An application of LARY_C : study of Cardio-vascular Rhythms Perturbations according to a Sleep Pathology (Periodic Leg Movements)

Claire Médigue, Christophe Vermeiren, Patrice Bourgin, Pierre Escourrou

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N 2597

Juin 1995

PROGRAMME 5

ISSN 0249-6399

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Programme 5 — Traitement du signal, automatique et productique
Projet Sosso

Rapport de recherche n ° 2597 — Juin 1995 — 35 pages

UnitØ de recherche INRIA Rocquencourt
Domaine de Voluceau, Rocquencourt, BP 105, 78153 LE CHESNAY Cedex (France)
TØlØphone : (33 1) 39 63 55 11 -- TØlØcopie : (33 1) 39 63 53 30

Abstract: LARY_C is a software package, developped in the synchronous, data flow, parallel language SIGNAL, primary dedicated to the Autonomic Nervous System (ANS), through the analysis of physiological signals and their correlations: Heart Rate (HR), Arterial Blood Pressure (ABP), breathing, motility and electroencephalographic activity (EEG).
Our aim is to illustrate the new approach given by LARY_C for the processing of polygraphic recordings, through a clinical application, the nocturnal Periodic Leg Movements (PLM).

Polygraphic recordings analysis, usually visually done, can't provide all the needed information, in particular the relations between rhythms are difficult to extract. The LARY_C library of medical signal processing provides a condense representation of the physiological rhythms; the SIGNAL synchronous environment provides the necessary tools to assess the relationships between these rhythms, in order to automatically produce a set of (cardiovascular) parameters related to an event (a PLM).

We analysed the magnitude of the changes on HR and systolic ABP, the ANS behaviour through their activity in high and middle frequencies, the delays betwee n the beginning of cardiovascular perturbations and the movement, and the relations with cortical activation reflected by an augmentation of α activity on the EEG. On one hundred PLM in a typical patient, cardiovascular changes related to movements are significant; the more often, they precede the movement and they are even more important in presence of high α-activity. These preliminary results show PLM not only like a central nervous system dysfunction addressed to the motor system but rather like a dysfunction of reticular excitability responsible for motor, ANS and cortical activation. They ask the question of long term consequences of these cardiovascular swings and therefore of their specific treatement in addition to sleep and motor desorders one.

Such an automatic approach seems appropriate for a better understanding of the physiopathology and to help the diagnostic in a large variety of clinical applications involving non-stationary, long duration polygraphic signals.

Dr. Patrice Bourgin and Pr. Pierre Escourrou are with Explorations Fonctionnelles, hôpital Antoine Béclère, Clamart

Key-words: time-frequency methods, synchronous language, autonomic nervous system, physiological signals, periodic leg movements

(Résumé : tsvp)

Une application de LARY_C: étude des Perturbations des Rythmes Cardio-vasculaires en relation avec une Pathologie du Sommeil (Les Myoclonies)

Résumé : LARY_C est un logiciel développé dans le langage synchrone flot de données et parallèle SIGNAL, essentiellement dédié à l'étude du Systèm Nerveux Autonome (SNA), à travers l'analyse des rythmes physiologiques et de leurs corrélations: Rythme Cardiaque (RC), Pression Artérielle (PA), respiration, motilité et activité électro-encéphalographique (EEG).
Notre but est d'illustrer la nouvelle approche apportée par LARY_C au traitement des signaux polygraphiques, à travers l'application clinique des Myoclonies.

L'analyse des enregistrements polygraphiques, géneralement faite de manière visuelle, ne peut fournir toutes les informations nécessaires, en particulier restituer les relations entre rythmes. La librairie de traitement du signal médical de LARY_C permet une représentation condensée des rythmes physiologiques; l'environnement synchrone de SIGNAL fournit les outils nécessaires à l'étude des relations entre ces rythmes, de manière à calculer automatiquement un ensemble de paramètres (ici, cardiovasculaires) liés à un évènement (ici, une myoclonie).

Nous avons analysé l'amplitude des changements du RC et de la PA , le comportement du SNA à travers l'activité de ces rythmes en haute et moyenne fréquence, les délais dans l'apparition des perturbations cardiovasculaires et des myoclonies, et leurs relations avec l'activation corticale reflétée par une augmentation de l'activité α sur l'EEG. Sur une centaine de myoclonies chez un patient typique, les modifications cardiovasculaires en regard du mouvement sont très significatives; le plus souvent elles précèdent le mouvement et sont en outre significativement plus importantes en présence d'activité α. Ces résultats préliminaires ne font plus des Myoclonies une maladie neurologique à destinée motrice, mais plutôt une dysfonction de l'excitabilité réticulaire responsable d'une activation motrice, autonomique et corticale.

Cette approche semble appropriée pour une meilleure compréhension de la physiopathologie et une aide au diagnostic dans une grande variété d'applications cliniques impliquant des enregistrements polygraphiques, non stationnaires et de longue durée.

Mots-clé : méthodes temps-fréquences, language synchrone, système nerveux autonome, signaux physiologiques, myoclonies

Contents

1 Introduction

The PLM are defined as unvoluntary short legs movements occurring during sleep; these movements last from 0.5 to 6 seconds, are repeated at least 4 times and separated by 5 to 90 seconds. PLM are accompanied or not by an arousal. They are sometimes associated with insomnia and excessive daytime sleepiness. This syndrome has a large prevalence, 29% over 50 years [5], but its etiology and its consequences on the cardiovascular system are unknown [19].
Very few studies analysed the cardio-vascular behavior during PLM: Ali reported one case [1]; Bourgin [6] focalised on this point by analysing six patients and showed ABP and HR changes associated with PLM. The aim of this study is to confirm these previous results and to analyse more precisely the ANS behavior during the PLM.

