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Complementary methodology in the analysis of rhythmic data, using examples from a complex situation, the rhythmicity of temperature in night shift workers

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Abstract
The methodology for analyzing a biological rhythm has already been the subject of much investigation. However, many questions still have no answer, for example, questions such as the periods chosen: fixed or determined. Throughout this article, we suggest a somewhat innovative methodology that makes it possible to define the steps that seem essential to us in the scientific analysis of rhythms. For some time, this methodology has been put into practice in our laboratory in various studies, some of which have given rise to publications. The notion of quality is a new notion that is present in industry and, when applied to sampling, can improve experimentation. In this way, one may judge the degree to which data samples can be explored as well as the degree of validity of the results of exploration. We provide several methods for achieving this. The search for periods is also important. For this, we have various methods but we must be able to determine those that are the most appropriate and reliable in a particular case. We propose spectral methods, two of which are new and complement 'Cosinor' methodology. On the other hand, modelling uses various methods such as those from, for example, periodic trigonometric functions or more complex chaos functions. We are interested in models from the field of regression (the cosine model) and complementary statistical tests that make it possible to validate the proposed model.

Keywords: *Methodology, quality of experimental data, modelling, search for periods, night work*

Introduction

In the field of statistical analysis of biological rhythms, the work of the Belgian school (de Prins et al., 1986) and the American school (Bingham et al., 1982), have formed the basis of a rigorous analysis; however, there is a great diversity in the methods used, and certain problems have not been fully solved. In particular:

(1) Absence of a common methodology in the scientific publications. The results can only be compared with difficulty.

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(2) The choice of periodic model. The sinusoidal model (cosine function) has been adopted because of its simplicity and because it still seems to be appropriate (de Prins & Waldura, 1993). However, there are several variants, depending on whether the model is mono-rhythmic, or has an amplitude or phase that is a complex function of time.

The search for period is still problematic and until now few spectral methods seem to be completely satisfactory.

In this overview, all the examples presented come from various studies that have been performed in our laboratory. These studies were:

(1) A study of the rhythmicity of oral temperature ($T°$) in eight night shift workers. The temperatures were read manually ($\Delta t = 30-60$ minutes, except for sleep periods) over five consecutive days (from Sunday to Friday) including night work (from 10:30 p.m. to 05:30 a.m.). The experimental data are not equispaced and their study remains complex. In the case of night work, one can expect to observe various periodicities in addition to one of 24 hours (Reinberg et al., 1988), a progressive reduction in amplitude over the course of the week (Motohashi et al., 1987), and phase shifts over the course of the week, particularly during the transition between the weekend recovery periods and resumption of the night shift (Barnes et al., 1998).
(2) Using an actimeter (with a sampling frequency of 1 minute), the study of the rhythm of activity can be recorded in subjects on night work. These data are equispaced.
(3) Finally, we also use data from other samples of standard functions (i.e. function of known period) that will confirm the reliability of each method. (The theoretical period must be found with this previous methods to improve the reliability.)

An important point in our methodological complement is standardization. This makes it possible to adopt a common language. The methodology that we present here is an alternative to classical Bayesian statistical analysis: Exploratory Data Analysis. (The references give some examples of package software that is available.) EDA is a method standardized by the US National Institute of Standards and Technology.

The main reasons we have selected methods from EDA are as follows: EDA (1) does not impose a specific type of modelling, (2) data analysis precedes modelling, (3) the methods of analysis are mainly graphical and therefore much more easily understood by a chronobiologist without mathematical training. High-performance complementary numerical statistical tests (for example the Kolmogorov–Smirnov test and the Ljung–Box test) complement the graphic studies and make it possible to test the hypotheses.

The graphs that we present come from EDA (Tukey et al., 1977; Mauvieux et al., 2003); they can be useful for comparing results.

Our approach relies on the three essential stages adopted by EDA. Because EDA is not a method that has been used in chronobiology, most of the graphics we present here come from the EDA graphical methods. This overview is divided into three sections: quality of data; search for periodicity; the model and statistical validation of the model.

Quality of data

The first stage that we propose in the analysis of data relies on quality, which is a notion that comes from industry (for example, the ISO from AFNOR quality norms, 'Normes de qualité ISO 9000', explained in the references) This idea was defined to improve productivity. It is already present in scientific research in other forms (for example, the quality procedure in the

'Institut National de Recherches Agronomiques' (INRA) France, 2002). We have sought to introduce this notion to sampling in the context of chronobiology data analysis.

