of h using fractional polynomials does not require such a choice. Ramsay and Silverman (1997) choose subjectively the smallest value of λ that still provided an interpretable estimate of the registered curve. They do not propose any strategy to determine the value of the smoothing parameter. We propose to use cross-validation to determine the optimal value of λ. However, that procedure is time consuming.

3.3 Marker registration and landmarks detection using wavelets

Matching several functions can be done by aligning individual locations of corresponding structural points (or landmarks) from one curve to another. Usually, an algorithm of landmarks based matching has the following steps:

- Definition of the structural points that will be used as markers of the signal: one can use minima, maxima or inflection points for example.
- Determination of landmarks that are common to a set of signals and of the landmarks that should be associated. This step is further complicated by the presence of outliers and by the fact that some landmarks of a given curve might have no counterpart in other curves.
- Computation of warping functions that synchronize the common landmarks.
- Deformation of the observed curves with the transformations obtained by landmarks based matching.

The two first steps could be performed manually but it is tedious if the number of signals is large. Bigot (2003 & 2005) proposed to use an automatic method, the scale-space approach to detect the structural points of a noisy signal.

Let $\hat{y}$ be a target function to which the function y_i is to be registered. Suppose we are given two sets of labelled landmarks $(\tau_{1,1}, \tau_{1,2}, \ldots, \tau_{1,N})$ and $(\tau_{2,1}, \tau_{2,2}, \ldots, \tau_{2,N})$ extracted respectively from the 2 curves $\hat{y}$ and y_i. The warping function h must satisfy:

$$\tau_{2,n} = h(\tau_{1,n}), \text{ for all } n = 1, 2, \ldots, N. \tag{7}$$

The Ramsay's method can be used to estimate h. A nonparametric approach based on the continuous wavelet transform is proposed in Bigot (2003 & 2005) to estimate the landmarks of a signal. A new tool, called the structural intensity, is introduced in Bigot (2003 & 2005) to represent the main features of a noisy signal via a probability density function which main modes are located at the significant landmarks of the unknown signal. In a sense, the structural intensity can be viewed as a smoothing method which highlights the main features of a curve observed with noise. In Bigot (2003), it is proposed to align the structural intensities to synchronize a set of a noisy curves. After registration the modes of the structural

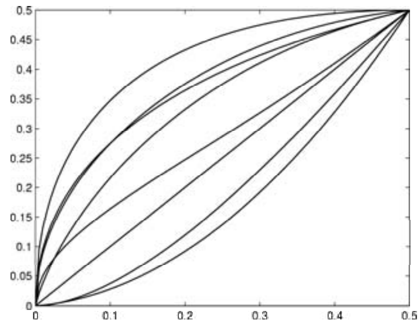

Figure 5: Some possible shapes of warping functions estimated using fractional polynomials.

intensities that are at the same locations correspond to the landmarks that have to be aligned. The computational cost of this approach only depends on the number of common landmarks and is therefore very low. Further details on this landmark-based registration technique can be found in Bigot (2003). This method can be sensitive to errors in feature location. Moreover, some features may be missing in some curves. We shall show in Section 6.5 that an adaptation of the method using fractional polynomials overcomes this problem.

4 Curve registration using fractional polynomials

Fractional polynomial regression models (Royston and Altman, 1997) is a flexible parametric method to model relationships in a sparse way. Models are chosen by including 2 powers from a predefined set $\mathcal{P}$. We used the set

$$\mathcal{P} = \{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}, \tag{8}$$

sufficiently rich for most practical purposes. The limited number of allowed values for the exponents in the fractional polynomials models limits the possible shapes for the warping functions. Some of these shapes are presented in Figure 5. The parametric model is:

$$\begin{aligned} h(t) = &\quad \alpha_0 + \alpha_1 t^{p_1} + \alpha_2 t^{p_2} && \text{if } p_1 \neq p_2 \text{ and} \\ h(t) = &\quad \alpha_0 + \alpha_1 t^{p_1} + \alpha_2 t^{p_1} \log(t) && \text{if } p_1 = p_2 \end{aligned} \tag{9}$$

with p_1 and $p_2 \in \mathcal{P}$. To estimate a warping function, we suppose that $h_i(t_1) = t_1$ and $h_i(t_N) = t_N$. That means:

$$\begin{aligned} \alpha_0 &= t_1 - \alpha_1 t_1^{p_1} - \alpha_2 t_1^{p_2}, & \alpha_2 &= \frac{t_N - \alpha_0 - \alpha_1 t_N^{p_1}}{t_N^{p_2}} && \text{if } p_1 \neq p_2 \\ \alpha_0 &= t_1 - \alpha_1 t_1^{p_1} - \alpha_2 t_1^{p_1} \log(t_1), & \alpha_2 &= \frac{t_N - \alpha_0 - \alpha_1 t_N^{p_1}}{t_N^{p_1} \log(t_N)} && \text{if } p_1 = p_2. \end{aligned} \tag{10}$$