Indeed, cardio-vascular perturbations are related to the Autonomic Nervous System (ANS) behaviour; this part of the Nervous System is involved in regulating all the vital functions, particularly the cardio-vascular and respiratory systems, to maintain the vital balance and to allow the organism to adapt to changes in its state. The study of the cardio-vascular rhythms (Heart Rate (HR), Arterial Blood Pression (ABP)) and their variabilities is already well known as a noninvasive mean of investigating the ANS [23].
On the raw rhythms, only the global, resulting effects of the two components, sympathetic and parasympathetic (vagal), of the ANS balance are seen. On the HR, for example, the global effect of a sympathetic activation is an acceleration, whereas the effect of a parasympathetic activation is a deceleration. It is possible to describe more precisely the participation of each composant of the ANS, through HR and ABP variabilities. Among the frequencies bands known to reflect the ANS activity, two of them are of interest for this study:
- An high frequency band (HF):
Above 0.15 Hz, it reflects the parasympathetic tone alone; on the HR, it is called Respiratory Sinus Arrhythmia (RSA) and it is the part of variability related to the respiratory cycles; RSA is described as an increase in heart rate during inspiration and a decrease during expiration. This high frequency activity is also found on the ABP variability with an opposite phase [12] . Within mechanisms involved, the blockade of the centrally generated inspiratory drive and the blockade of lung receptors during inspiration are responsible for a phasic vagal inhibition [8]; these respiratory effects, respiratory cycle and lung volume changes, modulate the ABP, through baroreceptors stimulation.

- A middle frequency band (MF):
Between 0.03 and 0.15Hz, it is related to the cardio-vascular control of the ANS, through the arterial baroreceptors and the peripheral vasomotor regulation. The baroreflexes involve the two components, sympathetic and parasympathetic whereas the vasomotor activity involves the sympathetic α effect on vessel contraction; the baroreflex frequential activity, called Mayer waves, gives a peak rather around 0.1Hz; the vasomotor one, rather around 0.04Hz [23, 24]
As baroreflex responses derive from interactions between multiple reflex inputs, the situation is very complex and the frequential activity could be increasedtoward 0.1Hz in case of preponderant vagal influence ; conversely, it could be reduced toward 0.05Hz in case of preponderant sympathetic influence [23].

This kind of pathology raises different questions:

1. How to automatically quantify the magnitude of the perturbations occurring on the cardio-vascular rhythms, in the surrounding of a PLM?
2. How to study the ANS behaviour, through the activity in the high and middle frequency bands of these rhythms, during these short periods ?
3. Can we precise relations of causality between the different rhythms? could PLM be responsible for the cardio-vascular perturbations, or a central command responsible for cardio-vascular and motility perturbations together?
4. Are these perturbations more important during cortical activation?

To answer these questions, we used in particular two properties of LARY_C:

1. The synchrone concept of SIGNAL:
   We had to respect temporal relations between heart beats occurrences, arterial systolic blood pressure peaks and PLM occurrences; the SIGNAL language has precisely the primary property to permit and to verify relations between rhythms. To our knowledge, no study so far, in this medical domain, has automatically established links between different rhythms; the more often, events on different signals are detected in parallel and their relations are visually determined.
   Thus, this property allowed us to automatically detect PLM and to average on line the cardio-vascular variables corresponding, over these specific periods. In the same way, it allowed us to measure delays between the beginnings of HR, ABP, motility perturbations to precise relations of causality between them.

2. The time-frequency method of the medical librairy:
   To study the ANS behaviour, we had to follow precisely short time variations in amplitude, as they happen surrounding a PLM in the high and middle frequency bands; as the classical FFT is not adapted to nonstationary signals, we used the Smoothed Pseudo Wigner Ville Transform (SPWVT).

2 Clinical material and methods

2.1 Subjects

Two patients, whithout another pathology were recorded during a night at the Antoine Béclère hospital. One presented a period with PLM of about two hours. On this period it was possible to study 97 episodes of PLM that we called 'PLM subjects': a subject is the period surrounding a movement which contains the HR and ABP perturbations. All preliminary statistic results were obtained from this first patient recording. The second patient recording was only visually examined to roughly control if he had the same behaviour. Indeed, this first study was mainly devoted to build a protocol and to see what other research axis has to be developped.

2.2 Recording

Standard polysomnographic recordings were performed during a night. Data were collected on paper tracings and simultaneously digitized by the DELTAMED software package at 128 Hz and stored on optic disk.
Five signals were of interest for this study and processed in LARY_C: electro encephalographic (EEG), electromyographic (EMG) on left and right anterior tibialis, electrocardiographic (ECG), arterial blood pressure (ABP). ABP is continously measured on finger by a non invasive mean, using the Finapres (Ohmeda 2300) [12]. Correspondence between paper tracings and digitized recordings was ensured by a time counter in LARY_C: it allowed to locate events of interest and to verify them on paper tracing.

3 Signal processing

The new approach given by LARY_C depends on two points: the use of the synchronous language SIGNAL to analyse relationships between rhythms and the library of medical signal processing methods to construct these rhythms.

3.1 The SIGNAL language

SIGNAL is a data flow, oriented synchronous language for describing relationships among signals at various sampling rates; signals are sequences of events with associated values. The conception of time in SIGNAL is a minimal one, serving only to describe an application in a determinist way (same computations always run in the same order); in particular, no duration is considered at this level. The discrete time associated with a signal is called the 'clock' of the signal. The relationships among events are:
- precedence: occurrences of a same signal are totally ordered;
- simultaneity: two occurrences of different signals may be simultaneous or not;
- functional: values associated with simultaneous events may by linked by a computation expression.
SIGNAL provides a small set of temporal operators, sufficient for expressing all kinds of synchronization relationships among the clocks of the signals.
The application may be seen as a directed graph; arcs represent signals and dependancies between inputs and outputs of the nodes; a node express temporal and functional constraints of the signals that it connects. The SIGNAL compiler verifies the global coherence of this complex relational system, and builds the corresponding automaton for a target machine [2, 13, 14, 15, 16].

