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The sigmoidally transformed cosine curve: A mathematical model for circadian rhythms with symmetric non-sinusoidal shapes

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SUMMARY

We introduce a family of non-linear transformations of the traditional cosine curve used in the modelling of biological rhythms. The non-linear transformation is the sigmoidal family, represented here by three family members: the Hill function, the anti-logistic function, and the arctangent function. These transforms add two additional parameters that must be estimated, in addition to the acrophase, MESOR, and amplitude (and period in some applications), but the estimated curves have shapes requiring many more than two additional harmonics to achieve the same fit when modelled by harmonic regression. Particular values of the additional parameters can yield rectangular waves, narrow pulses, wide pulses, and for rectangular waves (representing alternating 'on' and 'off' states) the times of onset and offset (hence duration, as when modelling the duration of the large night-time melatonin secretory epoch). We illustrate the sigmoidally transformed cosine curves, and compare them to harmonic regression modelling, in a sample of eight activity recordings made on patients in a nursing home. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS: cosine; anti-logistic function; Hill Function; arcsine function; circadian rhythms; non-linear Fourier analysis

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INTRODUCTION

Numerous biological processes follow predictable patterns that repeat approximately once every 24 h. These circadian rhythms (circa = 'about' and dies = 'day') have been the subject of considerable research efforts that have utilized varied mathematical approaches to understand their characteristics and responses to experimental manipulations. Biological rhythms typically display features of sinusoidal rhythms, ascending to a maximum value, steadily decreasing to a minimum value and then increasing again, *ad infinitum*. As such, mathematical approaches to modelling circadian rhythms have relied heavily on models that utilize sine and cosine functions, collectively falling under the heading of cosinor models as they were first termed by Halberg [1].

The cosinor model appears to provide a good fit to many types of circadian data, such as core body temperature. From this model, the amplitude (peak of the rhythm), MESOR (midline estimating statistic of rhythm) and acrophase (time of the peak of the rhythm) are traditionally derived. This approach has also been used extensively in rest/activity rhythms data, but not without criticism. Van Someron and colleagues have begun to rely on non-parametric statistics for the analysis of activity rhythms because these data are often non-sinusoidal in shape, more closely resembling a square wave pattern [2].

The data in Plate 1 illustrate this common problem in the modelling and analysis of circadian rhythms. In these plates, the data (described more fully below) are plotted as black dots (missing values represented by yellow bars), and the best-fitting cosine curve is plotted in blue [3, 4]. The circadian rhythm is evident to some degree in most of the data, and the cosine curve has its peak in about the right place for each set of data, but the data do not have the sinusoidal shape that makes the amplitude and acrophase estimates most meaningful. Indeed, for some of the data, there is no well-defined short interval of maximum activity for which the name 'acrophase' might be appropriate; instead, there is an interval of 10–15 h during which the data are 'relatively high', and a complementary interval during which they are 'relatively low'. The usual approach to modelling data that are not sinusoidal in appearance is to fit a truncated Fourier series, and the result of such a fit is displayed in Plate 1 for each panel in red. This is the linear projection of the data on the sine and cosine curves with periods of $24, 12, 8, \ldots, 1.2$ h, i.e. the base frequency and its first 19 harmonics [5–9]. It is clear that this model is a better fit to the data than the plain cosine, but it has a total of 40 parameters (plus the mean estimate), and a non-parsimonious wiggly shape. The truncated Fourier series requires a large number of parameters to fit curves that are simple to describe, mostly being rectangular waves. The extra parameters for the ultradian 'rhythms' are required by the limitations of the basis of sine and cosine curves, and are not evidence for 19 additional rhythm generators. Furthermore, the extra parameters are not very descriptive of prominent features that are relatively easy to describe after visual inspection of the graphs. A reader cannot tell from the table of parameter estimates which, if any, of these curves are most nearly rectangular; one cannot rank order of the curves by 'rectangularity'. A reader cannot tell from the parameters which of the curves have the widest 'relatively high' epochs, nor rank them by the width of the 'relatively high' epochs. In this paper, we introduce sigmoidally transformed cosine curves which remedy those deficiencies of truncated Fourier series for some data: they provide low-dimensional parameterizations, and the describable features of the rhythms are well-represented by the parameters. Our analyses are based upon data collected as part of a larger study of activity and light exposure rhythms in nursing home patients [10–13].

DATA COLLECTION

Subjects: Data from 92 nursing home residents (63 women) participating in an intervention trial to improve sleep and behavioural problems are included in this study. All lived in one of four San Diego area nursing homes for a minimum of 2 months (mean = 1.7 years; SD = 1.9, range = 0.2–13.0 years). The mean age of patients was 82.3 years (SD = 7.6, range = 61–99 years) and there was no significant difference in age between men (80.2 years) and women (83.3 years). Patients all had probable or possible Alzheimer's disease (AD) with an average mini mental state examination (MMSE) score of 5.7 (median 4.0, SD = 5.6, range 0–22). The average level of education was 13.8 years (SD = 3.3, range 5–20).

Apparatus: The Actillume recorder (Ambulatory Monitoring, Inc., Ardsley, New York) measured wrist activity. The Actillume, a wrist-mounted device, recorded both activity level and light exposure at 1 min intervals. Movement was recorded with a linear accelerometer and a microprocessor. Light was collected via a photosensitive cell. Activity and light data were both sampled every 10 s and stored every minute on a 32 kbyte memory chip, which was sufficient to record activity and illumination data for over 5 days. Three variables were measured: level of illumination, maximum activity level per minute, and mean activity level per minute. The data that are presented in this paper are the minute-by-minute recorded maximum activity level, named MAXACT, from the baseline phase of the study. The values actually modelled were the logarithms of the maximum activity, named LMAXACT $= \log_{10}(\text{MAXACT} + 1)$.

Procedure: Each patient's legal guardian was first contacted by research staff who explained the study protocol over the telephone. Once the guardian had given verbal approval for the study, a consent form, approved by the University of California San Diego Committee on the Investigation of Human Subjects (protocol number 990045), was mailed to the guardian for signature. Verbal consent was then obtained from both the patient and patient's physician.

The study included baseline wrist actigraphy data for all 92 residents. Actillumes were worn for three consecutive 24 h periods, i.e. 72 h. The experimental manipulations in the other phases, as well as other procedural details, can be found elsewhere [10–13].

