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The Sigmoidally-transformed Cosine Curve: A Mathematical Model for Circadian Rhythms with Non-sinusoidal Shapes

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Abstract

We introduce a family of nonlinear transformations of the traditional cosine curve used in the modeling of biological rhythms. The nonlinear transformation is the sigmoidal family, represented here by three family members: the Hill function, the 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 2 additional harmonics to achive the same fit when modeled 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. We illustrate the sigmoidally transformed cosine curves, and compare them to harmonic regression modeling, in a sample of 8 activity recordings made on patients in a nursing home.

Key Words: cosine, logistic function, Hill Function, arcsine function, circadian rhythms, nonlinear Fourier analysis

INTRODUCTION

Numerous biological processes follow predictable patterns that repeat approximately once every 24 hours. 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 modeling 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 and colleagues (1967).

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 (van Someron et al 1999).

The data in Figure 1 illustrate this common problem in the modeling and analysis of circadian rhythms. In these figures, the data (described more fully below) are plotted as black dots, and the best-fitting cosine curve is plotted in blue [Tong, 1977; Bingham *et al*., 1982]. 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 hours during which the data are "relatively high", and a complementary interval during which they are "relatively low". The usual approach to modeling data that are not sinusoidal in appearance is to fit a truncated Fourier series, and the result of such a fit is displayed in Figure 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, …, 1.2 hours, *i.e.* the base frequency and its first 19 harmonics [Fuller, 1976; Marler *et al.*, 1982; Brown and Czeisler, 1992; Gaffney et al. 1993; Fernandez et al, 2003]. 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 can not tell from the table of parameter estimates which, if any, of these curves are most nearly rectangular; one can not rank order 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. [Martin *et al.,* 2000； Ancoli-Israel *et al.,* 2003; Gehrman *et al.* 2003; Ancoli-Israel *et al.,* 2003]

DATA COLLECTION

Subjects: Data from 92 nursing home residents (63 women) participating in an intervention trial to improve sleep and behavioral problems are included in this study. All lived in one of four San Diego area nursing homes for a minimum of two 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 minute 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 seconds and stored every minute on a 32K byte memory chip, which was sufficient to record activity and illumination data for over five 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 modeled were the logarithms of the maximum activity, named LMAXACT = $\log_{10}$(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-hour periods, i.e., 72 hours. The experimental manipulations in the other phases, as well as other procedural details, can be found elsewhere. [Martin *et al.,* 2000; Ancoli-Israel *et al.,* 2003; Gehrman *et al.* 2003; Ancoli-Israel *et al.,* 2003]

MATHEMATICAL MODEL

Equations

The fundamental equation of the cosine model is:

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

where *r(t)* denotes the modeled 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 modeled value of r. The parameters can be estimated from data using linear least squares (projection on sine and cosine curves with a 24-hour period) followed by a nonlinear transformation of coefficients to obtain *amp* and ϕ; or they can be estimated by nonlinear 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.) Because of differences in the estimation procedures, *mes, amp*, and ϕ estimated by linear least squares may not exactly equal *mes, amp*, and ϕ estimated from the same data set by nonlinear least squares.

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, logistic function, and arctangent function.

The Hill function [Keener and Sneyd 1998; in neuronal modeling this is called the Naka-Rushton function: Wilson, 1999] is written $h(x) = x^{\gamma} /(m^{\gamma} + x^{\gamma})$. The function $h(x)$ is defined for $x \geq 0$, and rises from 0 to 1 as *x* increases. The parameter *m*, called the Michaelis constant, is the value of *x* at which $h(x) = ½$. The larger γ is, the more steeply the curve rises in a neighborhood of *m,* and the more it resembles a step function.

The logistic function is written $\ell(x) = \exp(\beta[x-\alpha])/\{1+\exp(\beta[x-\alpha])\}$. 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 $x = \alpha$, $\ell(x) = ½$. As β increases, $\ell(x)$ becomes steeper in a neighborhood of α, and increasingly resembles a step function.

The arctangent transform is written $\psi(x) = \tan^{-1}[\beta(x-\alpha)]/\pi + 1/2$, where the arctangent function is rescaled by π and has ½ added to it so the range is (0,1) instead of (-π/2, π/2). With $\beta > 0$, the parameters α and β have the same interpretation as in the logistic function: α is the value of *x* for which $\psi(x) = 1/2$; β determines how steeply $\psi(x)$ rises in a neighborhood 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 $h(c(t)) = c(t)^{\gamma}/(m^{\gamma} + c(t)^{\gamma})$; the 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 $\psi(c(t)) = \tan^{-1}[\beta(c(t)-\alpha)]/\pi + 1/2$.

The sigmoidally transformed cosine models of the data are given by: $r(t) = min + amp \cdot h(c(t))$; $r(t) = min + amp \cdot \ell(c(t))$; $r(t) = min + amp \cdot \Psi(c(t))$.