The study of experimental data quality concerns criteria which judge whether the sample of experimental data is significantly exploitable. This evaluation has the advantage of being visual and for this, we have various graphic tools such as:

(1) The lag plot (Box et al., 1994). A lag plot checks whether a data set or time series is random or not. Random data should not exhibit any identifiable structure in the lag plot. Non-random structure in the lag plot indicates that the underlying data are not random.
(2) The autocorrelation diagram (Box et al., 1994). Autocorrelation plots are a commonly used tool for checking randomness in a data set. This randomness is ascertained by computing autocorrelations for data values at varying time lags. If the data are random, such autocorrelations should be near zero for all time-lag separations. If non-random, then one or more of the autocorrelations will be significantly different from zero. In addition, autocorrelation plots are used in the model identification stage for Box–Jenkins autoregressive, moving average time series models.
(3) The graph of normal probability (Chambers et al., 1983). The normal probability plot is a graphical technique for assessing whether or not a data set is approximately normally distributed. The data are plotted against a theoretical normal distribution in such a way that the points should form an approximate straight line. Departures from this straight line indicate departures from normality. The normal probability plot is a special case of the probability plot.

The conditions necessary for high quality of data are now illustrated by our own data using these methods.

Absence of a random distribution of data

The absence of a random distribution of data translates into the existence of a coherent physical or biological phenomenon that may be represented by a model. The autocorrelation diagram brings out whether or not the data have a random character (Figures 1 and 2). In the

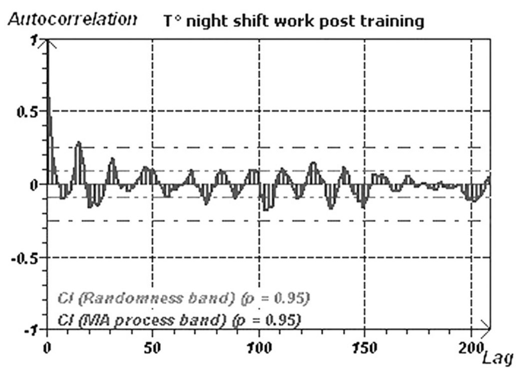

Figure 1. Autocorrelation curve: absence of a random character. Note the sinusoidal aspect of the curve. The absence of randomness in the data indicates the existence of a physical or causal stochastic phenomenon. The horizontal dashed lines closer to the $y = 0$ line are calculated to show the limits of randomness. (Study of the temperature in subjects during night shift work.)

absence of randomness, we can presume that the data are the expression of a stochastic process indicating the presence of a real biological or physical phenomenon (Box et al., 1994, EDA Autocorrelation)

Independence of data is desirable

This is because, if the experimental data are 'dependent' (dependent data mean highly correlated data), there is the possibility of the existence of extra mathematical relationships within the data, with the subsequent risk of false results when modelling (in particular by regression) and performing statistical tests. To test this characteristic by using the EDA graphic methods, we can use the Lag plot (Figures 3 and 4) complemented by a Q Ljung–Box test (Ljung & Box, 1978). However some authors maintain that data coming from

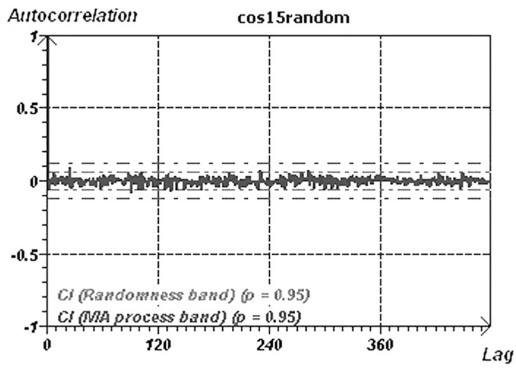

Figure 2. Autocorrelation curve: the random character is marked when the curve approaches zero. This result indicates the absence of some underlying physical or causal stochastic phenomenon.

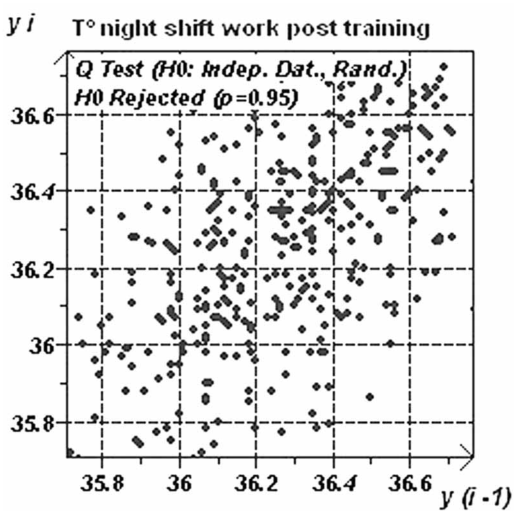

Figure 3. Lag plot and Q test: highly dependent data. The dependence of data indicates the existence of a complex mathematical relation that connects one piece of data to the next ($p = 0.95$, $\alpha = 0.05$). (Study of temperature in subjects performing night work.)

temporal series are often highly correlated i.e. dependent (Box et al., 1994); this complicates a reliable interpretation of the results.