MATHEMATICAL MODEL

Equations

The fundamental equation of the cosine model is

$$r(t) = \text{mes} + \text{amp} \cdot \cos([t - \phi]2\pi/24)$$

where $r(t)$ denotes the modelled response (in this case LMAXACT), mes (for 'MESOR') denotes the estimated middle of the data, amp denotes the maximum amount that the model deviates above and below mes (because the cosine ranges from -1 to 1), and ϕ denotes the time of day of the maximum modelled value of r. The parameters can be estimated from data using linear least squares (projection on sine and cosine curves with a 24 h period) followed by a non-linear transformation of coefficients to obtain amp and ϕ; or they can be estimated by non-linear least squares. When the parameters are estimated by linear least squares, the estimate of mes will be the mean of the data, and may not be the exact middle of the fluctuations when the data are not appropriately spaced, e.g. if there are more missing values at night, or more missing values at any other regularly repeated time of day (as may happen if a subject removes the actigraphy device for a shower at the same time each day).

Sigmoidal curves have an 'S' shape rising monotonically from low values (but bounded below) to high values (bounded from above) as the arguments increase from low to high values. There is a central small region of the domain in which nearly all of the increase from low to high occurs. In our work, we have used three sigmoidal transforms of cosine curves: the Hill function, anti-logistic function, and arctangent function.

There are many sigmoidally-shaped curves that could be used in place of these three. Every unimodal probability density function has a sigmoidally shaped distribution function, as long as the mode is in the interior of the support of the corresponding random variable. With a large number of sigmoidal transforms to choose from, some methods for deciding which to use may be developed over time, as with the many linear models of time series [14].

The *Hill function* [15] (in neuronal modelling this is called the Naka-Rushton function [16]) is written as $h(x) = x^{\gamma}/(m^{\gamma} + x^{\gamma})$. The function $h(x)$ is defined for $x \geqslant 0$, and rises from 0 to 1 as x increases. The parameter m, called the Michaelis constant, is the value of x at which $h(x) = \frac{1}{2}$. The larger the γ, the more steeply the curve rises in a neighbourhood of m, and the more it resembles a step function.

The *anti-logistic function* is written as $\ell(x) = \exp(\beta[x - \alpha])/\{1 + \exp(\beta[x - \alpha])\}$. The argument x can be any real number, and $\ell(x)$ increases from 0 to 1 as x increases from $-\infty$ to $+\infty$, for $\beta > 0$. For $x = \alpha$, $\ell(x) = \frac{1}{2}$. As β increases, $\ell(x)$ becomes steeper in a neighbourhood of α, and increasingly resembles a step function.

The *arctangent transform* is written as $\psi(x) = \tan^{-1}[\beta(x - \alpha)]/\pi + \frac{1}{2}$, where the arctangent function is rescaled by π and has $\frac{1}{2}$ added to it so the range is $(0, 1)$ instead of $(-\pi/2, \pi/2)$. With $\beta > 0$, the parameters α and β have the same interpretation as in the anti-logistic function: α is the value of x for which $\psi(x) = \frac{1}{2}$; β determines how steeply $\psi(x)$ rises in a neighbourhood of α and how much it looks like a step function.

For the sigmoidally transformed cosine curves, let $c(t) = \cos([t - \phi]2\pi/24)$. Then the Hill-transformed cosine curve is $h(c(t)) = [c(t)+1]^{\gamma}/(m^{\gamma} + [c(t)+1]^{\gamma})$; the anti-logistic-transformed cosine curve is $\ell(c(t)) = \exp(\beta[c(t)-\alpha])/\{1+\exp(\beta[c(t)-\alpha])\}$; and the arctangent-transformed cosine curve is $\psi(c(t)) = \tan^{-1}[\beta(c(t) - \alpha)]/\pi + \frac{1}{2}$.

Graphs of these three sigmoidal transforms, showing the effects of variations in β and γ are presented in Plate 2. For a curve of each family, there is one of each of the others that is roughly similar in shape, but (at least in this sample), it appears to be impossible to match members of different families to have exactly the same slope at the point and to be equally close to the asymptotes at 1 or 2 units away from the centre points. For example, for the largest values of β represented in Plate 2, the arctangent function has the steepest slope at the centre point, but the anti-logistic function is closer to the asymptote at 1 and 2 units from the centre point. These transforms have intrinsically different shapes, and in principle may yield qualitatively different conclusions when used in modelling, though the differences may be practically negligible.

The sigmoidally transformed cosine models of the data are given by: $r(t) = \min + \text{amp} \cdot h(c(t))$; $r(t) = \min + \text{amp} \cdot \ell(c(t))$; $r(t) = \min + \text{amp} \cdot \Psi(c(t))$. In this model, ϕ is still the