In this model, ϕ is still the 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 center 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, logistically transformed cosine, and arctangent-transformed cosine curves in Figures 3, 4, and 5 respectively (the same cosine curve has been used repeatedly.) Panel (a) in each figure displays the effect of variation in the width parameter, and 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, whether the MESOR of the cosine curve is estimated by linear or nonlinear least squares. 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 ½. 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 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 modeled high activity phase is above the midpoint between minimum and maximum modeled values.

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 [Chen *et al.*, 2001]

The least-squares estimates of the Hill-transformed, logistic transformed, and arctangent transformed cosine curves for the data of Figure 1 are presented respectively in Figures 6, 7, and 8. The coding is the same in these figures as in Figure 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 extended 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 logistic- and arctangent transforms produce curves with narrow peaks and wide troughs; (2) the Hill- and 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 nonlinear estimation of the extended cosine model. We call this F_{imp} for "F of improvement", and compute it by $F_{imp} = ((RSS_{\cos} - RSS_{ext})/2)/(RSS_{ext}/(n-5))$, where $RSS_{\cos}$ and RSS_{ext} are the residual sums of squares of the cosine and sigmoidally transformed cosine models respectively. These values are displayed in Table 1 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 nonlinear 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. The F_{imp} value for the truncated Fourier series is given by $F_{imp} = ((RSS_{\cos} - RSS_{Fou})/38)/(RSS_{ext}/(n-41))$. 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 percent, a similar claim is true of other measures of model fit such as model F and Akaike information (AIC). Rao and Wu (2001) review 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 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 AIC values of the transformed cosine curves are also much higher than the AIC 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 2 through 4 present the parameter estimates of the three sigmoidally transformed cosine curves corresponding to the data of Figure 1, as well as the $t_{1/2,\ell}$, $t_{1/2,r}$, and width ratios computed from them. The comparable parameters (*min*, *amp*, ϕ, *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 *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 [Gehrman *et al*, in preparation]) 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 hours when the patient was *never at rest*; the Hill-transform model is a rectangular wave with a relatively high value of the width ratio, whereas the 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 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 (SAS Institute Inc, 1999), 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 hours. 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 nonlinear 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 modeled 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-square 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; γ = 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 logistic-transformed cosine curve: *min* = mean – cosine amplitude; *amp* = 2 cosine amplitude; α = 0; β = 2. For the arctangent-transformed cosine curve: *min* = mean – cosine amplitude – (cosine amplitude)/2; *amp* = 2 cosine amplitude; α = 0; β = 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: $\beta \geq 0$ ensures the identifiability of β; $-1 \leq \alpha \leq 1$ 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 logistic-transformed model of data panel

H; the least-square 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 [James, 1963] 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 neighborhood of) the solution of the normal equations [Gallant, 1977]. Thus, the Hill-, 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* [Nering, 1963].

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.* (in press) found a positive relationship between survival and the rectangularity of activity circadian rhythms (represented by the parameter β of the logistic-transformed cosine curve) in institutionalized elderly patients. Gehrman *et al*. (in review) found a non-monotonic relationship between the Mini Mental Status Exam (Folstein *et al*., 1975; measure of cognitive functioning) and the width-ratio of activity circadian rhythms (represented by the parameter α of the 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. (2000) found a relationship between behavioral rhythm characteristics and medication use in Alzheimer's disease patients: γ scores were positively correlated with use of antidepressant medication. 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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Table 1 Fit statistics for models of data in Figures 1, 6, 7, 8.

	Cosine	Truncated Fourier		Hill-transformed		Logistic-transformed		Arctangent-transformed	
Subject	R^2	R^2	F_{imp} *	R^2	F_{imp} **	R^2	F_{imp} **	R^2	F_{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

Notes: * Numerator degrees of freedom equal 38. ** Numerator degrees of freedom equal 2. All Denominator degrees of freedom are greater than 4200.

Table 2 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[1]	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[2]	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

Notes: [1] times are in decimal hours. [2] 31.4 is equivalent to 7.4, but writing it this way facilitates computation of the width-ratio.

Table 3. Parameter estimates of 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[1]	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[2]	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

Notes: [1] times are in decimal hours. [2] 24.3 is equivalent to 0.3, but writing it this way facilitates computation of the width-ratio.

Table 4 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[1]	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[2]	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

Notes: [1] times are in decimal hours. [2] 25.0 is equivalent to 1.0 but writing it this way facilitates computation of the width-ratio.

Figure captions

Figure 1 Truncated Fourier series (24 hour base period and 19 harmonics) of selected data files. The black dots are the logarithms (base 10) of the maximum activity scores recorded at 2-minute intervals. The variable "cloktime" is referenced to midnight prior to the start of the recordings..
The blue line is the best fitting cosine curve. The red line is the best-fitting (linear least square) 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" periods and the "low" 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".