Absence of a stationary character

If the data are not stationary, assessment of rhythmicity is very complex. Adapted spectral analyses such as that of Blochner (Box et al., 1994) completed by autocorrelation and PACF (Partial Autocorrelation Function) calculations (Box et al., 1994) are the tools that are the most appropriate for studying this phenomenon (for example, we will refer to the work of Box et al., 1994).

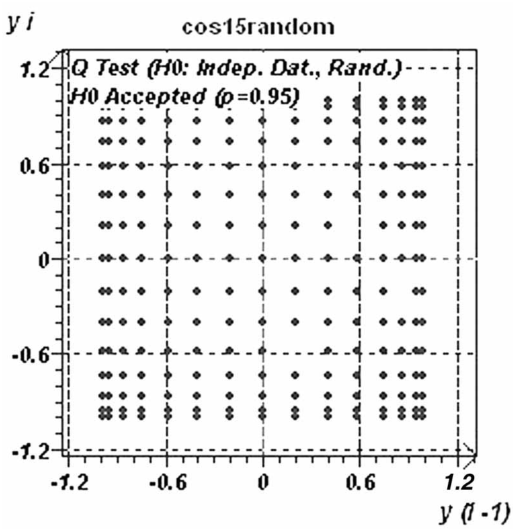

Figure 4. Lag plot and Q test: independent data. The non-dependence of data indicates that there is no complex mathematical relation that connects one piece of data to the next. In this case, the models that will be calculated, for example, by regression, will all be more exact ($p = 0.95$, $\alpha = 0.05$) (random standard measure function).

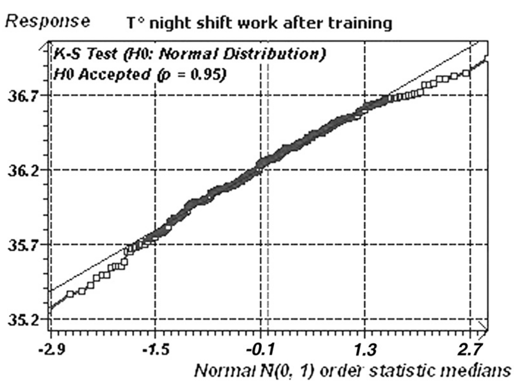

Figure 5. Normality graph. Distribution of data according to a 'Normal' distribution with a K–S test ($H_{(0)}$: accepted) here makes it possible to state that the experimental data on temperature follow a normal distribution ($p = 0.95$, $\alpha = 0.05$) (study of temperature in subjects during night work).

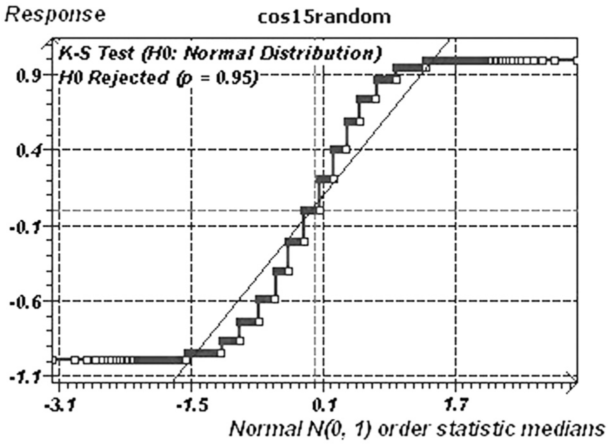

Figure 6. Normality graph. Distribution of data according to a non-'Normal' distribution with a K–S test ($H_{(0)}$: rejected); the absence of 'Normality' in the data will limit the statistical tests that can be performed legitimately, since, for many of them, this condition is necessary ($p=0.95$, $\alpha=0.05$) (standard measure cosine function with a period of 15).

Normal distribution of data

We use the normal probability graph, complemented by the Kolmogorov–Smirnov test (K–S test) that confirms or weakens the hypothesis that the distribution is normal ($H_{(0)}$: normal distribution) (see Figures 5 and 6). Studies of biological phenomena often show such normality, even though such normality is not systematically found in theoretical data resulting from pure mathematical functions. On the other hand, many statistical tests and analyses (for example, the Fisher periodogram) require this hypothesis to be upheld.

Conclusion relating to the quality of data

The conditions presented above presume that sampling is likely to be exploitable in the context of the study and modelling of rhythmic phenomena. These conditions provide criteria of measurement of the quality of this sampling. If most of the previous conditions are met, then the investigation of the data will arrive at valid results characteristic of the phenomenon under study. If these criteria are not met, then it becomes necessary to improve the sampling regimen.