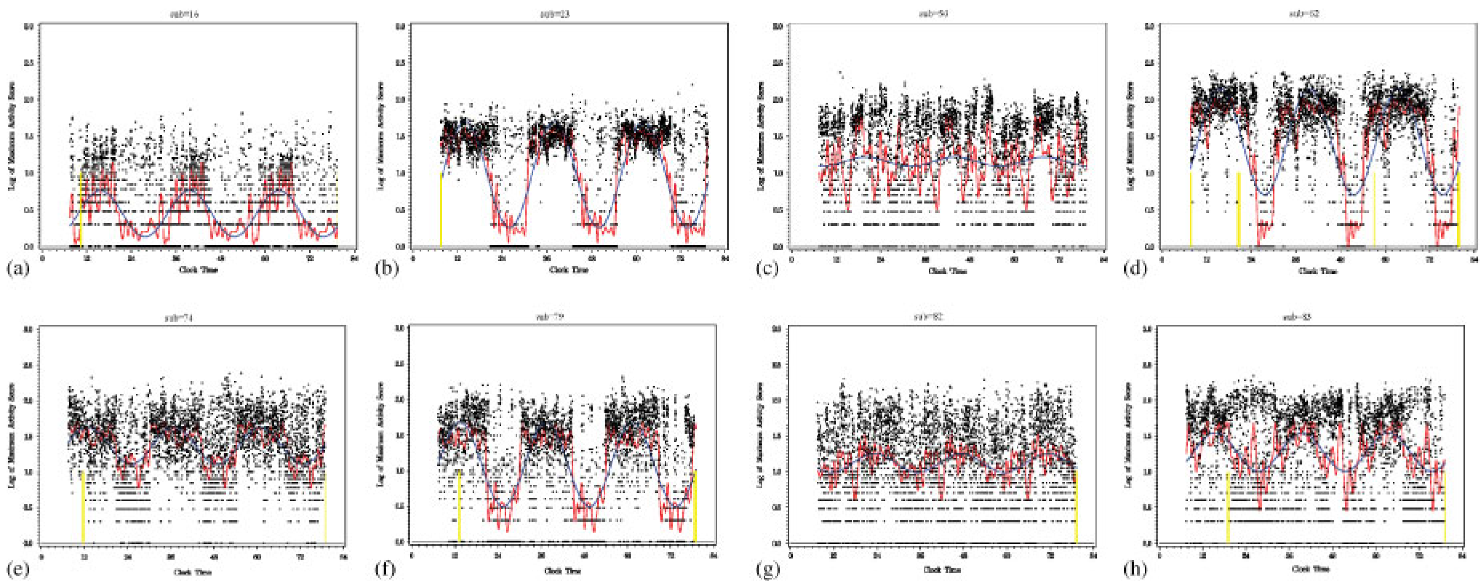

Plate 1. Truncated Fourier series (24 h base period and 19 harmonics) of selected data files. The black dots are the logarithms (base 10) of the maximum activity scores recorded at 1-min intervals; missing values are represented by yellow vertical bars. The variable ‘cloktime’ is referenced to midnight prior to the start of the recordings. The blue line is the best fitting cosine curve (linear least squares). The red line is the best-fitting (linear least squares) truncated Fourier series representation. These are from the baseline condition of the experiment. These panels have been chosen to suggest the variety of the data and the fitted models, and are not ‘representative’. Panel F, which displays a clear alternation between relatively ‘high’ levels of activity and ‘low’ levels of activity, is the most common ‘type’. All the panels illustrate a finding of this study, namely that the patients are almost never still or almost still for very long: all except panel D show many near maximum activity levels even during the ‘troughs’ of the activity cycle. Panel B shows a rhythm in which the ‘high’ activity periods and the ‘low’ activity periods are most nearly equal in duration. Panel D shows the widest high activity periods compared to low activity periods. Panels E, F, and G show abrupt transitions from periods of relatively high activity levels to relatively low activity levels, and vice versa; these are best represented by rectangular waves, which are notoriously hard to fit with truncated Fourier series. In each panel, at least 15 frequencies have statistically significant ‘power’.

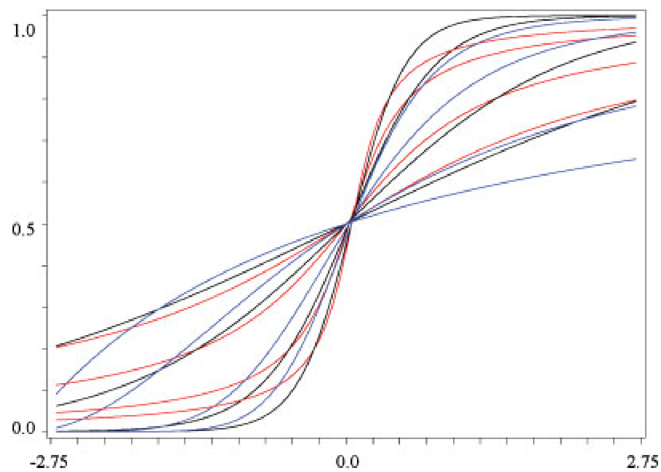

Plate 2. Several sigmoidal curves, plotted at half-maximum ± 2.75 for several values of the steepness parameters. Blue: Hill function with $\gamma = 1, 3, 5, 7$; black: anti-logistic function with $\beta = 0.5, 1.5, 2.5, 3.5$; red: arctangent function with $\beta = 0.5, 1.5, 2.5, 3.5$. For each curve, members of the other two parameterized families can be found that are similar in appearance, but not identical. In particular, when the curves have nearly equal slopes through the midpoint, the anti-logistic function exits the interval $(0.1, 0.9)$ at values nearer the midpoint than the Hill function, which in turn exits the interval $(0.1, 0.9)$ at values nearer the midpoint than the arctangent function.

time of day of the peak of the model, and hence serves as a model for the acrophase of the data. The parameter min is the minimum value of the function, and the parameter amp is the difference between the minimum and maximum value of the function (because the transformed cosine ranges from 0 to 1). The parameter β determines whether the function $r(t)$ rises and falls more steeply than the cosine curve: large values of β produce curves that are nearly square waves. When $r(t)$ has approximately a square-wave appearance, ϕ will represent the centre of what appears to be a flat region, and in this case the name 'acrophase' may appear to be a misnomer, though it is still technically the time at which $r(t)$ has its mathematically well-defined 'peak'. The parameter α determines whether the peaks of the curve are wider than the troughs: when α is small, the troughs are narrow and the peaks are wide; when α is large, the troughs are wide and the peaks are narrow. The parameters α and β (also m and γ) together determine how the shape of $r(t)$ differs from the shape of a cosine, so we call them collectively the 'shape parameters'; α and m we call the 'width' parameter; β and γ we call the 'steepness" parameter.

Sigmoidally transformed cosine curves illustrating the effects of variations in the shape parameters are presented for the Hill-transformed cosine curve in Figure 1. The underlying cosine curve is the same in all cases, as are the parameters min and amp. Panel (a) displays the effect of variation in the width parameter; panel (b) displays the effect of variation in the steepness parameter.

A measure analogous to the MESOR of the cosine model (or half the deflection of the curve) can be obtained from mes $=$ min $+$amp/2. However, it goes through the middle of the peak, and is therefore not equal to the MESOR of the cosine model, which is the mean of the data. The times of the day at which the curve rises through this half deflection point can be found from m and α from the fact that these are the values of the cosine at which the sigmoidal curve is $\frac{1}{2}$. For the Hill function, these quantities, denoted $t_{1/2}$, satisfy $c(t_{1/2})^{\gamma}/[m^{\gamma} + c(t_{1/2})^{\gamma}] = 1/2$, which for any γ occurs when $m = c(t_{1/2})$, which yields $\{1 + \cos[(t_{1/2} - \phi)2\pi/24]\}/2 = m$, so $t_{1/2} = \phi \pm \cos^{-1}(2m - 1)/(2\pi/24)$; the '$+$' gives the time that the function declines from above the half deflection to below, whereas the '$-$' gives the time that the curve rises from below the half deflection to above. For the anti-logistic transform, $1/2 = e^0/(1 + e^0)$, so for any β, $\cos[(t_{1/2} - \phi)2\pi/24] - \alpha = 0$, which implies that $t_{1/2} = \phi \pm \cos^{-1}(\alpha)/(2\pi/24)$. For the arctangent-transformed cosine curve, the arctangent is halfway from its minimum to its maximum when the argument is 0, and from this we can also derive $t_{1/2} = \phi \pm \cos^{-1}(\alpha)/(2\pi/24)$. In those cases where the curves are approximately rectangular waves, the $t_{1/2}$ values estimate the 'switching times' from low (or no) activity to high (or some) activity and back. If we denote the 'upper' and 'lower' $t_{1/2}$ values by $t_{1/2,u}$ and $t_{1/2,l}$, respectively, then the duration of the 'above middle' activity is given by $t_{1/2,u} - t_{1/2,l}$. In the cosine model this value is 12. In the truncated Fourier series, it is difficult to compute from the coefficients. Equivalently, we can compute the fraction of the day that the model is above the middle value, i.e. a 'width-ratio' as $(t_{1/2,u} - t_{1/2,l})/24$. The width-ratio is not the fraction of time that activity is above average or above the median, it is the fraction of time that the modelled high activity phase is above the midpoint between minimum and maximum modelled values.