Figure 2 Several sigmoidal curves, plotted at half-maximum +/- 2.75 for several values of the steepness parameters. Blue: Hill function with γ = 1, 3, 5, 7; black: logistic function with β = 0.5, 1.5, 2.5, 3.5; red: arctangent function with β = 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 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.

Figure 3 Hill transformed cosine curves illustrating the effects of variation in *m* (a) and variation in γ (b**).** In (a) $\gamma = 5$, $\alpha = 0.05, 0.10, \ldots, 0.95$. In (b), $\alpha = 0.5$, $\gamma = 3.0, 3.5, \ldots, 13$.

Figure 4 Logistic-transformed cosine curves illustrating the effects of variations in α (a), and β (b**).** In (a), $\beta = 10$, $\alpha = -0.9, -0.8, \ldots, 0.9$. In (b), $\alpha = 0$, $\beta = 1, 3, \ldots, 41$.

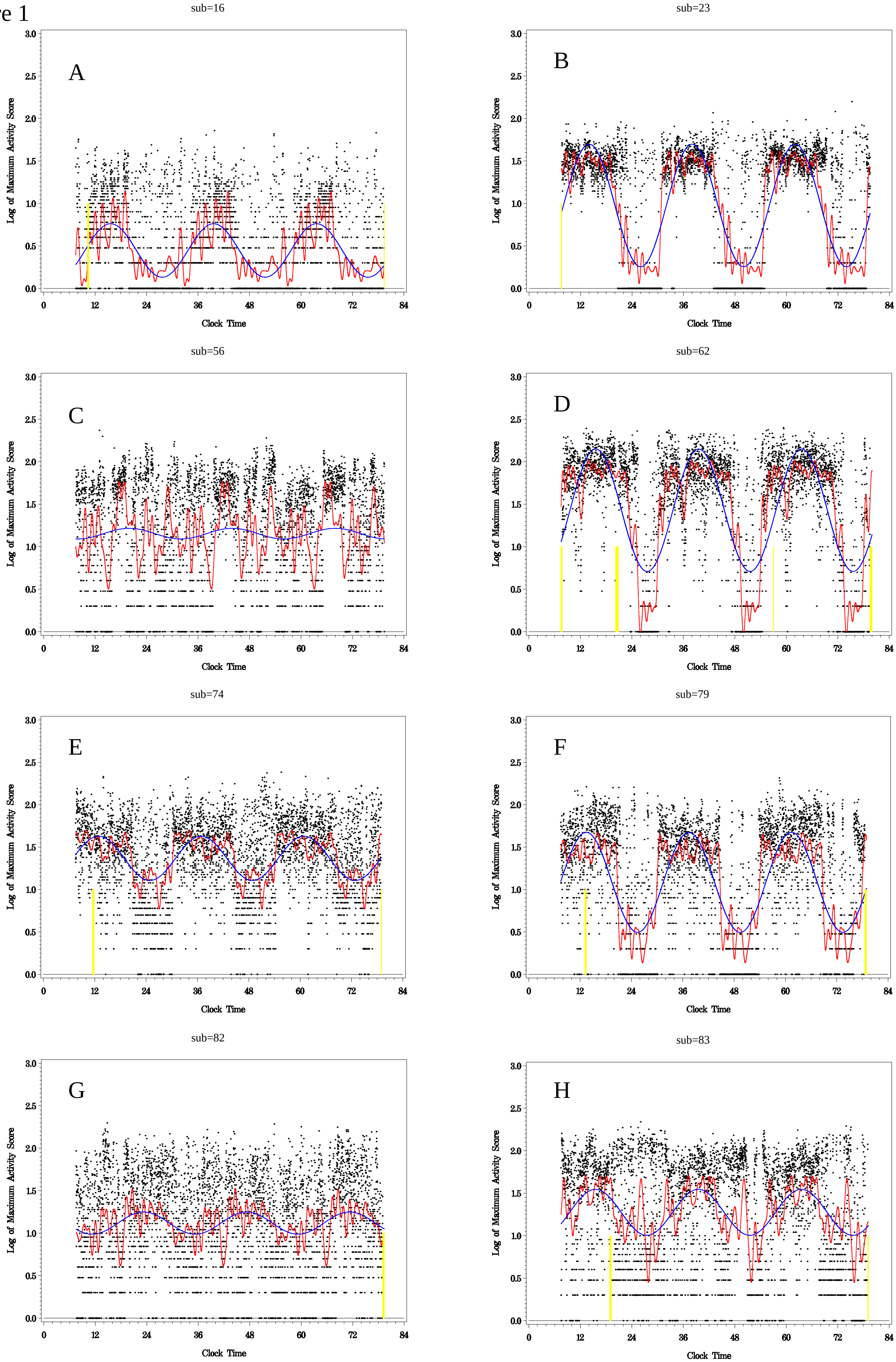
Figure 5 Arctangent-transformed cosine curves illustrating the effects of variations in α (a), and β (b). In (a), $\beta = 20$, $\alpha = -0.9, -0.8, \ldots, 0.9$. In (b), $\alpha = 0$, $\beta = 1, 5, \ldots, 81$.