Search for periodicity

The search for periodicity will depend on whether the data in the sample are equispaced or non-equispaced. This directly influences the choice of the spectral method used. We will therefore distinguish the specific methods that apply to data that are equispaced or non-equispaced, and methods that apply to both formats of experimental data.

Data that are non-equispaced

If the data are not equispaced, only three methods may be envisaged. We recommend the following methods as providing the greatest reliability for determination of the period

The Percent Rhythm spectrum (PRS). The Percent Rhythm Spectrum is calculated from the null amplitude test (Bingham et al., 1982; Mauvieux et al., 2003) (Figures 7 and 8).

Reverse Elliptic spectrum (RES). The Reverse Elliptic Spectrum (RES) is calculated from the surface of a confidence ellipse. Results obtained using this method have been published (Deschatrette et al., 2004; Mauvieux et al., 2003). This spectrum also provides a confidence interval for determination of period according to the Ellipse test (Bingham et al., 1982; Mauvieux et al., 2003) (Figures 9 and 10).

These spectral analyses can also be applied to the search for the periodicities present within a population. When applied to a population, the analysis considers all the data series that describe a population's behaviour. This notion is similar to that described in the definition of the Population Mean Cosinor (Bingham et al., 1982).

Lomb and Scargle Periodogram. The Lomb and Scargle periodogram (Scargle, 1982) combines the principles of regression analysis and Fourier transforms (Figures 11 and 12).

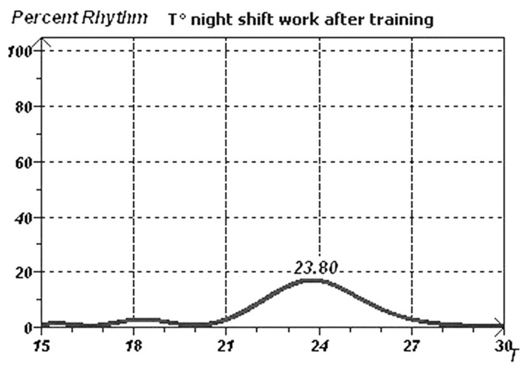

Figure 7. The Percent Rhythm Spectrum detects a fundamental (main period) of 23.8 hours. A harmonic (secondary period) is also detected at around 18 hours ($p = 0.95$, $\alpha = 0.05$) (study of temperature in subjects during night work).

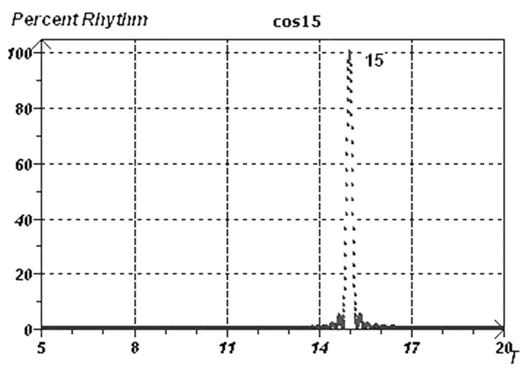

Figure 8. The Percent Rhythm Spectrum detects a fundamental (main period) of 15 hours ($p = 0.95$, $\alpha = 0.05$) (study of a standard measure cosine function with a period of 15 hours).

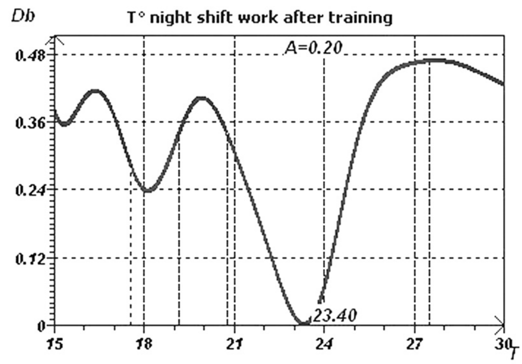

Figure 9. Normalized Reverse Elliptic Spectrum detects the main period (fundamental) of 23.4 hours. A harmonic (secondary period) is also detected at around 18 hours. The confidence interval for the period is determined by the dotted vertical straight lines ($p = 0.95$, $\alpha = 0.05$) (approximately 21 – 27.5 hours for the 23.4 hour period) (study of temperature in subjects during night work).

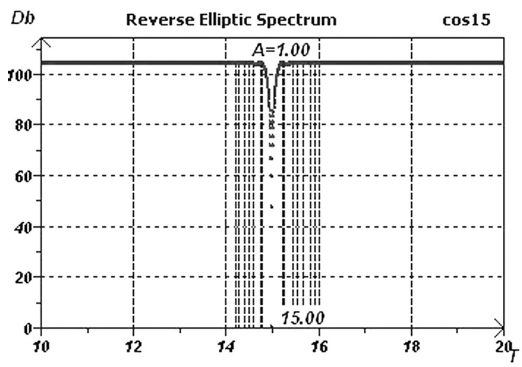

Figure 10 Normalized Reverse Elliptic Spectrum detects the main period (fundamental) of 15 ($p = 0.95$, $\alpha = 0.05$) (standard measure cosine function with a period of 15 hours).