The least-squares estimates of the Hill-transformed, anti-logistic-transformed, and arctangent-transformed cosine curves for the data of Plate 1 are presented, respectively, in Plates 3–5. The coding is the same in these Plates as in Plate 1: the data are represented by black dots, blocks of missing data by yellow bars, the standard cosine curve by the blue line, and the

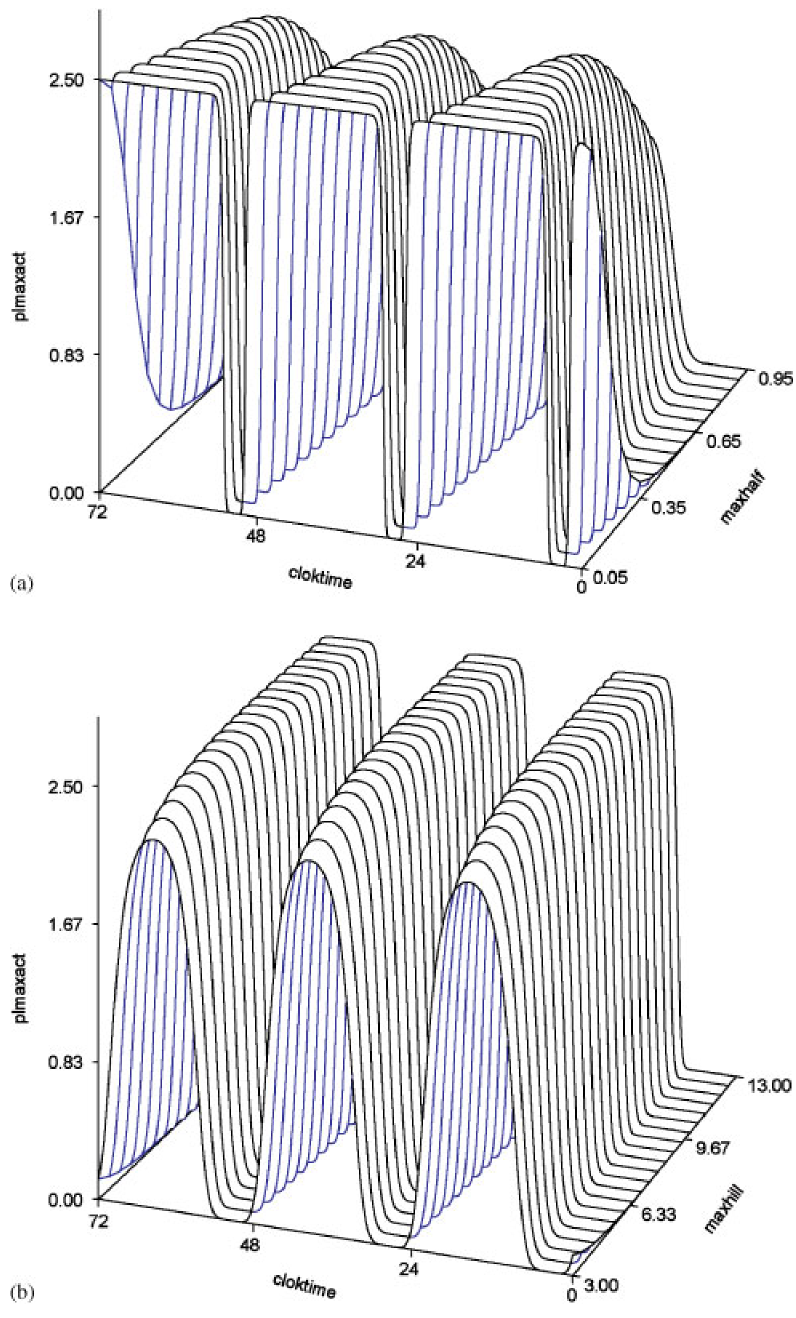

Figure 1. Hill-transformed cosine curves illustrating the effects of variation in m (a) and variation in γ (b). The parameters min, amp, and φ are constant. The transformed function is displayed on the vertical axis and is called 'plmaxact'. In (a) $\gamma = 5$, m (called 'maxhalf') = $0.05, 0.10, \ldots, 0.95$. In (b) $m = 0.5, \gamma$ (called 'maxhill') $= 3.0, 3.5, \ldots, 13$. Figures showing the effects of variation in α and β are similar in appearance.