Figure 6 Hill transformed cosine curve fit to data in figure 1, A-H. Black dots are data, blue line is best-fitting cosine curve, and red line is best-fitting Hill-transformed cosine curve.

Figure 7 Logistic transformed cosine curve fit to data of figure 1, A-H.

Figure 8 arctangent-transformed cosine curves fit to data displayed in figure 1, A-H.

Figure 1



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B
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C
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F
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G
sub=83
H
Log of Maximum Activity Score
Clock Time
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3.0
0
12
24
36
48
60
72
84

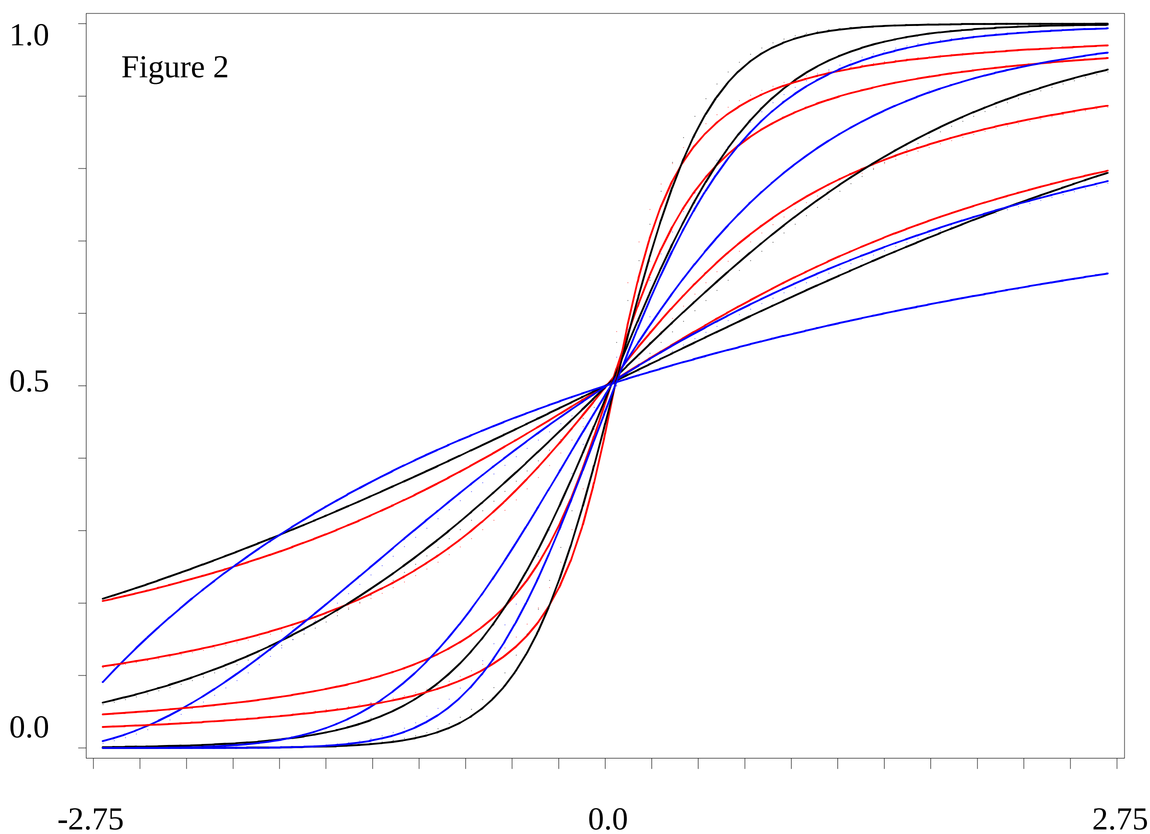

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Figure 2
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0.0
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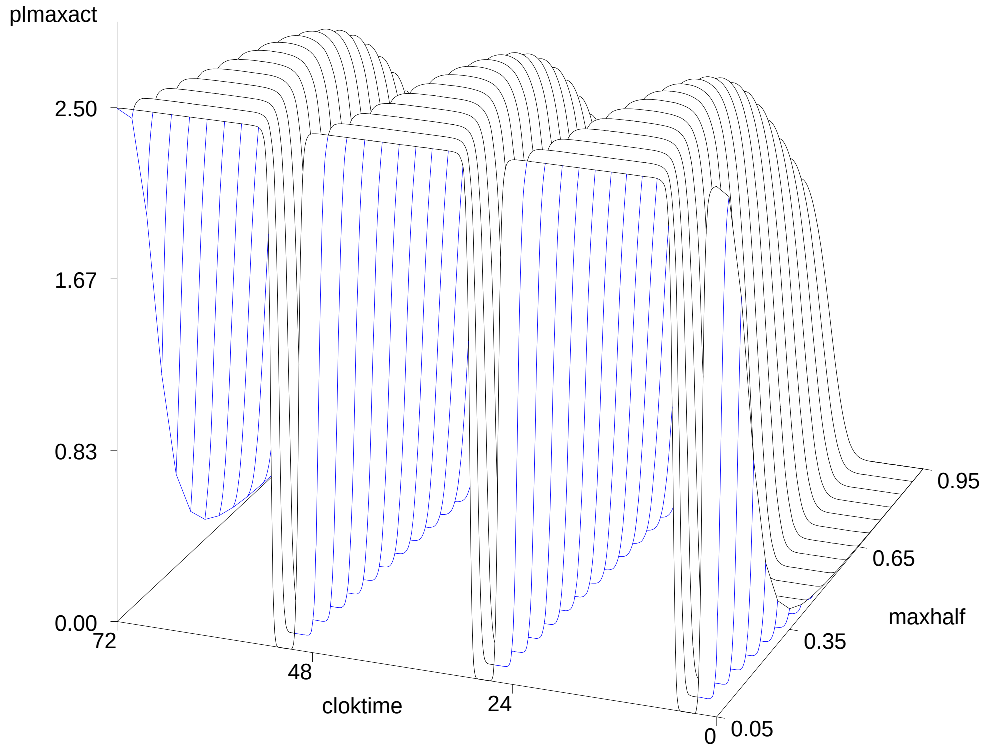
0.0
2.75

Figure 3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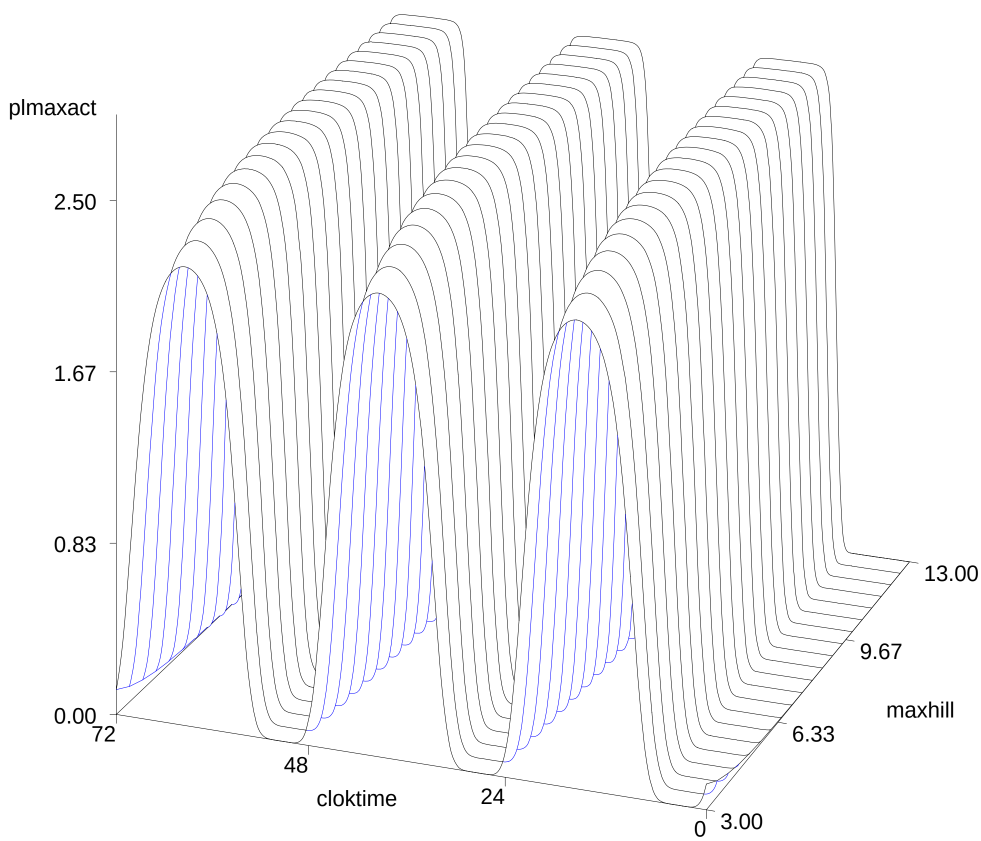
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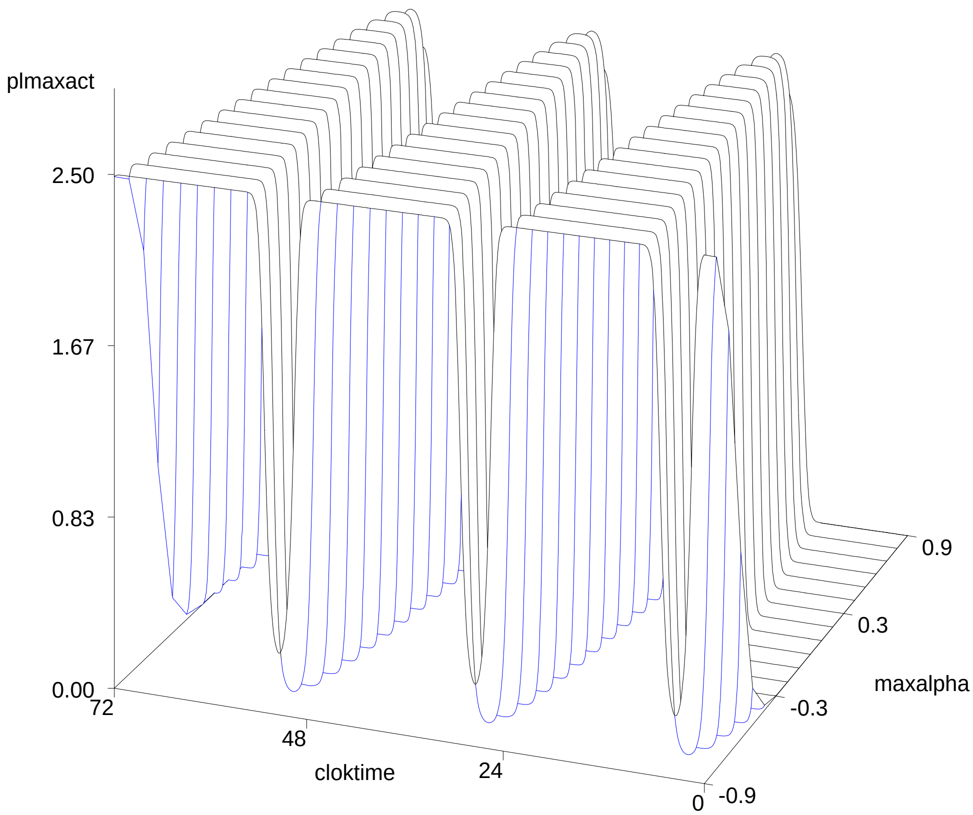
13.00