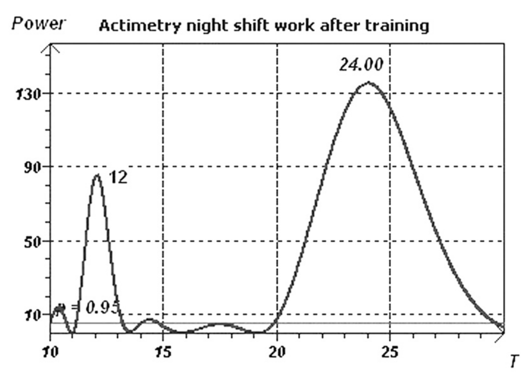

Figure 11. The Lomb and Scargle periodogram (not normalized here) detects a fundamental period at 23.5 hours and several harmonics of which one is at 12 hours, with a reliability close to that found by the previous methods (actimetric study of athletic subjects working night shifts).

Data that are equispaced in time

The spectral methods derived from Fourier analysis are only applicable if the data are equispaced. The methods derived from regression analysis can also be applied in this case (see previous paragraph).

We will present the highest performance methods that we have implemented in our studies on rhythmic markers, and the interest they have. They come mostly from methods used in astronomy (Spectral Analysis, 2002). Their drawback is their average reliability relative to the methods that come from regression. Reliability, as we have defined it, is characterized by repetitivity in determination of exact results when searching for periods in the samples of data generated from periodic mathematical functions. We present the following spectral analyses.

Autospectral Spectrum according to Jenkins and Watts (Jenkins & Watts, 1968). This is a spectrum from the Fourier transform of the autocorrelation function, with some mathematical modifications (Figures 13 and 14)

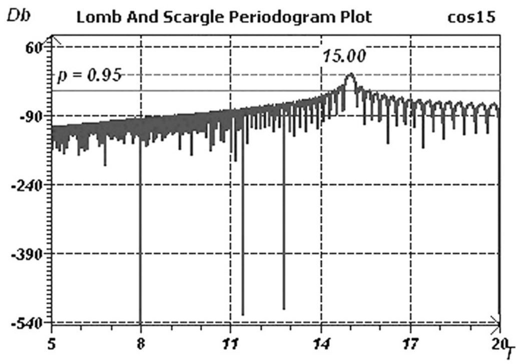

Figure 12. The Lomb and Scargle periodogram (normalized here) presents a main peak at 15 hours (standard measure cosine function of a period of 15 hours).

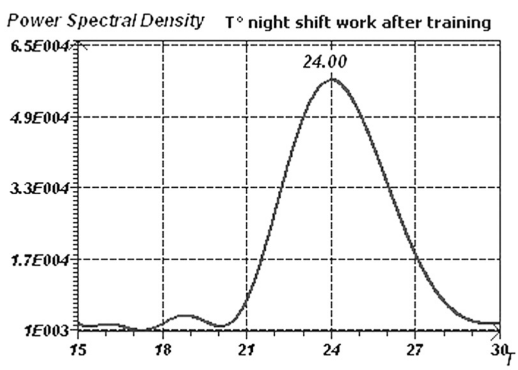

Figure 13. The Jenkins and Watts periodogram presents a good reliability in this case and here detects a period at 24 hours (study of temperature in subjects during night work).

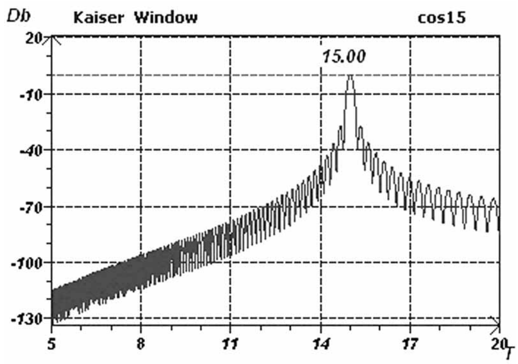

Figure 14. Autospectral Spectrum (normalized) according to Jenkins and Watts (1968) (Kaiser windowing). An exact estimate of period is produced (standard measure cosine function with a period of 15 hours).

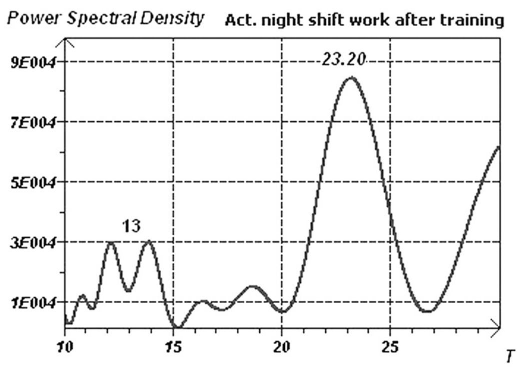

Figure 15. Autoperiodogram (not normalized here) according to Jenkins and Watts (1968). Two noticeable peaks at 13 and 23.2 hours are detected for the wake/sleep rhythm (actimetric study of athletic subjects during night work).