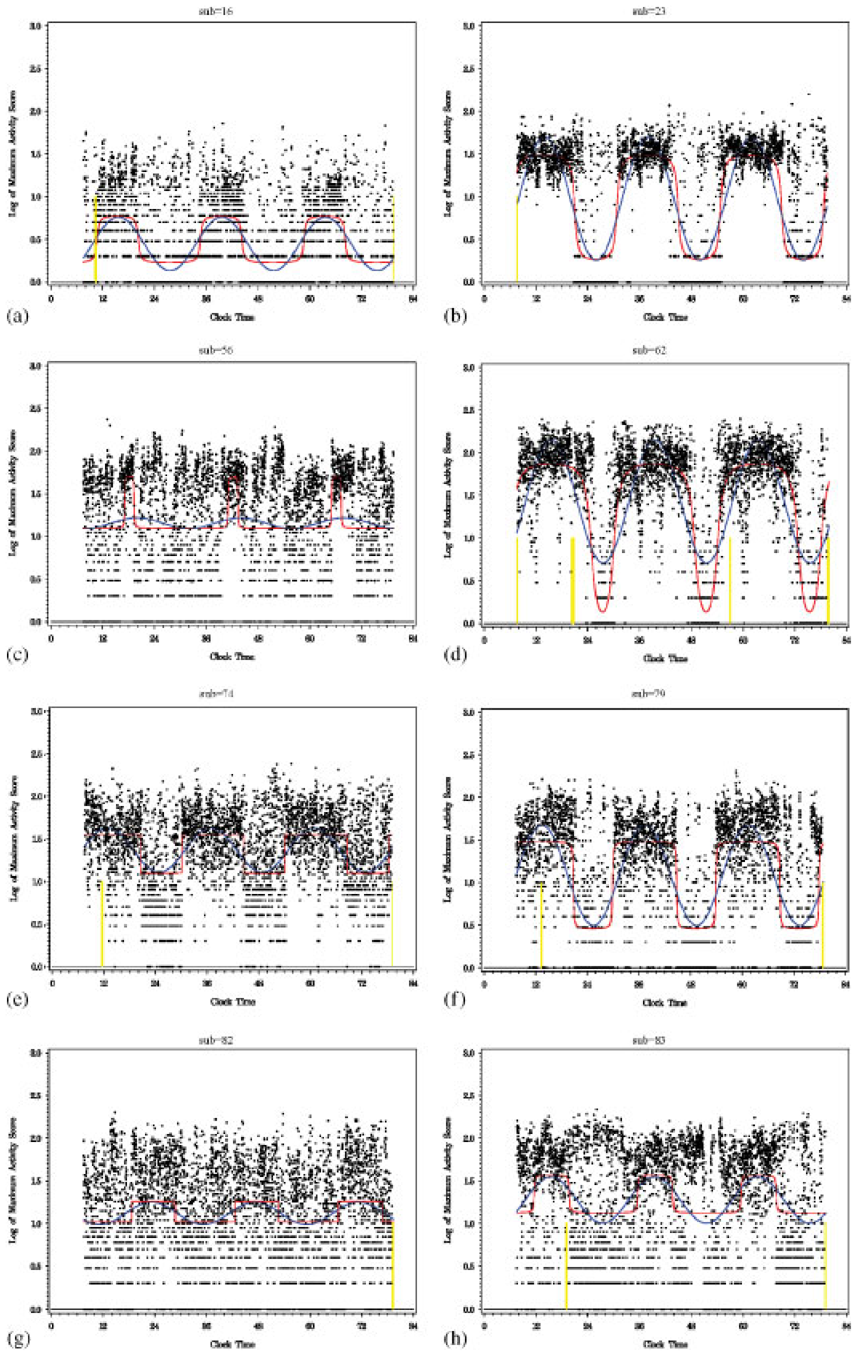

Plate 3. Hill-transformed cosine curve (red line) fit to data in Plate 1, A–H, with plain cosine (blue line).

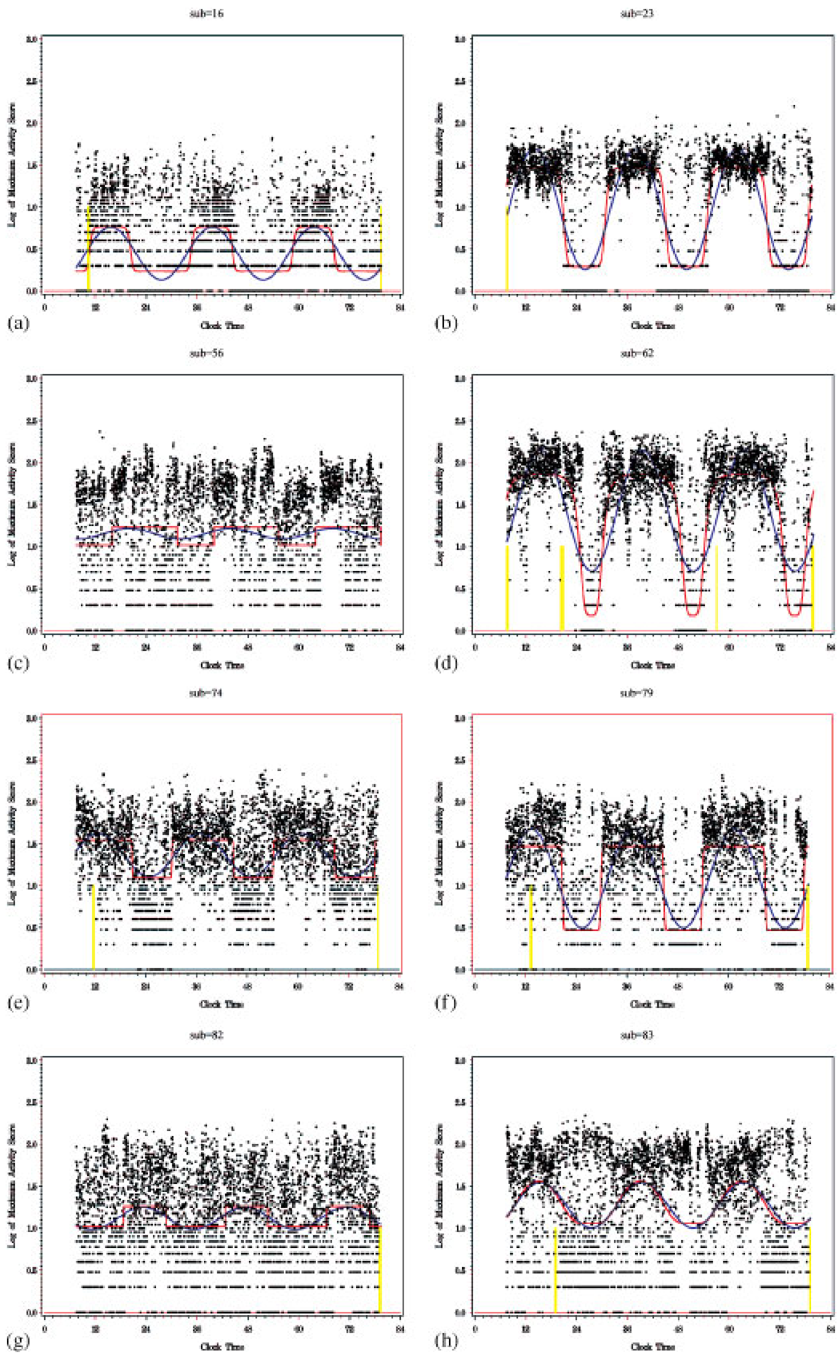

Plate 4. Anti-logistic-transformed cosine curve (red line) fit to data of Plate 1, A–H, with plain cosine (blue line).