Consequently:

$$\begin{aligned} \alpha_2 &= \frac{t_N - \alpha_0 - \alpha_1 t_N^{p_1}}{t_N^{p_2}} = \frac{t_N - t_1 - \alpha_1 (t_N^{p_1} - t_1^{p_1})}{t_N^{p_2} - t_1^{p_2}} && \text{if } p_1 \neq p_2 \\ \alpha_2 &= \frac{t_N - \alpha_0 - \alpha_1 t_N^{p_1}}{t_N^{p_1} \log(t_N)} = \frac{t_N - t_1 - \alpha_1 (t_N^{p_1} - t_1^{p_1})}{t_N^{p_1} \log(t_N) - t_1^{p_1} \log(t_1)} && \text{if } p_1 = p_2. \end{aligned} \tag{11}$$

For each of the 28 combination of exponents (p_1, p_2), we must only estimate parameter α_1 to determine the warping function $h_i(t)$. α_1 can be estimated by minimizing the following least squares criterion :

$$\sum_{n=1}^{N} \Big\{ \hat{y}(t_n) - y_i(h_i(\alpha_1, t_n)) \Big\}^2, \forall\, (p_1, p_2) \in \mathcal{P}, \tag{12}$$

which is equal to

$$\begin{aligned} &\textstyle\sum_{n=1}^{N} \Big\{ \hat{y}(t_n) - y_i(\alpha_0 + \alpha_1 t_n^{p_1} + \alpha_2 t_n^{p_2}) \Big\}^2 && \text{if } p_1 \neq p_2 \text{ and} \\ &\textstyle\sum_{n=1}^{N} \Big\{ \hat{y}(t_n) - y_i(\alpha_0 + \alpha_1 t_n^{p_1} + \alpha_2 t_n^{p_1} \log(t_n)) \Big\}^2 && \text{if } p_1 = p_2, \end{aligned} \tag{13}$$

where α_0 and α_2 are defined in Equations (10) and (11). The registered curves $y_i(h_i(\alpha_1, t_n)$ are estimated using B-spline. To obtain a strictly increasing warping curve, we add a penalty to the least squares criterion if the slope is negative:

$$\hat{\alpha}_1 = \arg\min \sum_{n=1}^{N} \Big\{ \hat{y}(t_n) - y_i(h_i(\alpha_1, t_n)) \Big\}^2 + \lambda \sum_{n=1}^{N-1} I\Big\{ h_i(t_n) > h_i(t_{n+1}) \Big\}, \tag{14}$$

where $\sum_{n=1}^{N-1} I\Big\{ h_i(t_n) > h_i(t_{n+1}) \Big\}$ is the number of points where the slope of the warping function is negative that means where $h_i(t)$ is not strictly increasing. Large values of λ have worked well over a range of applications (say 10^3, for example). We obtain 28 estimations of $h_i(t)$ for each of the 28 pair of powers (p_1, p_2) from $\mathcal{P}$. We select the model which minimizes the least squares criterion (12).

Non reported simulations mimicking the shape of the ERP curves in Section 6 revealed similar performances for the fractional polynomial method and the wavelet based method. The performance of the Ramsay and Silverman nonparametric method strongly depends of the choice of the smoothing parameter.

5 Example: Growth acceleration

We shall compare the acceleration in height of boys and girls. This example was presented by Ramsay and Silverman and use data from The Berkeley Growth Study (Tuddenham and Snyder, 1954). This study recorded the height of 54 girls and 39 boys between the ages of 1 to 18 years. Averaged acceleration curves for girls and boys are given by solid and dashed line in Figure 6. Girls and boys seem to go through the same pubertal growth cycles, but differ in 2 ways: the maximum acceleration is earlier for girls, but more intense for boys. The time shift prompts us to warp time for one gender in order to render its growth equivalent to the other. We can compare the registration of the boys' data to the girls' for the 3 above detailed