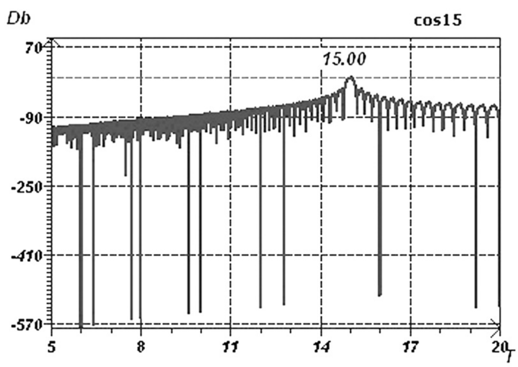

Figure 16. Autoperiodogram (normalized here) according to Jenkins and Watts (1968). A noticeable peak at 15 hours is observed (measure of standard cosine function with a period of 15 hours).

Autoperiodogram according to Jenkins and Watts (Jenkins and Watts, 1968). The principle of this spectrum is the same as that of the previous one, but with different mathematical modifications (Figures 15 and 16).

Fisher Periodogram (Bloomfield, 1976). The Fisher periodogram is used in chronobiology. It is an acceptable method and can be compared with the methods already cited above. However, according to the tests that we have carried out, it presents the same drawbacks as the Discrete Fourier Transforms, in particular, in its reliability in determining period (Figure 17).

Table I gives a summary of the methods described above.

Period to be chosen

'How to choose which period, using which method?' is a question that often recurs and which it is difficult to answer. We propose carrying out searches for periods using the various methods that have just been described in the first part of this paper and that, in our view, present the highest reliability when applied to our data. The choice of method is made in terms of: the distribution of data (whether or not it is equispaced with respect to the timing of its collection), the reliability of the method used, and, finally, the results obtained from tests of the validity of the model for a fixed period (to be considered below).

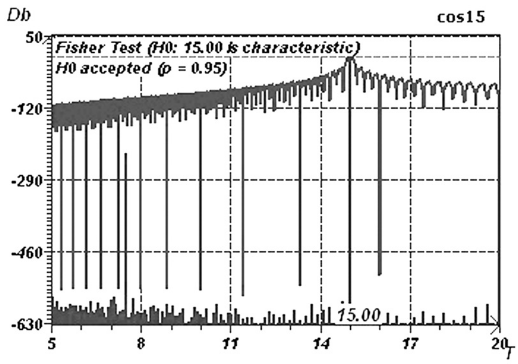

Figure 17. The Fisher Periodogram (normalized) is a method that comes directly from the DFT (Discrete Fourier Transforms) with a statistical test on the fundamental at 15 hours in this example (H_0 accepted $p = 0.95$, $\alpha = 0.05$) (study of a standard measure cosine function with a period of 15 hours).

Table I Methods and conditions on the data

Percent Rhythm Spectrum (PRS)	Reverse Elliptic Spectrum (RES)	Lomb and Scargle periodogram	Autospectral according to Jenkins and Watts	Autoperiodogram according to Jenkins and Watts	Fisher periodogram
Equispaced data					
Not required	Not required	Not required	Required	Required	Required
Unevenly spaced data					
Not required	Not required	Not required	Not available	Not available	Not available
Normal distribution					
Not required	Not required	Not required	Not required	Not required	Required

The model and its statistical validation

Modelling by regression

In the context of a study of a model with only one rhythmic component, the use of the classic cosine function calculated by regression seems to be the most appropriate method (de Prins et Waldura, 1993) (Figures 18 and 19). However, it is necessary to check that amplitude and phase remain constant over time. This is because biological phenomena with only one rhythmic component do not seem to follow this type of model exactly. We often observe a

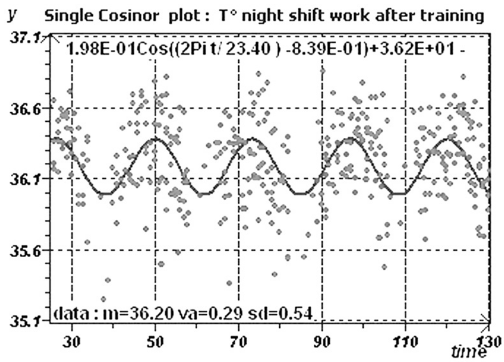

Figure 18. Model with a 23.4 hour period calculated by cosine regression $y(t) = a\mathrm{Cos}(2\pi t/T + \Phi) + M$. The points represent all the experimental temperature data for all subjects ($n = 8$) (**a**: average; **va**: variance; **sd**: standard error) (study of temperature in subjects working night shifts).