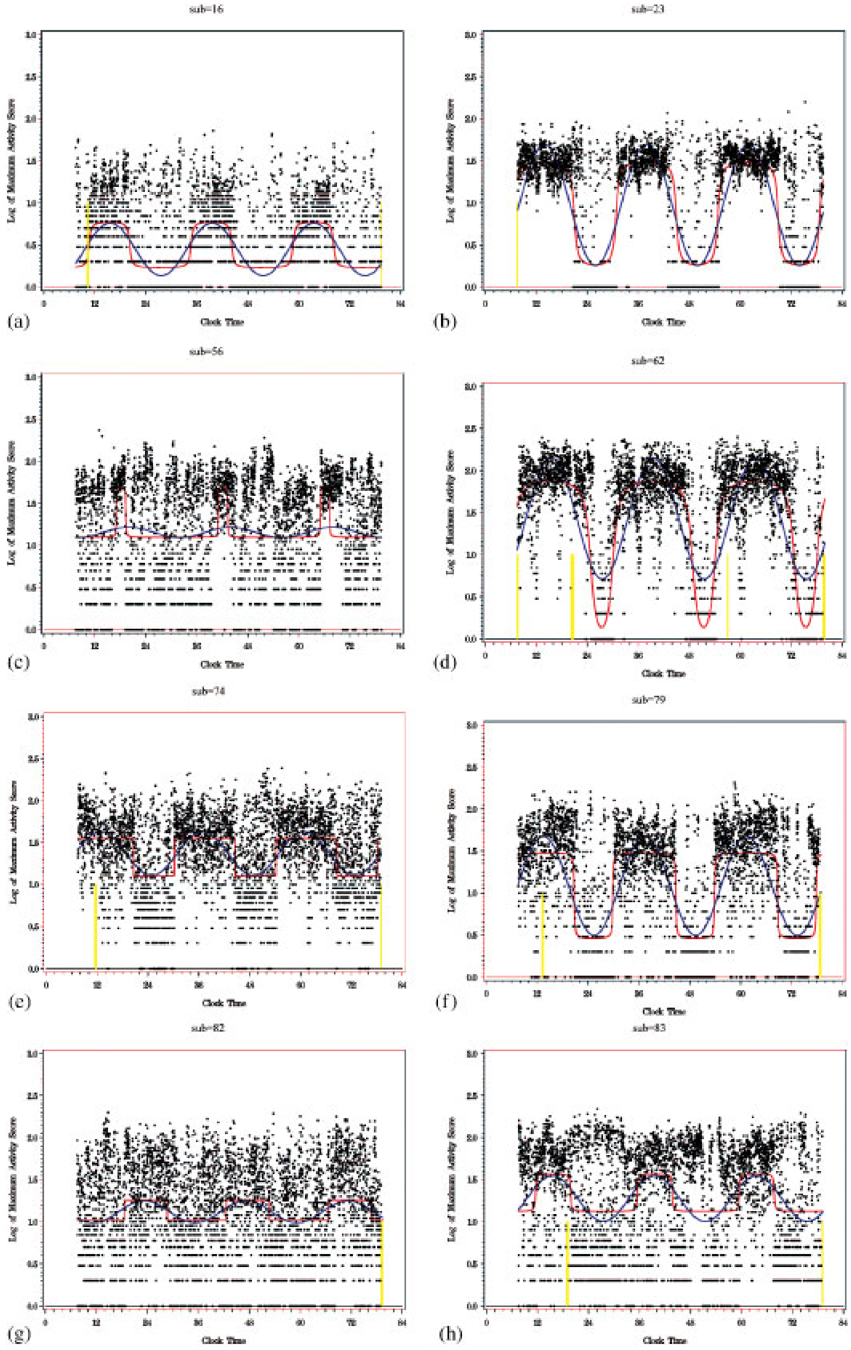

Plate 5. Arctangent-transformed cosine curve (red line) fit to data displayed in Plate 1, A–H, with plain cosine (blue line).

Table I. Fit statistics for models of data in Plates 1, 3, 4 and 5.

	Cosine	Truncated Fourier		Hill transformed		Anti-logistic transformed		Arctangent transformed	
Subject	R^2	R^2	F^{*}_{imp}	R^2	$F^{\dagger}_{\mathrm{imp}}$	R^2	$F^{\dagger}_{\mathrm{imp}}$	R^2	$F^{\dagger}_{\mathrm{imp}}$
A	0.19	0.33	23.7	0.24	117.4	0.24	116.9	0.23	109.3
B	0.51	0.61	30.2	0.56	272.2	0.56	267.8	0.56	276.7
C	0.04	0.19	26.1	0.02	42.7	0.06	126.2	0.06	127.9
D	0.43	0.67	77.9	0.62	1037.2	0.62	1012.7	0.62	1020.3
E	0.14	0.24	15.1	0.20	159.2	0.20	159.2	0.20	157.4
F	0.34	0.48	28.0	0.44	381.4	0.44	381.9	0.44	379.3
G	0.02	0.10	9.1	0.04	32.8	0.04	34.3	0.04	33.2
H	0.08	0.19	15.1	0.08	−0.3	0.08	2.5	0.09	16.8

*Numerator degrees of freedom equal 38.
†Numerator degrees of freedom equal 2.
All denominator degrees of freedom are greater than 4200.

sigmoidally transformed cosine curve by the red line. The fitted curves are similar, with two exceptions: (1) the Hill-transform produces a rectangular wave for data (C), whereas the anti-logistic- and arctangent transforms produce curves with narrow peaks and wide troughs; (2) the Hill- and anti-logistic-transformed cosine curves for data (H) are nearly indistinguishable from a cosine curve, whereas the arctangent transform produces a square wave.