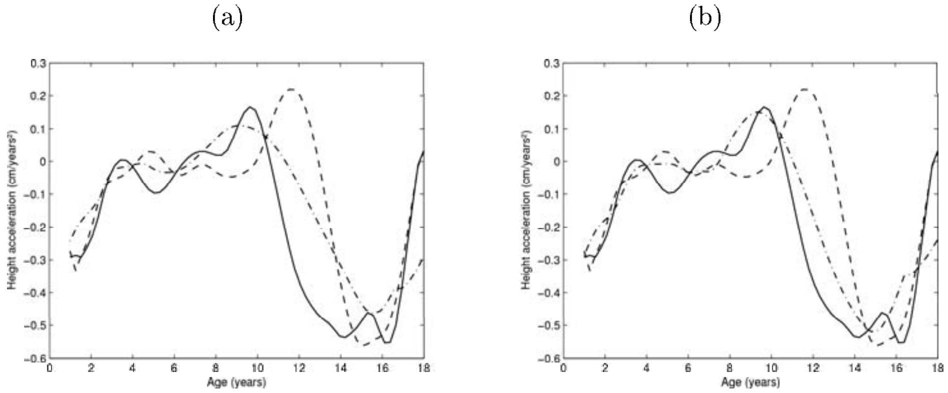

Figure 6: (a) The dashed curve corresponds to the average acceleration for boys, the solid curve is the average acceleration curve for girls and the dot-dashed curve correspond to the average acceleration for boys registered using Ramsay and Silverman nonparametric estimation of the warping function. (b) The dashed curve corresponds to the average acceleration for boys, the solid curve is the average acceleration curve for girls and the dot-dashed curve correspond to the average acceleration for boys registered using alignment of landmarks (maxima and minima) located using wavelets.

methods in Figure 6 and 7. The left panel of Figures 6 and 7 shows the Ramsay and Silverman nonparametric estimation of the average registered acceleration for boys in dot-dashed line. The average acceleration for boys registered using alignment of landmarks (maxima and minima) located using wavelets is shown in dot-dashed line in Figure 6(b). Figure 7(a) show average registered acceleration for boys (dot-dashed line) obtained using fractional polynomials. This result is better than for the 2 other methods (because the slopes are aligned). The warping function follows the parametric model:

$$h(t_n) = -5.1459 + 0.6909 t_n^{-2} + 5.4550 t_n^{1/2}, \qquad (15)$$

for $n = 1, \ldots, N$.

The corresponding warping functions $h(t)$ that register the boys' data to the girls' are shown in Figure 7(b). (Ramsay and Silverman nonparametric estimation in dot-dashed line, landmarks registration in solid line and our method of alignment based on fractional polynomials in dashed line). Because boys mature more slowly, the warping function is above the diagonal, shown as a solid line. In the following, we shall apply the presented registration techniques in the context of electroencephalograms (EEG) analysis.

6 Application of fractional polynomials registration to EEG analysis

6.1 Study presentation

We use data kindly made available by the pharmaceutical company Eli Lilly (Lilly Clinical Operations S.A., Louvain-la-Neuve, Belgium). They are part of a randomised, double-blind, placebo-controlled cross-over study performed with 15 healthy

(a) (b)

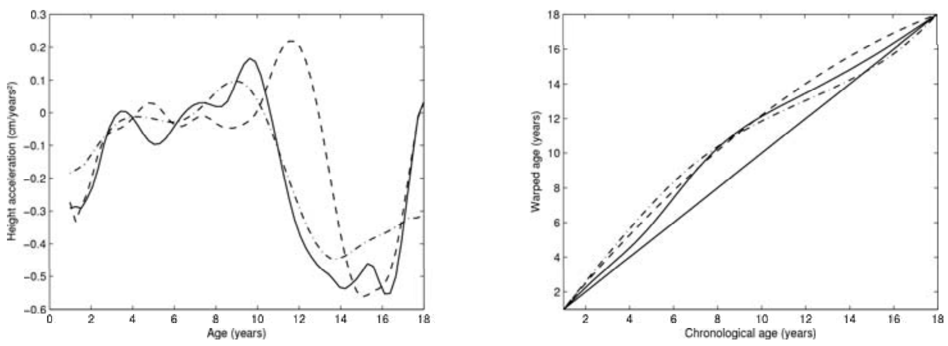

Figure 7: (a) The dashed curve corresponds to the average acceleration for boys, the solid curve is the average acceleration curve for girls and the dot-dashed curve correspond to the average acceleration for boys registered using our method of alignment based on fractional polynomials. (b) Warping functions for registering the boys' average acceleration to that of the girls (Ramsay and Silverman nonparametric estimation in dot-dashed line, landmarks registration in solid line and our method of alignment based on fractional polynomials in dashed line). Because boys mature more slowly, the warping function is above the diagonal, shown as a solid line.

male subjects. It is designed to assess the effects of a benzodiazepine (Lorazepam) on the cognitive functions through the analysis of EEGs. Lorazepam is extensively used as a sedative and anti anxiety agent in clinical practice (Sally and Roach, 2003). High concentrations of Lorazepam cause disorders of the memory (Danion et al., 1992). Two periods are scheduled, separated by a wash-out period of at least 7 days: in each period, one of the 2 treatments will be randomly administered once a day to each of the 15 volunteers. For each treatment and each subject, 12 EEGs are recorded for 3 minutes. Recordings start 1.5, 1 and 0.5 hours before the drug administration and 0.5, 1.5, 2.5, 3.5, 4.5, 5.5, 6.5, 7.5 and 25.5 hours after the Lorazepam (or placebo) administration.