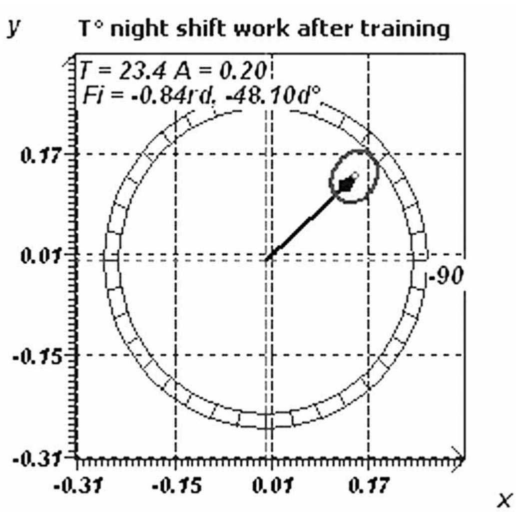

Figure 19. Confidence ellipse according to the Single Cosinor ($p = 0.95$, $\alpha = 0.05$). The period is 23.4 hours. The smaller the surface of the ellipse, the higher precision is in the determination of the period. The fact that the origin is outside of the confidence ellipse indicates that the coefficients of the cosine curve are significantly greater than the pair of values (0, 0) and so the existence of this model has been validated (study of temperature in subjects working night shifts).

more complex expression of phase and, slightly less often, of amplitude. The use of complex demodulation spectra makes it possible to verify whether the classic model:

$y(t) = a\mathrm{Cos}(2\pi t/T + \Phi) + M$; is not a complex function of time (Figures 20 and 21)

Statistical validation of the model

A model that is calculated using regression analysis must fulfil the following criteria; if it does not, then the statistical value of the study is open to serious question (de Prins, 1986). The criteria are:

(1) Independence of residue (Figure 22)
(2) An average residue equal to zero (Figure 23)
(3) Normality of residues (Figure 24)
(4) Homogeneity of variance of the residues (Figure 25).

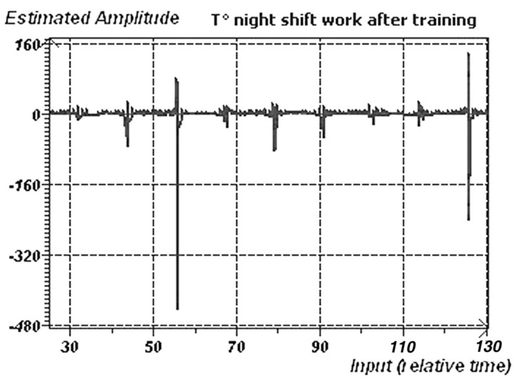

Figure 20. Complex amplitude demodulation spectrum. The amplitude for a 23.4 hour period remains sufficiently constant (signal close to 0) to allow us to affirm that it is not a complex function of time. It would seem to be the case that the extreme points are artifacts (study of temperature in subjects during night work).

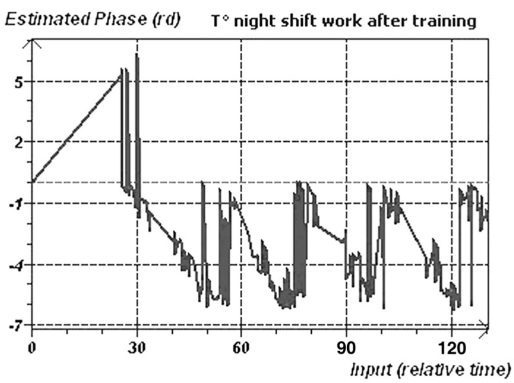

Figure 21. Complex phase demodulation spectrum. Phase does not remain constant over time. The signal moves from positive to negative at 30 hours, which indicates that, at the time of the weekend/resumption of work transition, the phase of temperature rhythm shifts. In this case, phase can be a complex function of time and the model is written: $y(t) = a\mathrm{Cos}(2\pi t/T + \Phi(t)) + M$ (study of temperature in subjects during night work).

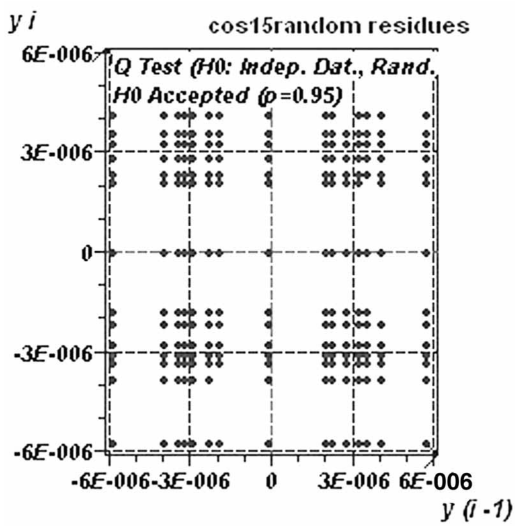

Figure 22. Lag plot with Q test ($p = 0.95$, $\alpha = 0.05$) on the residues from a model with a period of 15 hours study of a standard cosine function of period 15 hours).