The residuals from the cosine fitting and the extended cosine fitting were used to compute a 'pseudo-F' statistic to measure the improvement of the fit obtained by the non-linear estimation of the transformed cosine model. We call this F_{imp} for 'F of improvement', and compute it by $F_{\mathrm{imp}} = ((\mathrm{RSS}_{\cos} - \mathrm{RSS}_{\mathrm{ext}})/2)/(\mathrm{RSS}_{\mathrm{ext}}/(n-5))$, where $\mathrm{RSS}_{\cos}$ and $\mathrm{RSS}_{\mathrm{ext}}$ are the residual sums of squares of the cosine and sigmoidally transformed cosine models, respectively. These values are displayed in Table I with the R^2 values. Technically, F_{imp} measures the improvement of the sigmoidally transformed model over the restricted model that is used as the starting model for the non-linear estimation procedure. Because the starting model fits the cosine curve very well, F_{imp} is by inference a measure of the improvement of the extended cosine over the cosine curve from which it is computed. This F_{imp} is called 'pseudo-F' because it has the same form as the F-statistic in linear regression ([mean explained SS]/[mean residual SS]), but cannot be proved to have an exact F distribution; with Gaussian error and a large enough sample (so that the respective sums of squares are nearly independent), the 'pseudo-F' has approximately an F distribution (Reference [17] Chapter 12 review the asymptotic theory). The F_{imp} value for the truncated Fourier series is given by $F_{\mathrm{imp}} = ((\mathrm{RSS}_{\cos} - \mathrm{RSS}_{\mathrm{Fou}})/38)/(\mathrm{RSS}_{\mathrm{ext}}/(n-41))$. When estimation is by linear least squares, this is an exact F statistic not a 'pseudo-F' statistic.

The truncated Fourier series based on 20 frequencies has 41 estimated parameters, whereas each extended cosine model has five estimated parameters. The rank orders of the R^2 values of the curves in the sample are highly consistent across the four models. Because the denominator degrees of freedom are extremely high and equal within a few per cent, a similar claim should be true of other measures of model fit such as model F and Akaike information (AIC); see Reference [18] for a review of model selection criteria. All such criteria take into account the number of parameters and the residual least squares. Additionally, the degrees of freedom for the comparison of the two models is constant, so the rank orders of the model choice

Table II. Parameter estimates of Hill-transformed cosine curves.

Data	min	amp	ϕ	m	γ	$t_{1/2,\ell}$	$t_{1/2,r}$	Width-ratio
A	0.24	0.53	15.5*	0.65	16.8	10.7	20.3	0.40
B	0.29	1.18	13.9	0.37	6.9	6.8	20.9	0.57
C	1.02	0.21	23.7	0.29	566.6	16.0	31.4†	0.64
D	0.18	1.70	15.4	0.13	2.2	6.3	24.6	0.77
E	1.09	0.46	13.5	0.33	45.2	6.2	20.8	0.61
F	0.47	1.00	13.3	0.32	21.6	5.9	20.8	0.62
G	1.02	0.24	23.7	0.62	1464.5	18.6	28.8	0.41
H	1.06	1.01	15.0	1.00	2.2	9.0	21.0	0.50

*Times are in decimal hours.
†31.4 is equivalent to 7.4, but writing it this way facilitates computation of the width-ratio.

Table III. Parameter estimates of anti-logistic-transformed cosine curves.

Data	min	amp	ϕ	α	β	$t_{1/2,\ell}$	$t_{1/2,r}$	Width-ratio
A	0.24	0.53	15.4*	0.32	13.1	10.7	20.2	0.40
B	0.28	1.19	13.8	−0.26	9.2	6.8	20.9	0.59
C	1.08	1.18	18.3	0.99	19.7	12.3	24.3†	0.50
D	0.00	1.84	15.4	−0.74	7.5	5.6	25.2	0.82
E	1.09	0.46	13.5	−0.33	70.8	6.2	20.8	0.61
F	0.47	1.00	13.3	−0.37	33.0	5.9	20.8	0.62
G	1.02	0.24	23.9	0.35	170.0	19.1	28.7	0.40
H	0.95	1.27	15.4	1.00	1.2	9.4	21.4	0.50

*Times are in decimal hours.
†24.3 is equivalent to 0.3, but writing it this way facilitates computation of the width-ratio.

statistics, across subjects, depend primarily on some monotonic transform of the residual sum of squares compared to the total sum of squares. The rank orders of the F_{imp} statistics of the curves are also highly consistent across the models. Thus the model fit statistics agree as to (a) which curves are well fit, and (b) which curves are not well fit by the simple cosine curves. Although the R^2 values of the truncated Fourier representations are somewhat higher than the R^2 values of the transformed cosine curves, the F_{imp} statistics of the transformed cosine curves are much higher than the F_{imp} statistics of the truncated Fourier series. The small number of parameters of the transformed cosine curve provides a more efficient (and parsimonious) representation of the information than the truncated Fourier series.

The parameter estimates of the transformed cosine curves represent describable features of the curves better than the (41!) parameter estimates of the truncated Fourier series. Tables II–IV present the parameter estimates of the three sigmoidally transformed cosine curves corresponding to the data of Plate 1, as well as the $t_{1/2,\ell}$; $t_{1/2,r}$, and width-ratios computed from them. The comparable parameters ($\min, \text{amp}, \phi, m$ and α, γ and β) have very high rank correlations across this data set (selected to display the variety of shapes in the full data set, rather than to be 'representative'). The rank order of the min values is highly consistent, implying that all model summaries 'agree' which of these subjects have the best and worst rest (measured by the Actillume as periods of extremely low activity). The rank order of the

Table IV. Parameter estimates of arctangent-transformed cosine curves.

Data	min	amp	ϕ	α	β	$t_{1/2,\ell}$	$t_{1/2,r}$	Width-ratio
A	0.22	0.58	15.4*	0.32	11.3	10.7	20.2	0.40
B	0.19	1.33	13.9	−0.28	7.9	6.8	21.0	0.59
C	1.09	0.63	18.3	0.96	191.5	17.1	19.3	0.09
D	−0.42	2.36	15.4	−0.81	5.7	5.8	25.0†	0.80
E	1.10	0.45	13.4	−0.30	1188.3	6.2	20.6	0.60
F	0.45	1.04	13.3	−0.37	37.3	5.9	20.8	0.62
G	1.02	0.24	23.7	0.24	10149.2	18.6	28.7	0.42
H	1.12	0.45	15.6	0.48	32.7	11.6	19.7	0.34

*Times are in decimal hours.
†25.0 is equivalent to 1.0 but writing it this way facilitates computation of the width-ratio.

amp values is also highly, though not perfectly, consistent across the models, implying that the models agree which subjects have the greatest disparity between well-defined inactive and active periods. Similar statements apply, in these selected data, to the other parameters, and interpretations inferred from them. Any analyses of these summary statistics (as dependent variables or as covariates) that depend on their ordinal scale properties (such as analyses based on normal score transforms [19, 20] are likely to have results that are robust with respect to choice of sigmoidal transform.