3.2 LARY_C

We elaborated a complete processing chain in LARY_C, a software package for physiological rhythms analysis, previously described. [16, 26, 27] ; LARY_C is based on the SIGNAL industrial environnement of development , SILDEX [1]. LARY_C is supported by UNIX and X Windows. The flow chart of the whole parallel processing for this application is shown on Fig.1; it is divided into the following major blocks:

3.2.1 Rhythms detection

A parallel preprocessing of the raw signals gives the resulting rhythms:
- From the electro-cardiographic signal (ECG) to the heart rate (HR)
- From the arterial blood pressure signal to the systolic pressure rhythm (ABP)
- From the legs movements signal (EMG) to a boolean rhythm 'movement-state/no movement state' (lm)
- From the electro-encephalographic signal (EEG) to the α activity signal

[1] TNI,Technopôle Brest-Iroise, ZI du Vernis, 29608 Brest Cedex (France)

3.2.2 Rhythms processing

A time-frequency processing of the HR and the systolic ABP, by the mean of the Smoothed Pseudo Wigner Ville Transform (SPWVT), studies the variabilities of interest on these two rhythms

3.2.3 Cardiovascular parameters extraction accompaning the PLM

After the resynchronisation of the delays introduced by the different steps, an automatic establishement of links between resulting rhythms makes the selection of specific periods (e.g. epochs at the beginning of rhythms changes, at the maximum of the changes, in the surrounding of a movement) and allows to compute over them elementary statistics; it gives also the delays between perturbations on the different rhythms.

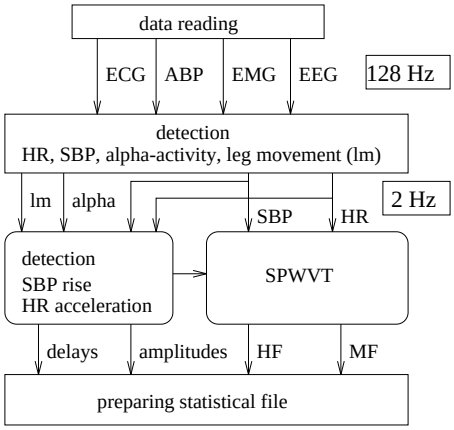

Figure 1: *Flow chart of the whole parallel processing of the polygraphic recording*

3.3 Signal processing methods

3.3.1 ECG signal processing

From the ECG signal, we extract the heart rate.
The raw ECG is prefiltered with a Finite Impulse Response filter (FIR), in order to derivate it and to reinforce the QRS complexes. The detection is based on the correlation between the filtered ECG and the filter response whose shape is a derivated QRS: each time a detection occurs, the response is modified by the current

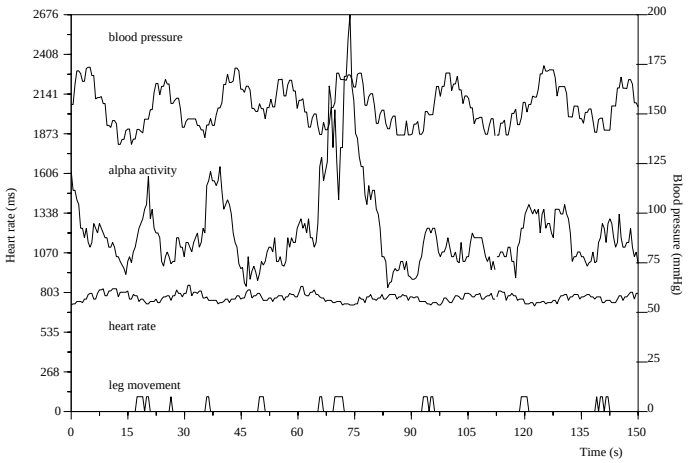

Figure 2: *The different rhythms at 2 Hz after resynchronisation. The α-activity is in arbitrary units and the leg movement signal is a boolean one: true during the movement and false elsewhere.*

QRS derivated complex on the ECG (eq. 1); the filter response is initialized with a derivated QRS shape and the forgetting factor$a$ is fixed to 0.1 [26, 14].

$$\text{response}[i] = a * \text{response}[i-1] + (1-a) * QRS'[i] \tag{1}$$

An adaptative threshold detects the R peaks and returns the RR signal or heart rate; this RR signal is the serie of the distances between two R peaks, e.g. the number of ECG samples between two R peaks; this distance is usually translated in ms. This heart rate is in fact an unregularly sampled signal. An equidistant resampling [3] at 2Hz is applied.

3.3.2 ABP signal processing

From the ABP signal, we extract the maximal systolic blood pressure (SBP).
The detection is based on a modified version of the algorithm of Pan [22, 11, 26].
A sample and hold technique is used for the construction of an equidistant sampled signal at 2Hz.

3.3.3 EEG signal processing

From the EEG signal, we extract the α activity.
The original EEG signal is subsampled at 64Hz. A Fast Fourier Transform is performed on a sliding window of 256 points. The area from 8 to 11Hz is integrated and the resulting signal is subsampled at 2Hz.

3.3.4 Body Movements signal processing

The raw legs movements signals of the two sensors are added and a variance signal is calculated on a sliding window of 50 points. A fixed threshold is applied on this short term variance and detects the beginning and end of a movement; it determines a boolean signal corresponding to the states motility/no motility.