For each recording, 28 EEG leads are recorded using an ear linked reference (see Jasper, 1958 for details about leads positions). Each EEG is recorded with a sampling frequency of 250 Hz for the 28 electrodes.

EEG were recorded while the subjects were submitted to auditory stimuli and asked to perform some task in response to the stimuli. This is the standard auditory "oddball" paradigm (Näätänen, 1992). Subjects have to listen to a series of stimuli involving two types of tones: frequent tones at 500 Hz and infrequent tones at 2000 Hz. Subjects are asked to count infrequent tones. The tones are presented as a randomised sequence with the infrequent tones representing 15% of the 130 submitted stimuli.

The goal of our work is to detect and to quantify the effects of the drug on the brain through the analysis of specific features of the recorded electroencephalograms named event-related potentials (see next section).

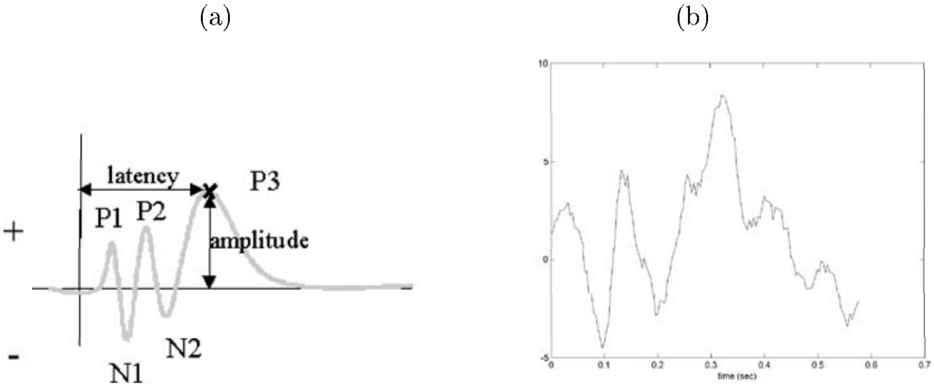

Figure 8: (a) Typical peaks in ERP. (b) Example of time averaged of ERP curve for electrode Cz.

6.2 Event-related potentials

EEG activity is present in a spontaneous way. It is affected by external stimuli (e.g. tone or light flash). The alteration of the ongoing EEG due to stimuli is named an event related potential (ERP).

ERP can be visualised during a short period following the stimulation time, with a response pattern which is more or less predictable under similar conditions. We call an ERP episode, the EEG signals observed several seconds after a stimulation. The amplitude of ERP is low comparing with the ongoing EEG. So, it is common practice to average in time several ERP episodes aiming to increase the signal to noise ratio in order to visualize the evoked activity.

The averaged ERP episodes present some well-known peaks (see Figure 8a). The ones usually pointed are the P100 or P1 (peak latency approximately 100 ms after stimulation), the P200 or P2 ($\sim$ 200 ms), and the P300 or P3 ($\sim$ 300 ms) peaks (see Figure 8a). The P300 peak is a good indicator of brain performance. It is often studied by neurophysiologists as an amplitude change or a delay in the occurrence of the peak* are signs of memory problem like with Alzheimer's disease or indication that a drug is affecting the brain. P300 can be considered as an expression of the central nervous system (CNS) activity involved in the processing of new information when attention is solicited to update memory representations.

We shall register the ERP curves to try to detect a treatment effect. In particular, we shall try to identify a significant treatment effect on the latency of the P300 peak. In the next section, we shall compare the registration using fractional polynomials with other registration techniques in the context of the alignment of ERP curves.

6.3 Registration of ERP curves

In this section, we shall compare the shapes of the registered curves obtained using the 2 classical nonparametric curve alignment techniques with our proposal.

Suppose that we want to align the 2 curves in Figure 9. Using the non parametric estimation of Ramsay and Silverman (1997), we find the warping function

*This delay is named latency (see Figure 8a).