Figure 4



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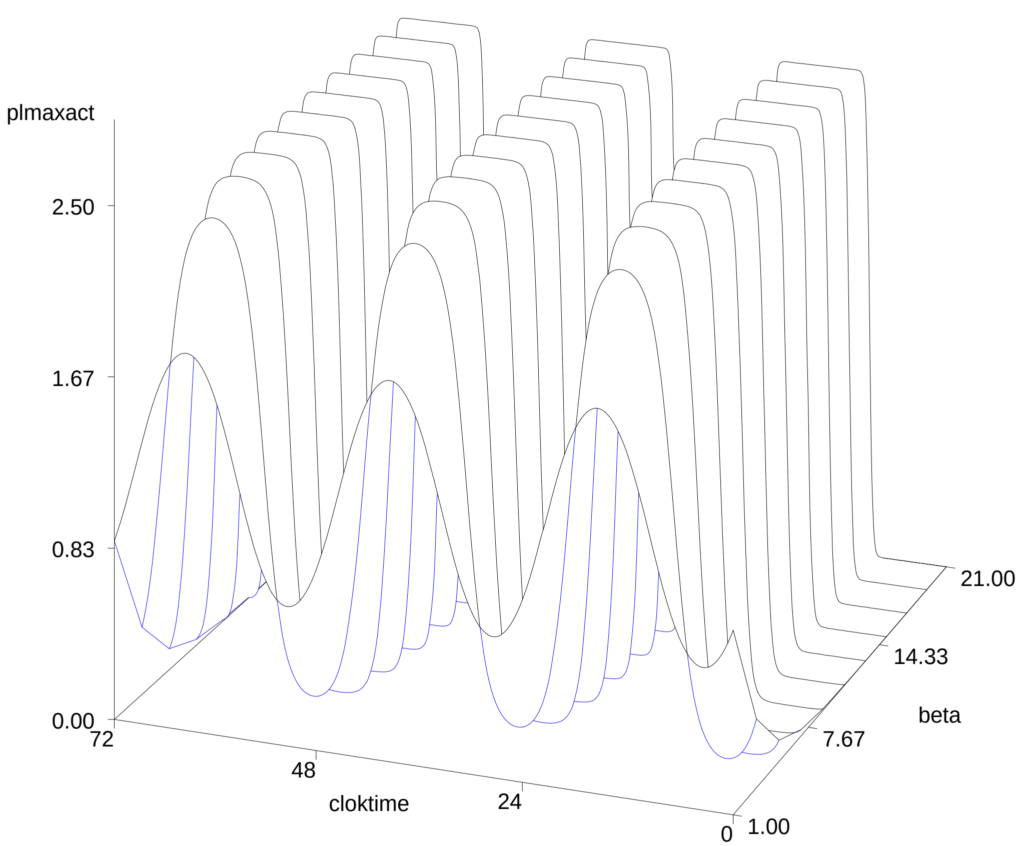