3.3.5 HR and systolic ABP variabilities analysis

The RR and systolic ABP rhythms are processed by a time-frequency method, the Smoothed Pseudo Wigner Ville Transform (SPWVT), which gives the possibility to have a dynamic evaluation of the spectral power and to precisely follow the short time transitions of non-stationary signals like the HR and ABP. Time-frequency mapping is based on the discrete Wigner distribution and decomposes the signal as a function of time and frequency [9, 21, 25]. A maximal time and frequency resolution is achieved by using independent time and frequency smoothing. Before the SPWVT, the RR signal was processed by a detrending to avoid low frequencies below 0.03Hz, which could affect the higher frequency bands of interest for this application.

$$\mathrm{spwvt}(n,\nu) = 2 \sum_{k=-N+1}^{N-1} |h[k]|^2 \left[\sum_{m=-M+1}^{M-1} g[m]x[n+m+k]x^*[n+m-k] \right] e^{-4i\pi\nu k} \tag{2}$$

- x is the analytic signal derived from the RR or the systolic ABP rhythm, sampled at twice the Nyquist frequency
- x^* is the complex conjugate of x.
- a temporal smoothing on *2M-1* samples is computed, using the window g, here with a rectangular form

- each sample resulting from this operation is windowed with h, the frequencial window with a gaussian form on *2N-1* samples
- the Fast Fourier Transform of this window provides a spectrum at one instant n on *2N-1* frequency bins (0.5 normalised frequency)
- the frequencial smoothing (*h[k]*) is of 128 samples.
- the temporal smoothing (*g[m]*) is of 24 samples.

In this study, the chosen frequency bands from the ν spectrum were the HF and the MF frequency bands [23]; these bands were adjusted to the patient spectral activity in HF and MF as shown on Fig 3; so, the HF band was chosen between 0.24-0.6Hz; indeed, this patient presented a very fast breathing, around 0.3 and sometimes 0.5Hz; the MF band was chosen between 0.03-0.015Hz; the 'instantaneous' power spectrum was computed each instant, over each frequency band and results are expressed in ms^2/Hz.

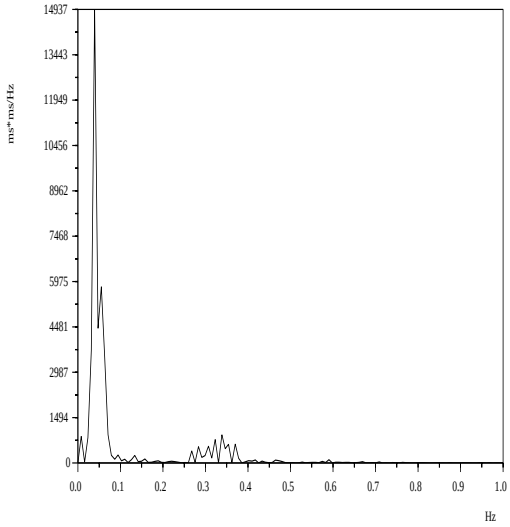

Figure 3: *Power spectrum of the PLM patient*

3.3.6 Rhythms changes detection

The rhythms changes are an HR acceleration and a systolic ABP augmentation. They were processed by a low-pass Finite Impulse Response filter (FIR) to avoid short term oscillations; A simple change of the filtered signals slope on a sliding

window of 5 points determined the beginning and end of the changes. As ABP changes were not as smooth as RR changes, a criterium of change percent (5%) was added to ABP augmentation detection.

3.4 Establishment of links between resulting rhythms

We established links between the following rhythms: HR, systolic ABP, the signals of amplitude in HF and MF for HR and ABP, and the rhythm of PLM occurrences. They were all resampled at 2Hz to be processed together and resynchronised because the different processing steps introduce delays; this was done by using filters with a linear phase, producing a constant time delay which can be exactly known.
After resynchronisation, a 'PLM subject' was automatically defined in LARY_C: a 'PLM subject' is the set of cardiovascular variables extracted in the surrounding of a movement; these variables are stored at the beginning and at the end of a change (HR acceleration and systolic ABP rise) accompaning a movement and are averaged on 5 points (2.5 sec). Only PLM subjects whose movement starts were separated by at less 30 points (15 seconds) were automatically selected; this is done to have a sufficient period for studying the rhythms changes between two PLM.

3.5 Application on a patient: methods parameters

Table I summarises the main parameters used in the signal processing chain, for the studied patient; some of them will be modified for a generalised study: new recordings will be digitalized at 256Hz and the threshold of the HF band could be lower, to include the respiratory activity of all subjects.

Table I: Methods parameters

Parameters	Values
Sampling frequency on raw signals	128 Hz
Resampling frequency on resulting rhythms	2 Hz
Threshold of amplitude for PLM detection	6000
High frequency band (HF)	0.24 Hz - 0.6Hz (peak on 0.3)
Middle frequency band (MF)	0.03 - 0.15 Hz (peak on 0.05 Hz)
Threshold of amplitude for ABP rise detection	5 %
Minimal duration between two starts of PLM	30 points/15 sec
Window length for means	5 points/2.5 sec

Figure 4: *Definition of a PLM subject*

4 Statistical processing

All tests were performed on the 97 'PLM subjects' as they were defined above: a 'PLM subject' is the set of cardiovascular variables stored at the beginning and at the end of a change; when stored at the beginning of the change, they make the 'basic-state' variables (or control); when stored at the end of the change, they make the 'maximal-change-state' variables (Fig.4). This set of variables includes:
- the raw RR and its variables in HF and MF
- the raw systolic ABP and its variables in HF and MF

Differences according to states : the analysis of differences between 'basic-state' and 'maximal-change-state' was done to evaluate the importance of the cardio-vascular perturbations on the raw RR and ABP rhythms and on the HF and MF signals.

Differences according to α cortical activity : we studied the relations of amplitude between the cardio-vascular changes and the α cortical activity. Thresholds of

Figure 5: *PLM, systolic ABP and α activity on EEG*

4.1 Classical hypothesis tests

For the first approach, the between-states differences were assumed by the non parametric test of Wilcoxon which is a paired test, comparing differences within the same subject (and also by its parametric equivalent, the t-test paired).
For the second approach, the between-α groups differences were assumed by the non parametric test of Mann-Whitney, an unpaired test.

4.2 Mutivariate Data Analyses (MDA)

We choose the most significant variables at the classical hypothesis tests to perform the following analysis: Principal Component Analysis (PCA), Linear Discriminant Analysis (LDA) and Factorial Discriminant Analysis (FDA). Their principle is based on the choice of the best linear combination of the chosen variables to describe a population and to explain the contribution of each of them in the between-groups discrimination.
For the first approach, one group was constitued by the 'basic-state' variables, the other one by the maximal-change-state variables.
For the second approach, each group was constitued by the whole 'PLM subject' (variables in basic and maximal state), but one group was $\alpha +$ and the other, $\alpha -$.