The discordances between the models are as noteworthy as the concordances. In panel C, the only evidence for circadian rhythmicity consists of the short epochs of a few hours near 16–20, 40–44, and 64–68 h when the patient was *never at rest* (‘sundowning’); the Hill-transform model is a rectangular wave with a relatively high value of the width-ratio, whereas the anti-logistic transform and the arctangent transform models are curves with narrow peaks above those restless epochs, and they have small width-ratios. In panel H, the rhythmicity is subtle, and consists of a somewhat increased prevalence of low activity readings in the ‘trough’ portion of the curve; the Hill model and the anti-logistic model are practically indistinguishable from a sinusoidal curve, but the arctangent model is a rectangular wave. These discordances between models occurred in the panels that display very little rhythmicity in the activity recordings, but that is not necessarily always true.

Parameter estimation

All analyses were performed in SAS *v*. 9.0 [21], using PROC NLIN with the Levenburg-Marquardt algorithm. Parameter estimation was performed in two stages. In stage 1 the parameters of the traditional cosine curve were estimated by linear least squares projection of the data onto sine and cosine curves of period 24 h. The coefficients of this linear model were non-linearly transformed into MESOR (estimated by the mean in this case), amplitude and acrophase. Then the parameters of the extended cosine model were estimated by non-linear least squares, with the starting values of the parameters computed from the MESOR, amplitude and acrophase of the best-fitting cosine curve. The data of all patients in the study were modelled independently of each other and graphed. All graphs were reviewed to determine the adequacy of the fitted models before analyses of the parameter estimates were conducted.

The starting values for each of the extended cosine models were calculated in such a way as to produce an extended cosine curve which had nearly the same form as the least-squares cosine curve, and hence nearly equal residual sum of squares. For each model, the starting value of ϕ was unchanged from the least-squares cosine model. For the Hill-transformed cosine curve: min $=$ mean $-$ cosine amplitude; amp $= 2.8$ cosine amplitude; $m = 0.5$; $\gamma = 1.4$. 'Cosine amplitude' denotes the amplitude estimate from fitting the cosine curve; for the cosine curve, the amplitude is half of the maximum minus the minimum. These values, 2.8, 0.5, and 1.4 were determined by trial and error to produce curves that looked extremely similar to cosine curves. For the anti-logistic-transformed cosine curve: min $=$ mean $-$ cosine amplitude; amp $= 2$ cosine amplitude; $\alpha = 0$; $\beta = 2$. For the arctangent-transformed cosine curve: min $=$ mean $-$ cosine amplitude $-$ (cosine amplitude)/2; amp $= 2$ cosine amplitude; $\alpha = 0$; $\beta = 2$. When the data oscillate near 0, even if they are all non-negative like the data presented here, the min estimate for the arctangent-transformed cosine may be negative when the data have approximately the sinusoidal shape.

We estimate the parameters with constraints: $\beta \geqslant 0$ ensures the identifiability of β; $-1 \leqslant \alpha \leqslant 1$ permits the inversion of the cosine function in the computation of $t_{1/2,\ell}$ and $t_{1/2,r}$; $-6 < \phi < 30$ prevents the estimation algorithm from jumping around indefinitely between values separated by a multiple of 24 (Mary Ann Hill, 1987, personal communication), and it also permits the algorithm to find values that are close to the starting values but 'just beyond' 0 or 24 (e.g. when the cosine estimate is 23.5 and the transformed cosine estimate is 24.5). These constraints are seldom active in the solution, but one case where they are active is noteworthy, and is illustrated by the anti-logistic-transformed model of data panel H; the least-squares estimate of α is 1 and is active and statistically significant as judged by the Lagrange multiplier test. For this data set, that is a trivial improvement over the starting values, so the curve is judged to be equivalent to the cosine; $t_{1/2,r}$ and $t_{1/2,\ell}$, are set equal to $\phi \pm 6$. In H, the constraint is not active in the estimate of the arctangent model.

DISCUSSION

The parameter estimates are solutions to the normal equations. We might expect from the implicit function theorem [22] that there would be a function mapping the parameter estimates for one model to the parameter estimates from the other models. However, the output from the SAS fitting program shows that the Jacobian matrices do not always have full column rank, when evaluated at (or in a neighbourhood of) the solution of the normal equations [17]. Thus, the Hill, anti-logistic, and arctangent transforms (and other sigmoidal transforms) of cosine curves do not generally provide equivalent parameterizations of the same class of functions to be fitted to the data. It is at least conceptually possible that analyses of the parameter estimates of some of the sigmoidally transformed cosine curves might yield different conclusions from analyses of parameter estimates of other sigmoidally transformed cosine curves fitted to the same data. This is different from linear models of time series data, where the coefficients with respect to one basis may be transformed to the coefficients with respect to another basis using a transformation matrix computed *a priori* [23].

Compared to the harmonic regression analysis of circadian rhythms, the extra parameters of the sigmoidally transformed cosine curves are parsimonious representations of easily describable features of some data sets that are not parsimoniously representable in other parameterized families of functions. Those features may be clinically important. Gehrman *et al.* [19] found a positive relationship between survival and the rectangularity of activity circadian rhythms (represented by the parameter β of the anti-logistic-transformed cosine curve) in institutionalized elderly patients. Gehrman *et al.* [20] found a non-monotonic relationship between the mini mental status exam [24] measure of cognitive functioning and the width-ratio of activity circadian rhythms (represented by the parameter α of the anti-logistic-transformed cosine curve) in a subsample of those patients who had 'good' circadian rhythms (defined by a median split on the *F*-statistic of model fit). Martin *et al.* [10] found a relationship between behavioural rhythm characteristics and medication use in Alzheimer's disease patients: γ scores were positively correlated with use of anti-depressant medication. We have also extended the sigmoidally transformed cosine curve (and sigmoidal transforms of other 'clock' models such as the van der Pol oscillator) to more complex problems and multiple measurements: core body temperature, wheel running and gross body movement of Syrian hamsters; simulated multimodal circadian rhythms such as social rhythms; salivary melatonin measurements and measurements in urine of the major metabolite AMT6s in humans; core body temperature, cortisol, and activity, simultaneously measured in humans; REM and slow wave sleep countercyclical rhythms in all night EEG recordings in drug-free and drug-present conditions; ambulatory diastolic and systolic blood pressure recordings in humans. We have presented our results in posters at scientific meetings, and copies of the posters are available from the corresponding author. Such results must be replicated and extended before sigmoidally transformed cosine curves can be said to be an important contribution to the mathematical analysis of circadian rhythms, but they show that the technique has the potential to be informative and useful.

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