Residuals distribution - Goodness of fit :

- **Ajusted r²** : 1.00E+00

- **Residual Sums of Squares** : 1.11E-08

- Chi² Test (H0: Normal residuals distribution) H0 rejected: 0.95

- K-S Test (H0: Normal residuals distribution) H0 rejected: 0.95

- **Average Test (H0: RS Average = 0) H0 accepted**: 0.95

- **Q Test (H0: Independent Residues) H0 accepted**: 0.95

- K--S Test is the Kolmogorov and Smirnov test

- Average Test (H0: RS Average = 0) is a test of average on the average sum of residues

- Q Test is the Ljung--Box Q-statistic lack-of-fit hypothesis test

Figure 23. Tests of goodness of fit on a model with a period of 15 hours. In this case, we do not observe normality in the distribution of the residues (study of a standard cosine function of period 15 hours).

Discussion/conclusion

The methods described here do not call the results of all previous studies into question; rather they should be considered as providing supplementary help for improving the results

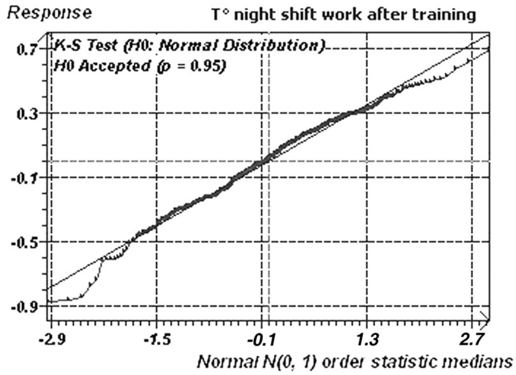

Figure 24. Normal probability graph and K–S test ($p = 0.95$, $\alpha = 0.05$) on residues of a model with a 23.4 hour period. The test shows normality of distribution of the residues for $p = 0.95$, $\alpha = 0.05$ (study of temperature in subjects during night work).

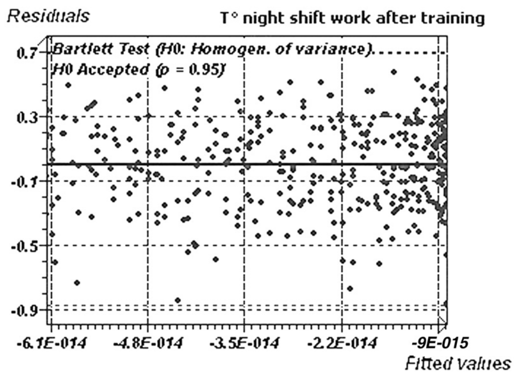

Figure 25. Graph of homogeneity in variance and Bartlett test of residues ($p = 0.95$, $\alpha = 0.05$). The test shows good homogeneity in variance (study of temperature in subjects during night work).

obtained. The methods also allow greater precision in the approaches to studying rhythms in complex situations where periods are not known (de-synchronization, temporal isolation, etc.). They also allow re-analysis of some data, in particular in studies where the period was defined a priori as being 24 hours in length. The methodology described here through EDA graphics has several advantages:

(1) It first proposes a formal analysis allowing chronobiologists to adopt a common approach.
(2) It also introduces the notion of quality of sampling. This may be used to determine the minimum size of the sample. This has already been addressed by some authors (de Prins et al., 1986) but its application in the context of chronobiology seems difficult. We can also try to determine the minimum size of the sample after modelling, by studying the behaviour of the residues using specific model-validating tests (studies of residues and goodness of fit).
(3) To address the problem of period determination in the light of variations obtained from the spectral methods. The spectral methods that come from regression analysis have shown a greater reliability than those that come from Fourier analysis. In particular, the

Reverse Elliptic Spectrum is an innovative, very reliable method that makes it possible to obtain the best period for a Cosinor calculation (Best Cosinor fit). It presents the advantage of being able to easily visualize the spectrum (the peaks of periods are quite detached), and of giving a confidence interval for the value of the period. We have found these methods to be valuable for the analysis of data from several experiments (Deschatrette et al., 2004; Mauvieux et al., 2003).

We have sought to present these methods and their use in the most accessible way possible for the chronobiologist. The reader will find the theoretical background associated with these methods by consulting the bibliography.

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