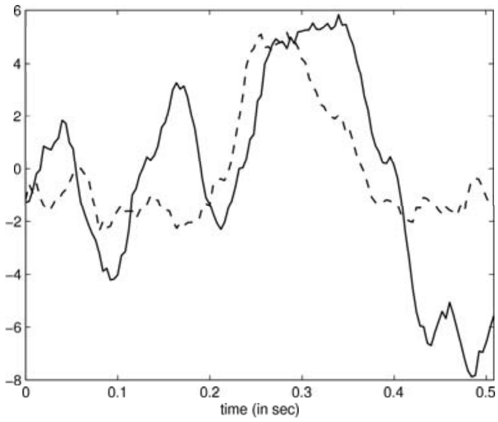

Figure 9: Two ERP curves to register: target function is the solid line.

and the aligned curves in Figure 10(a). The P300 peak of the aligned curve is right shifted compared with the original curve. However, the shape of the P300 peak is modified for the aligned curve: the peak is more thin than for the original curve. If the curves to register are too different (like here), the solution minimizing the difference between the curves could knock out important shape features. The large flexibility of the method is clearly a drawback here. As mentioned in Section 3.2, one can improve the result by increasing the number of knots in the B-spline basis or the smoothing parameter (λ). The problem is to determine an optimal value for it. Using the alignment of inflection points located using wavelets (Bigot, 2003 & 2005), one obtains the aligned curves in Figure 10(b). The P300 peak of the aligned curve is even more right shifted compared with the original curve than with the first method. However, the distortion of the peak is not so important. We could have chosen to align other landmarks, like maxima or minima, for example. However, the alignment of extrema (maxima and minima) led to a worse result: the P300 peaks do not seem to be correctly registered because the slopes of the peaks are not aligned. Finally, we use our method of alignment based on fractional polynomials (see Section 4). There is no distortion of the P300 peak (see Figure 11(a)) and the peaks are correctly aligned: the slopes of the peaks are aligned. The corresponding warping functions are compared in Figure 11(b). The shape of the warping functions is quite simple for the 3 methods. You can compare the registered curves in Figure 12.

In this section, we showed that methods which align the more correctly the P300 peaks without distortion are the alignment of inflection points detected with wavelets and the proposed method using fractional polynomials.

6.4 Results of the ERPs registration

We registered each curve under treatment on the corresponding curve under placebo for each of the 161 available paired curves (161 curves under placebo and the corresponding 161 curves under treatment).

You can see an example of registration for one curve under placebo on the corresponding curve under treatment and the warping function estimated by fractional

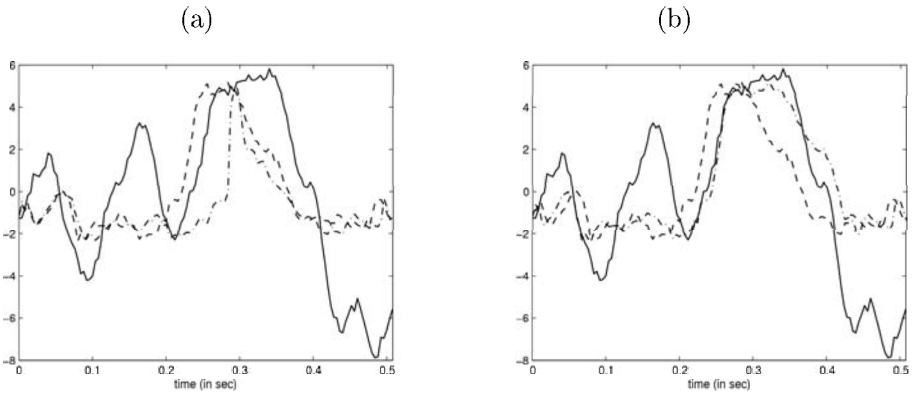

Figure 10: (a) Registered ERP curves using Ramsay and Silverman nonparametric method (dot-dashed line). The target function is the solid line and the curve to align is the dashed line. (b) ERP curves registered using alignment of inflection points located using wavelets. The target function is the solid line and the curve to align is the dashed line.

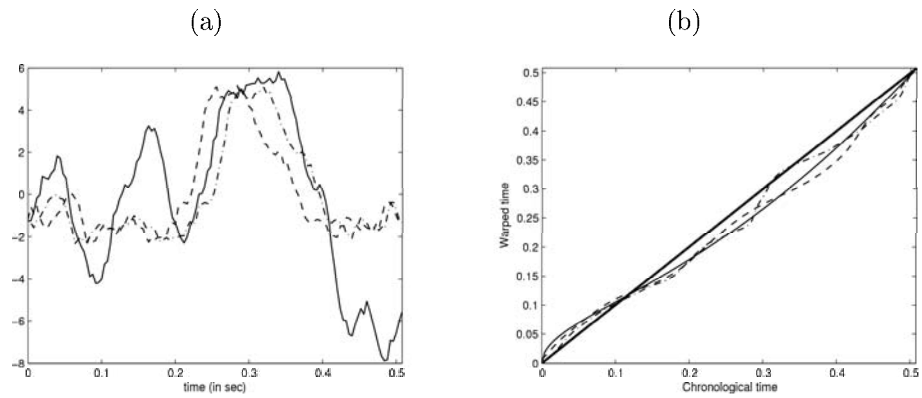

Figure 11: (a) Registered ERP curves using our method of alignment based on fractional polynomials (dot-dashed line). The target function is the solid line and the curve to align is the dashed line. (b) The corresponding warping functions estimated using Ramsay and Silverman nonparametric method (dashed line), using alignment of inflection points located using wavelets (dot-dashed line) and using our method of alignment based on fractional polynomials (thin solid line). Because the aligned curves are right shifted compared with the original curve, the warping functions are below the diagonal, shown as bold solid line.