Figure 6: *PLM, ABP, RR signals on a 5 mn sleep recording Each PLM is separated from each other by approximatively 25 seconds; the mean amplitude of the HR acceleration is 55 ms with a maximum of 100ms; the mean amplitude of the ABP augmentation is 30 mmHg with a maximum of 60 mmHg.*

5 Clinical results

5.1 Cardiovascular and autonomic perturbations

The figures 6, 7 and 8 illustrate the results.

Classical hypothesis tests give the following results, with a great significance for all the variables.
The HR presents a significant global acceleration (mean value: 55.19 $\pm$ 18 ms) accompanied by a fall of HF and an increase of MF amplitudes (Table II).

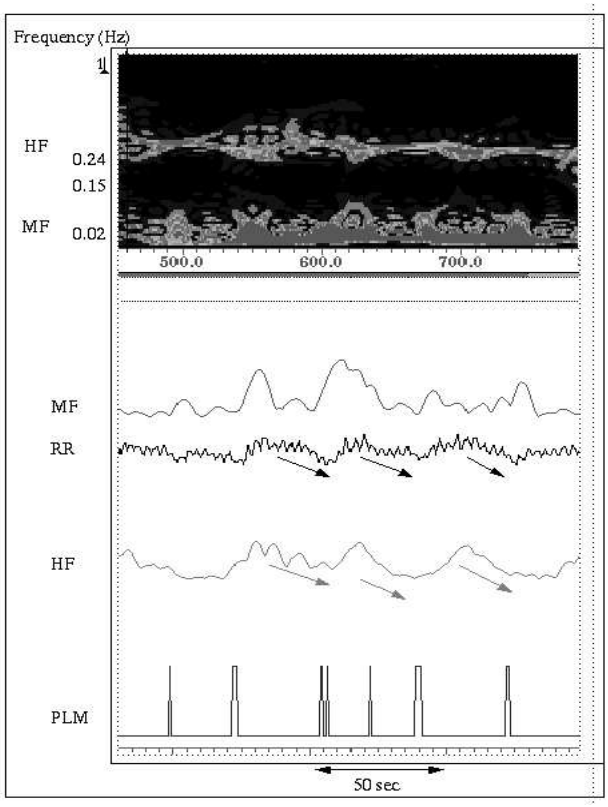

Figure 7: *SPWVL applied to the HR: evolution in HF and MF powers during a 2 mn sleep recording. It clearly appears that the HF power falls whereas the MF power increases during HR acceleration. Two representations of the SPWVL are done: on the grey-scale picture, one can follow the time (in x axis), the frequency (in y axis) and the variations of the HF and MF instantaneous powers in grey-scale (as a matter of fact, a color-scale); under, these power variations can be followed along the y axis.*

The systolic ABP presents a significant global increase (mean value: 30 ± 9 mmHg), accompanied by a great increase of MF amplitude but no significant modification in HF amplitude (Table III).

Figure 8: *SPWVL applied to the ABP: with the same representation as previously, one can see that the MF power on ABP has greater variations than the MF on RR whereas the HF power has little ones.*

Table II: Heart Rate (RR)

	Basic state	Max of change	Amplitude	Probability
RR (ms)	810.6	755	55.19±18	****
HF (ms/Hz)	791 500	574 600	217 000	****
MF (ms/Hz)	1.17 e6	1.4e6	267 300	***

(*:p≤.05;**:p≤.01;***:p≤.001;****:p≤.0001;NS:non significant)

Table III: Systolic Arterial Blood Pressure (ABP)

	Basic state	Max of change	Amplitude	Probability
ABP ($mmHg$)	142	172	30± 9	****
HF ($mmHg^2/Hz$)	36 316	39 000	2700	NS
MF ($mmHg^2/Hz$)	273 000	514 300	268 000	****

(***:p≤.001;****:p≤.0001;NS:non significant)

For multivariate data analysis the chosen variables were the raw RR, the HF of the RR, the raw systolic ABP, the MF of the ABP; one group was constitued by the 'basic-state' variables, the other group was constitued by the 'maximal-change-state' variables.

The LDA shows a very significant discrimination (98.97 % at LDA) between the two groups of variables.

The FDA details the participation of the cardiovascular variables in this discrimination: it shows opposite correlation in RR and ABP variables; this correlation is strongest for the raw RR and ABP rhythms , then for the MF of the ABP (Table IV).

The PCA describes this discrimination: the variables of the 'basic state' occupy the left part of the principal factor plane whereas the variables of the 'maximal-change-state' occupy the right part of it (Fig.9).
The first factor, x represents the between-states separation with 61% of the whole variance: it represents the opposition between the RR and the ABP variables, e.g.**the RR and HF-RR diminution in opposite to the ABP and MF-ABP augmentation** in the 'maximal-change-state' compared to the 'basic-state'.
The second factor, y representing 25.5% of total variance of the statistical cloud, shows a greater dispersion of the PLM subjects for the high values of the ANS variables.