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beta
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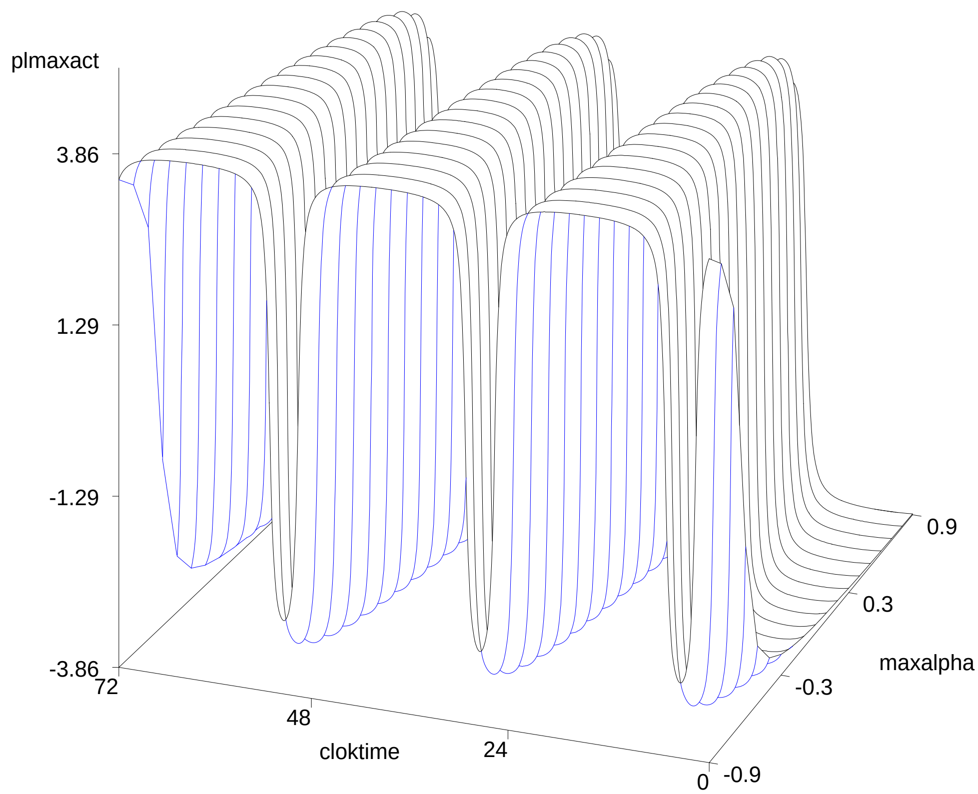
21.00

Figure 5



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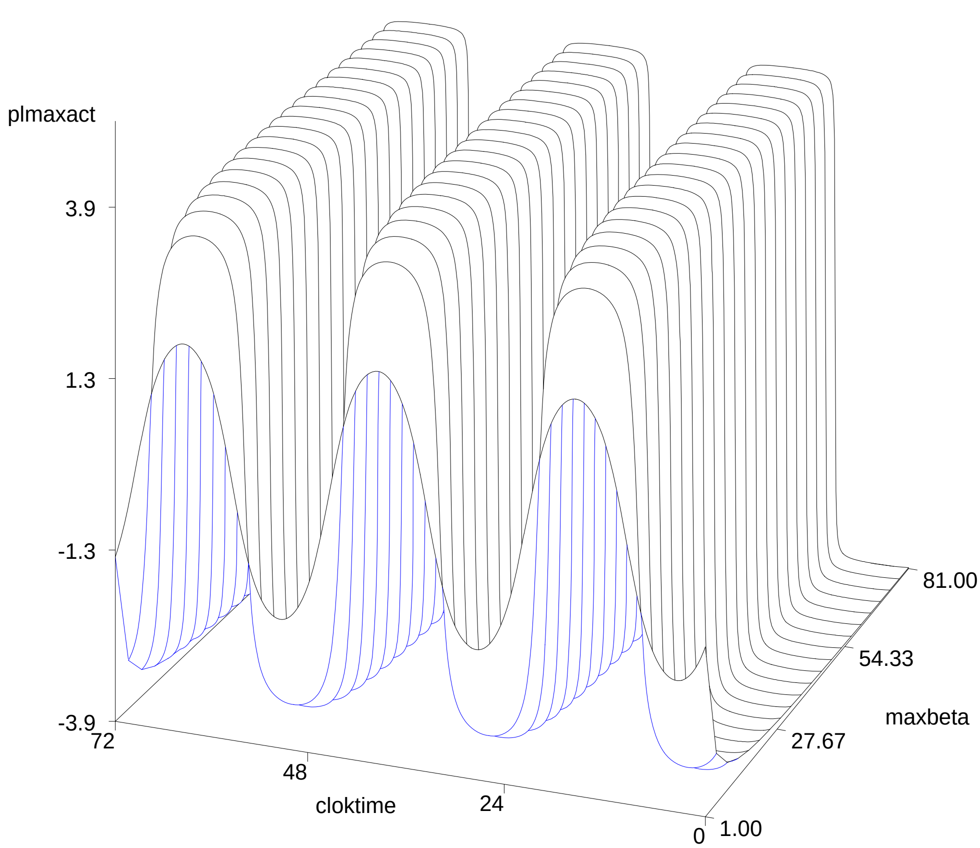