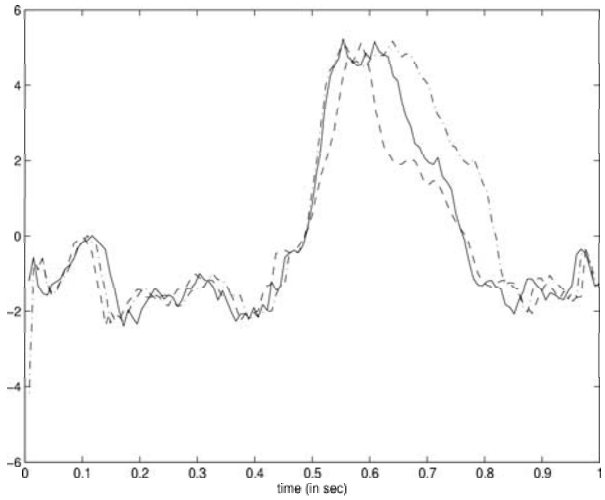

Figure 12: Comparison of the registered functions using Ramsay and Silverman non parametric method (dashed line), estimated using the alignment of inflection points with wavelets (dot-dashed line) and using fractional polynomials (solid line).

polynomials in Figure 13(a) and 13(b). The curvature of the warping function indicates that the curve is delayed under treatment. We found that more than 63% of the warping functions have a value larger than 0.3 for the time point corresponding to 300 msec after stimulus. You can see on Figure 14 the warping functions resulting from the registration of the curves under placebo on the corresponding curves under treatment for EEGs number 1, 6, 8 and 12. These EEGs were respectively recorded before, 2.5 hours, 3.5 hours (when Lorazepam reaches its peak plasmatic concentration) and 25.5 hours after the Lorazepam administration (when Lorazepam concentration in the plasma is almost null). Each curve corresponds to a subject.

The increase of latency is largest when Lorazepam reaches its peak plasmatic concentration (EEG 6 and 8) and lowest at the end of the experiment (EEG 12).

The limited number of allowed values for the exponents in the fractional polynomials models limits the possible shapes for the warping functions. The most common shapes are represented in Figure 5 (see Section 4). Among these shapes, the most used (more than 25% of the estimated warping functions) follows the parametric model:

$$\begin{aligned} h_i(t_n) &= \alpha_0 + \alpha_1 t_n^{1/2} + \alpha_2 t_n, \\ &= \alpha_1 t_n^{1/2} + \tfrac{t_N - \alpha_1 t_N^{p_1}}{t_N^{p_2}} t_n, \text{ because } t_1 = 0, \end{aligned} \tag{16}$$

for $n = 1, \ldots, N$. For the P300 curves registration, $t_1 = 0$, $N = 128$ and $t_N = 0.508$ msec. The functions h_i have a value larger than t_n (for $n = 1, \ldots, N$) if and only if the parameter α_1 is larger than 0. We found that more than 91% of the warping functions following the above model have α_1 positive.

The increase of latency under Lorazepam is due to a slower treatment of the information (which is associated with lower attention and bad performance of the

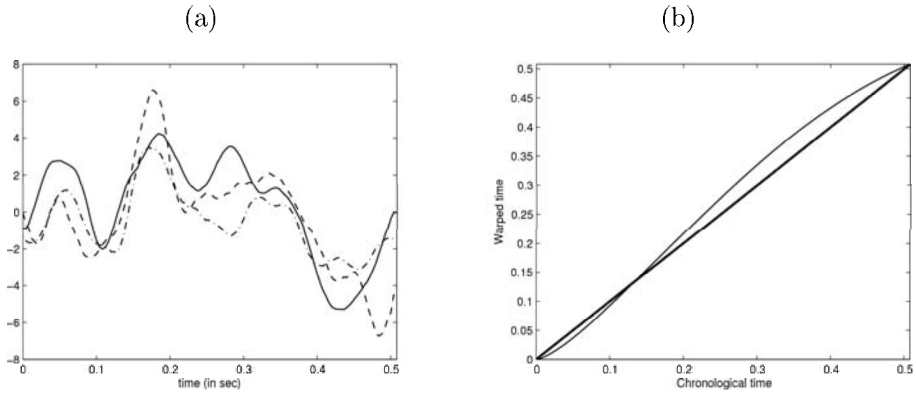

Figure 13: (a) An example of registration of one curve under treatment on the corresponding curve under placebo: the original curve under treatment is in dashed line, the target curve (curve under placebo) in solid line and the registered curve in dot-dashed line. (b) The corresponding warping function (thin solid line). Because the aligned curve is left shifted compared with the original curve, the warping function is above the diagonal, shown as bold solid line.