Table IV: Factorial Discriminant Analysis

	Correlation
RR (ms)	0.927
HF-RR (ms^2/Hz)	0.340
ABP$(mmHg)$	- 0.971
MF $(mmHg^2/Hz)$	- 0.538

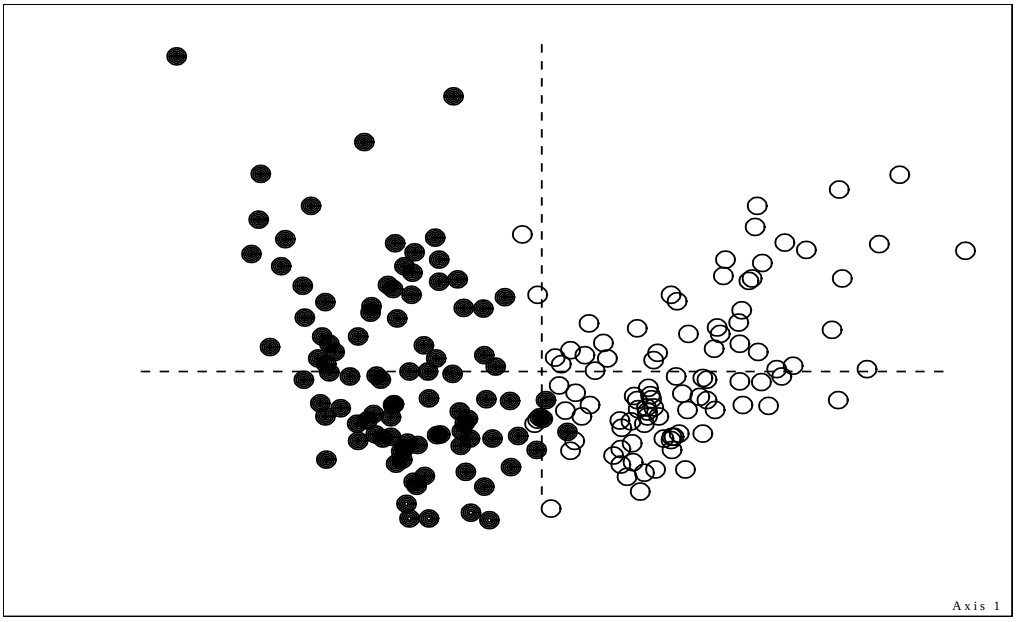

Figure 9: *Component Principal Analysis on 97 PLM subjects: Projection onto the principal factor plane of 97 PLM subjects (x=-.93RR,-.44HF-RR,.92PAS,.73MF-PAS), (y=0.86HF-RR,0.52MF-PAS) ; full dots represent basic state, empty dots maximal-change-state.*

5.2 Durations and delays of cardiovascular and motility perturbations

All the PLM last between 0.5 and 6 seconds, corresponding to a strict PLM definition; the mean HR increase is longer than the mean ABP one, as shown in Table V. The beginning of the HR acceleration always precedes the beginning of a PLM: the mean delay is of 9± 6 seconds ; the beginning of the ABP increase is near simultaneous with the beginning of a PLM: the mean delay is of 0± 3 seconds: it means that the ABP augmentation either precedes the beginning of a PLM or follows it; in this last case, the PLM never precedes the ABP augmentation by more than 5.5 seconds. The HR increase always precedes the ABP one, by a mean of 9± 4 seconds, with a minimal delay of 4.5 seconds (Fig.10).

Figure 10: *Durations and delays of cardiovascular and motility perturbations*

5.3 Relations between cardiovascular perturbations and cortical α-activity

The two groups of 'PLM subjects' show significant differences in cardiovascular modifications, according as they are or not accompagnied by a great α-activity. The different thresholds applied for the groups selection are seen on Fig. 5.

First selection

Hypothesis tests were made on the first selection of the 2 groups of PLM subjects: 21 $\alpha+$ PLM subjects over the threshold 2, 21 α- PLM subjects under the threshold 1. For each raw rhythm, RR and ABP, there is a significant enhancement of the amplitude of changes in the $\alpha+$ group : no significant difference in the basic rates but a greater ABP and HR increase. On the opposite, for the ANS variables, there is no significant difference in the amplitude of the changes but all the values are increased, on the basic state as well as at the maximum of the changes (Tables VII, VIII).

For the Multivariate Data Analysis, the chosen variables were the most significant at hypothesis tests: for the HR, it was the mean value of RR at the maximum of the HR acceleration; for the ABP, it was the mean value of ABP at the maximum of its augmentation and the mean values of HF and MF in the two states (basic and at the maximum-state-change).
The PCA shows a clear separation between the two groups. Fig.11 shows the projection onto the principal factor plane of all the 42 PLM subjects, 21 α-, 21 $\alpha+$. In this figure, it is clear that α- PLM subjects occupy the right part of the principal factor plane and the $\alpha+$ PLM subjects occupy the left one, with a greater dispersion in it. One can therefore see the first factor, x (56% of total variance of the statistical cloud), as an 'α-activity' factor; it mainly represents that **cortical activity is accompagnied by stronger HR accelerations (shorter RR), greater ABP increase and by an enhancement of the HF and MF activities**. There is no separation among the second factor, y. The LDA gives a satisfying percentage of well-classified subjects of 90.47%.

Other selections

An intermediate selection in three groups was done with all the PLM subjects: the first over threshold 2, the second between threshold 1 and 2 and the third

under threshold 1; the second and the third groups were mixed on PCA, when the first was well separated from the two others.

A selection in two groups was finaly done: 53 α+ PLM subjects over the threshold 2, 44 α- PLM subjects under the threshold 2. Fig.12 shows the same projection onto the principal factor plane. The separation between the 2 groups is still satisfying with 84% well-classified.

Table VII: HR variables in α- and α+ PLM groups

HR	Basic state			Maximum of change			Amplitude		
mean RR	α-	α+	p	α-	α+	p	α-	α+	p
	813±15	810±18	NS	767±12	748±14	****	46±16	62±18	**
mean HF	α-	α+	p	α-	α+	p	α-	α+	p
	6.6e5	7.5e5	NS	4.6e5	5.2e5	NS	2e5	2.3e5	NS
mean MF	α-	α+	p	α-	α+	p	α-	α+	p
	6e5	1.7e6	****	9.5e5	1.7e6	**	3.5e5	6e4	NS

(*:p≤.05;**:p≤.01;***:p≤.001;****:p≤.0001;NS:non significant)

Table VIII: ABP variables in α- and α+ PLM groups

ABP	Basic state			Maximum of change			Amplitude		
mean ABP	α-	α+	p	α-	α+	p	α-	α+	p
	53±4	54±7	NS	78.3±487±7		***	25.4±5	32.6±11	**
mean HF	α-	α+	p	α-	α+	p	α-	α+	p
	2e4	4.15e4	****	2.4e4	42.5e4	****	4.5e3	1e3	NS
mean MF	α-	α+	p	α-	α+	p	α-	α+	p
	1.3e5	3.9e5	****	4.1e5	6.4e5	**	2.8e5	2.5e5	NS

(*:p≤.05;**:p≤.01;***:p≤.001;****:p≤.0001;NS:non significant)

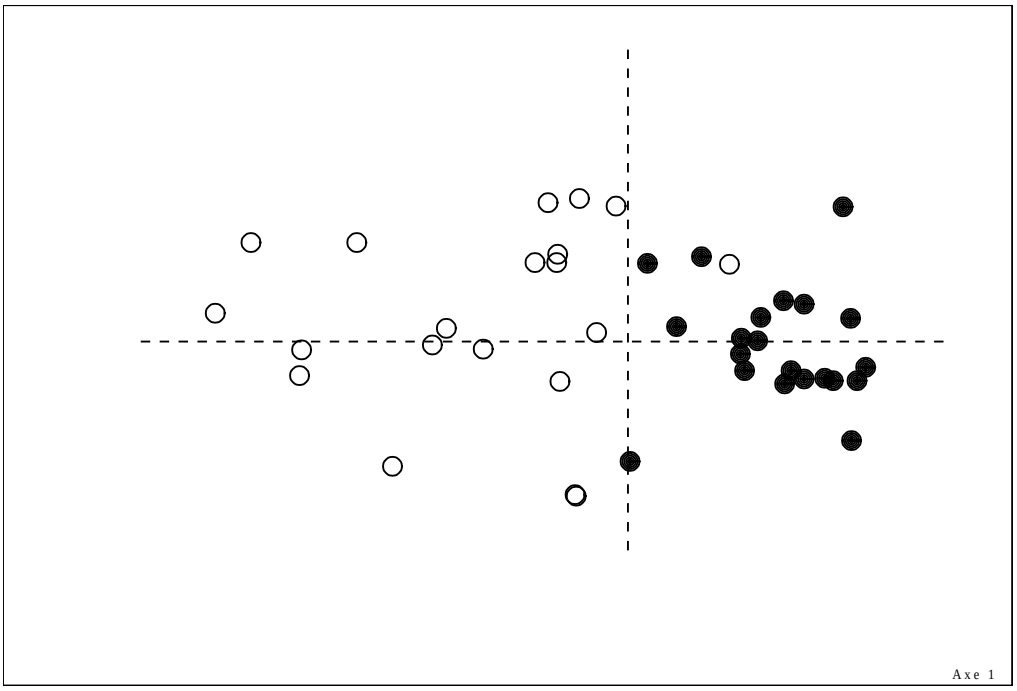

Figure 11: *Projection onto the principal factor plane of 42 PLM subjects (x=.82RR,-.68ABP,>-.80ABP HF and MF variables); full dots represent* α*- PLM, empty dots* $\alpha+$ *ones.*

6 Discussion

6.1 About Clinical results

6.1.1 Cardiovascular and autonomic perturbations

This preliminary study whom goal was mainly to build a correct form of procedure, has to be validated on other patients.

On the global cardiovascular rhythm: however, it confirms the existence of HR and ABP changes during PLM, according to the previous manual study of Bourgin [6]; it underlines the importance of these changes whom amplitude can reach 60mmHg for the ABP and 100ms for the RR.

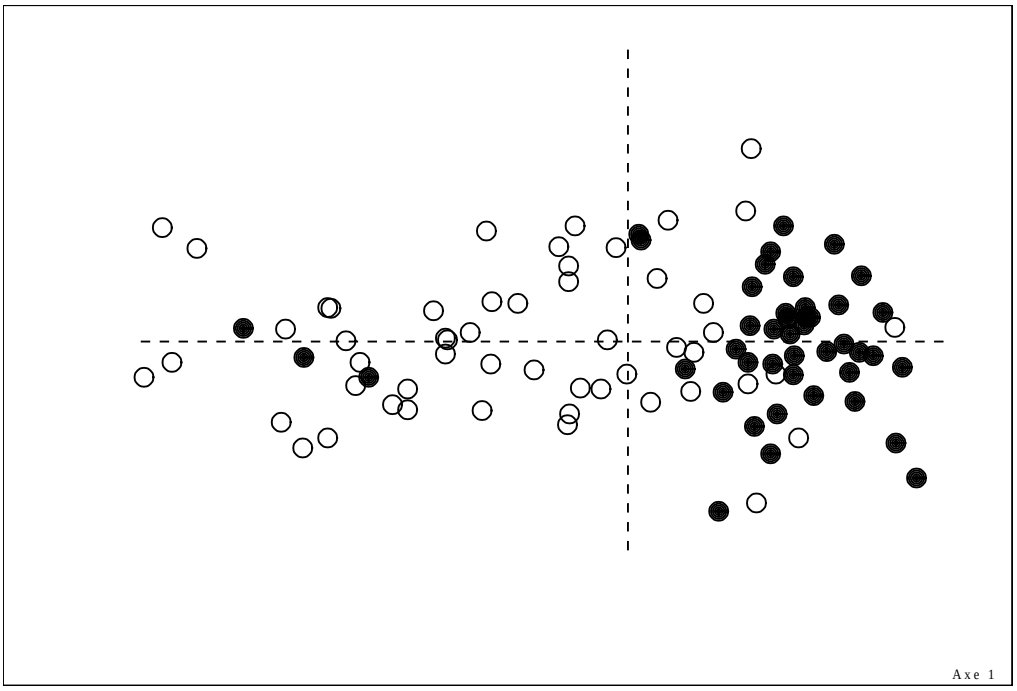

Figure 12: *Projection onto the principal factor plane of all the 97 PLM subjects (x=.73RR,-.68ABP,>-.70ABP HF and MF variables); full dots represent α- PLM, empty dots α+ ones.*

On the ANS parameters, HF and MF:

The HR acceleration is accompagnied by a decrease in HF variability; even when using the normalized variables (hf/rr and mf/rr), to abstain from this part of HF which can be correlated with the mean RR level, results remain very significant ($p \leq 10000$), that confirms a real parasympathetic inhibition.