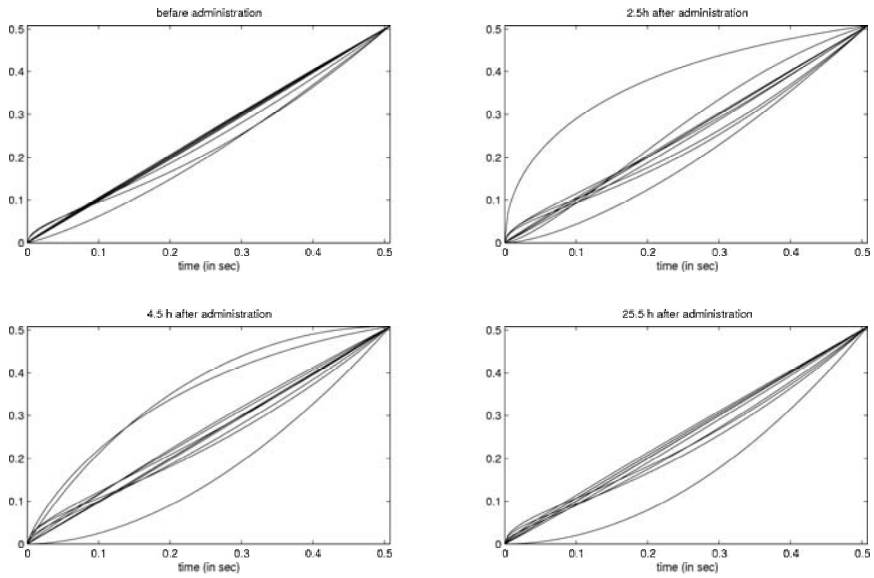

Figure 14: Warping functions resulting from the registration of the curves under treatment on the curves under placebo for EEG number 1 (before Lorazepam administration, upper left panel), 6 (2.5 h after administration, upper right panel), 8 (4.5 h after administration, lower left panel) and 12 (25.5 h after administration, lower right panel), each curve in a frame corresponding to one of the 15 subjects.

(a) (b)

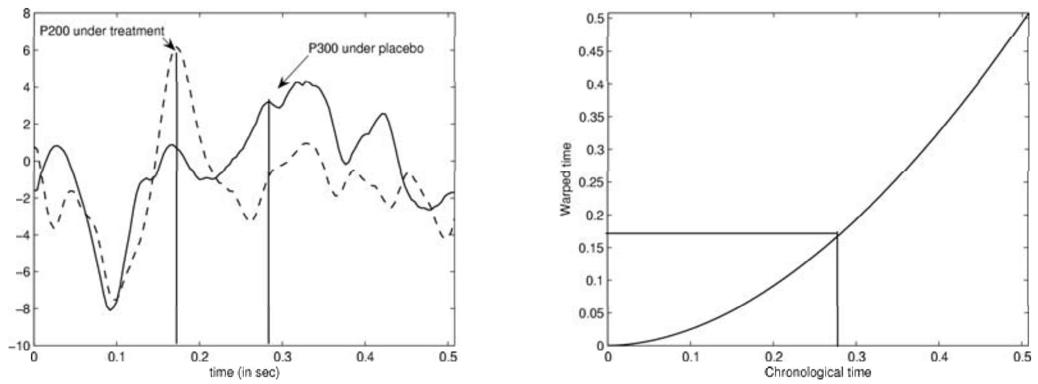

Figure 15: An example of the bad registration of one curve under treatment on corresponding curve under placebo: the P300 peak under treatment is sometimes aligned to the P200 peak under placebo (The solid line is the curve under placebo, the dashed line is the curve under treatment)

memory, see Herrmann and Knight, 2001).

6.5 Discussion and improvement

We found that more than 63% of the warping functions have a value larger than 0.3 for the time point corresponding to 300 msec after stimulus. When the registration seems to show that the P300 peak is in advance under treatment (27% of the estimated warping functions), it is often due to a big decrease of the amplitude of the peak under treatment. For example, in Figure 15(a), the decrease of the amplitude of the P300 peak is paired with an increase of the amplitude of the P200 peak. Actually, the estimated warping function (see Figure 15) erroneously aligns the P300 peak under treatment on the P200 peak under placebo. Moreover, you can see in Figure 16 that the maximum difference $h(t) - t$ can be more than 0.1 (diagonal shown as the bold line). That means that some peak can be erroneously registered on another peak as the time lag between 2 peaks is about 100 ms. For example, the P300 peak under placebo is sometimes aligned with the P200 peak under treatment (see Figure 16).