On the other hand, there is no significant modification in the HF amplitude on the ABP; one can express the following hypothesis: on the HR, the HF fall is due to a parasympathetic inhibition followed by a sympathetic activation of the sinus node; on the ABP, the persistance of an HF activity could be due to the a mechanical effect of HR increase: the inspiration induces an intra-thoracic

pression lower than the venous one which increases the venous return and the volume of systolic ejection (VSE), at each respiratory cycle.

A significant MF variability increase, centred around .05Hz, accompagnies HR and ABP increases; this effect is more important on the ABP; it could be explain by the fact that HR modifications are more periodic than ABP ones, in this patient; this periodicity provides a more continous activity in the MF band, which is always maintained at a high level.

6.1.2 Durations and delays of cardiovascular and motility perturbations

The way of determining criteria of changes detection can induce a fluctuation on a few samples but can't reverse the evaluation of the delays: HR acceleration then ABP increase, then leg movement.

The fact that HR and often ABP precedes the movement could discard the hypothesis of the responsability of the motor disorder in the cardio-vascular perturbations. Even if the ABP increase follows the movement, it is never by more than 5.5 seconds.

The HR increase always precedes the ABP one in this patient; so, one can express the following hypothesis: the first manifestation could be a cardiac vagal inhibition which activates the brain stem; the brain stem secondary could induce a SNA activation.

One can make the assumption of a central activation of the ANS and motor system in parallel, but with a faster cardiac reaction due to the parasympathetic chronotrope inhibition ?

6.1.3 Relations between cardiovascular perturbations and cortical α-activity

The frequency band of 8-11Hz in the EEG was chosen to avoid the spindles that occur above 11Hz and to discard the θ-activity below 8Hz; this signal is a raw measure of the changing α-activity of the brain. This first approach tried to be more precise than the visual analysis of sleep states, by pointing out an intrusion of the α rhythm, which is one of the possible criteria for detecting arousal.
The cortical activation is associated with movements in some periods. The different thresholds selection indicates that there is not a progression in the increase of the cardio-vascular variables amplitude according to the α-activity one but a threshold.

The cortical activation is correlated with a greater amplitude of cardio-vascular perturbations and a greater SNA activation.
One can assume that a greater reticular stimulation either induces in parallel a greater cortical and SNA activation, or induces a cortical activation which reinforces the SNA activation.

6.1.4 Clinical and therapeutic Perspectives for PLM

PLM have a large prevalence; such cardio-vascular manifestations, reflect of a nocturnal repetitive sympathetic activation, could be responsible for a diurnal HTA; this possible consequence asks for a study of the diurnal prevalence of HTA in this pathology. If the diurnal and nocturnal importance of cardio-vascular perturbations is confirmed on a large population, it asks the question of the treatement of nocturnal ANS perturbations, in addition to the actual one addressed only to arousal manifestations and motor activity [20, 10].

6.2 About LARY_C

6.2.1 Methods

About the sampling frequency, we have just to notice that 128Hz is not a quite sufficient frequency for the HR to keep a good signal-to-noise ratio. [18]; the following recordings will be sampled at 256Hz.
The discussion is mainly about the time-frequency method used here: whereas the FFT gives only frequencial information, the SPWVT permits to follow a dynamic 'instantaneous' spectral power. The temporal and frequencial windows can be adapted to reduce to a maximum the interferences between the different spectral components and to obtain a maximal time and frequency resolution. So, the SPWVT gives a clearer vision on the time-frequency behaviour of short time transitions in non-stationary signals like the Heart Rate and the ABP; in a first time, the SPWVT is well suited to investigate signals; in a second time, the SPWVT permits to quantify HRV on various and short periods related to events of interest, such as a movement or a respiratory pause; so, it is well suited for studying relationships between physiological rhythms [17, 27].

6.2.2 The synchronous language SIGNAL

Whithout this language it would be certainly difficult to keep temporal relations between the events occurring on the different signals, e.g. occurrences of leg move-

ments and occurrences of heart beats etc. As a signal is defined as a set of values occurring at a given rhythm, we always keep temporal information: we know if an event occurring on one signal precedes or is simultaneous with an event occurring on the second. After synchronisation, we can compute them together, knowing that all is verified by the compiler, whereas it is not possible with a sequential language.

7 Conclusion

For the application studied, our approach confirms previous results about cardio-vascular perturbations and gives a better understanding of it's physiopathology. Consequently, it asks the question of long term consequences of these perturbations and therefore of their specific treatement in addition to disorders traditional one.

On a general point of view, our approach, based on the automation of the construction of the different rhythms and their inter-relationships can be an help for the specialist to obtain a faster diagnosis of in a large variety of clinical applications involving non-stationary, long time duration signals : indeed, such an application can be adapted to changing needs of the specialist thanks to the modular aspect of the different processing blocks (detection of sleep apnoeas ...)
In addition, this application, carried out on recordings, led us to think that the same methodology could be applied in real time execution: it would be possible to study HR reactions to an event, for example to a physiological stress, by computing on line the ANS parameters, as HF and MF variabilities, or to follow a post infactus.

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UnitØ de recherche INRIA Lorraine, Technopôle de Nancy-Brabois, Campus scientifique,
615 rue du Jardin Botanique, BP 101, 54600 VILLERS L¨S NANCY
UnitØ de recherche INRIA Rennes, Irisa, Campus universitaire de Beaulieu, 35042 RENNES Cedex
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Éditeur
INRIA, Domaine de Voluceau, Rocquencourt, BP 105, 78153 LE CHESNAY Cedex (France)
ISSN 0249-6399