To avoid this problem, we propose to add a large penalty to the least squares estimation criterion when $h(t) - t$ is greater than 0.1. For the previous example, we obtain the results in Figure 17.

When we registered each curve under treatment on the corresponding curve under placebo for each of the 161 paired curves available (161 curves under placebo and the corresponding 161 curves under treatment), we found the same results as before. We found that more than 65% of the warping functions have a value larger than 0.3 for the time point corresponding to 300 msec after stimulus. Once again, this indicates that the P300 curve is delayed under treatment.

We would have had the same problem using landmarks registration because this method can be sensitive to errors in feature location or if some features are missing

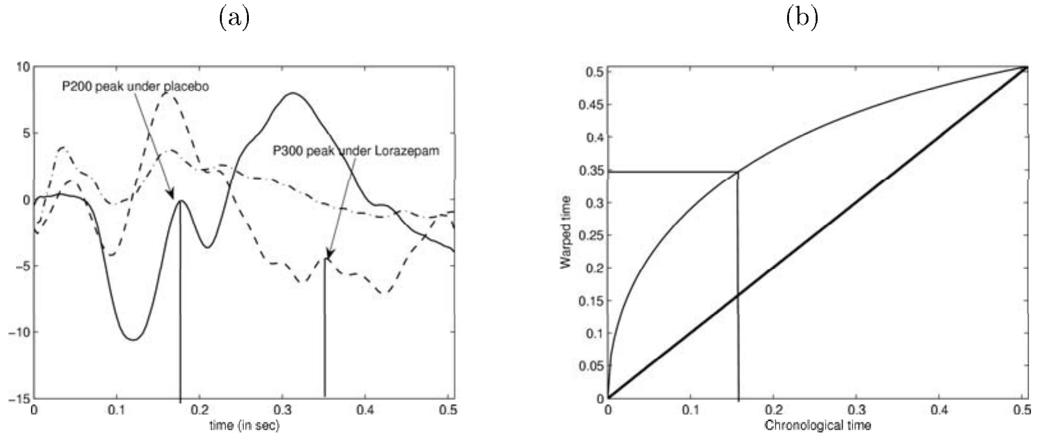

Figure 16: An example of the bad registration of one curve under treatment on corresponding curve under placebo: the P300 peak under placebo is sometimes aligned with the P200 peak under treatment (The solid line is the curve under placebo, the dashed line is the curve under treatment and the dot-dashed line is the registered curve.)

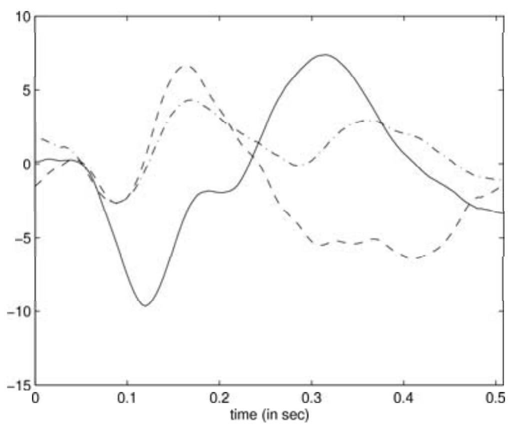

Figure 17: An example of the improved registration of one curve under treatment on corresponding curve under placebo. The solid line is the curve under placebo, the dashed line is the curve under treatment and the dot-dashed line is the registered curve.

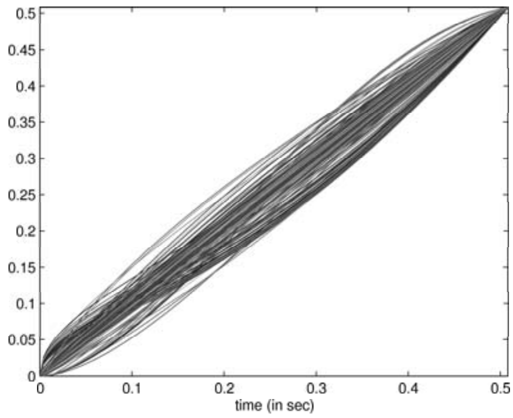

Figure 18: Warping functions result of the improved registration of the curves under treatment on the curves under placebo.

in some curves. This adaptation of the registration using fractional polynomials overcomes this problem.

Conclusion

In this paper, we presented a new method of registration based on the estimation of the warping functions using fractional polynomials. This method restricts the shape of the warping functions and avoid major distortions of important peaks like the P300 peak. This is a clear advantage over nonparametric registration methods. We used this new method to detect a treatment effect. The analysis of the estimated warping functions showed an increase of the latency of the P300 peak after Lorazepam administration. The method can be adapted to avoid some peak to be erroneously registered on another peak.

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