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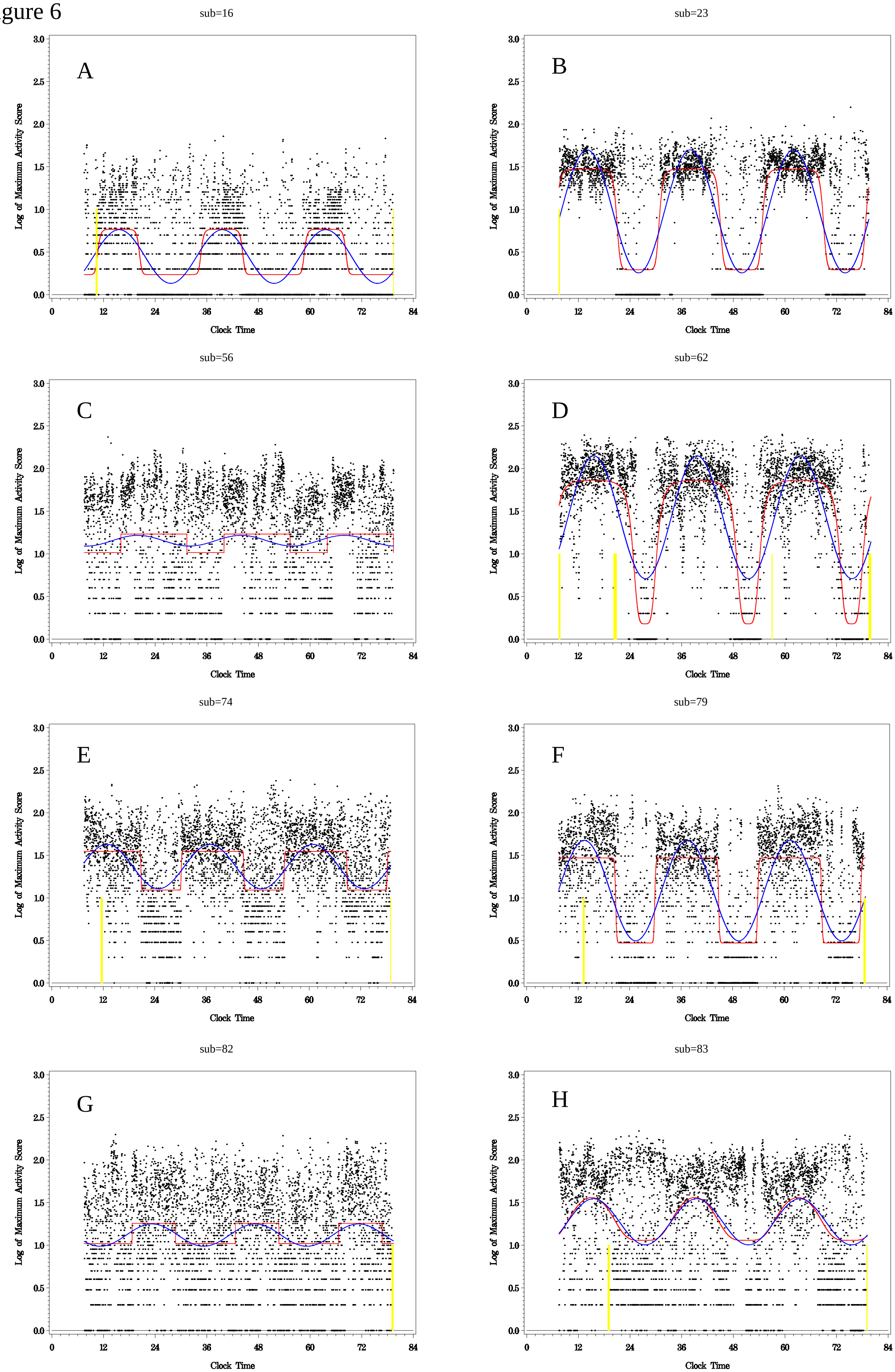
81.00

Figure 6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Log of Maximum Activity Score
Clock Time
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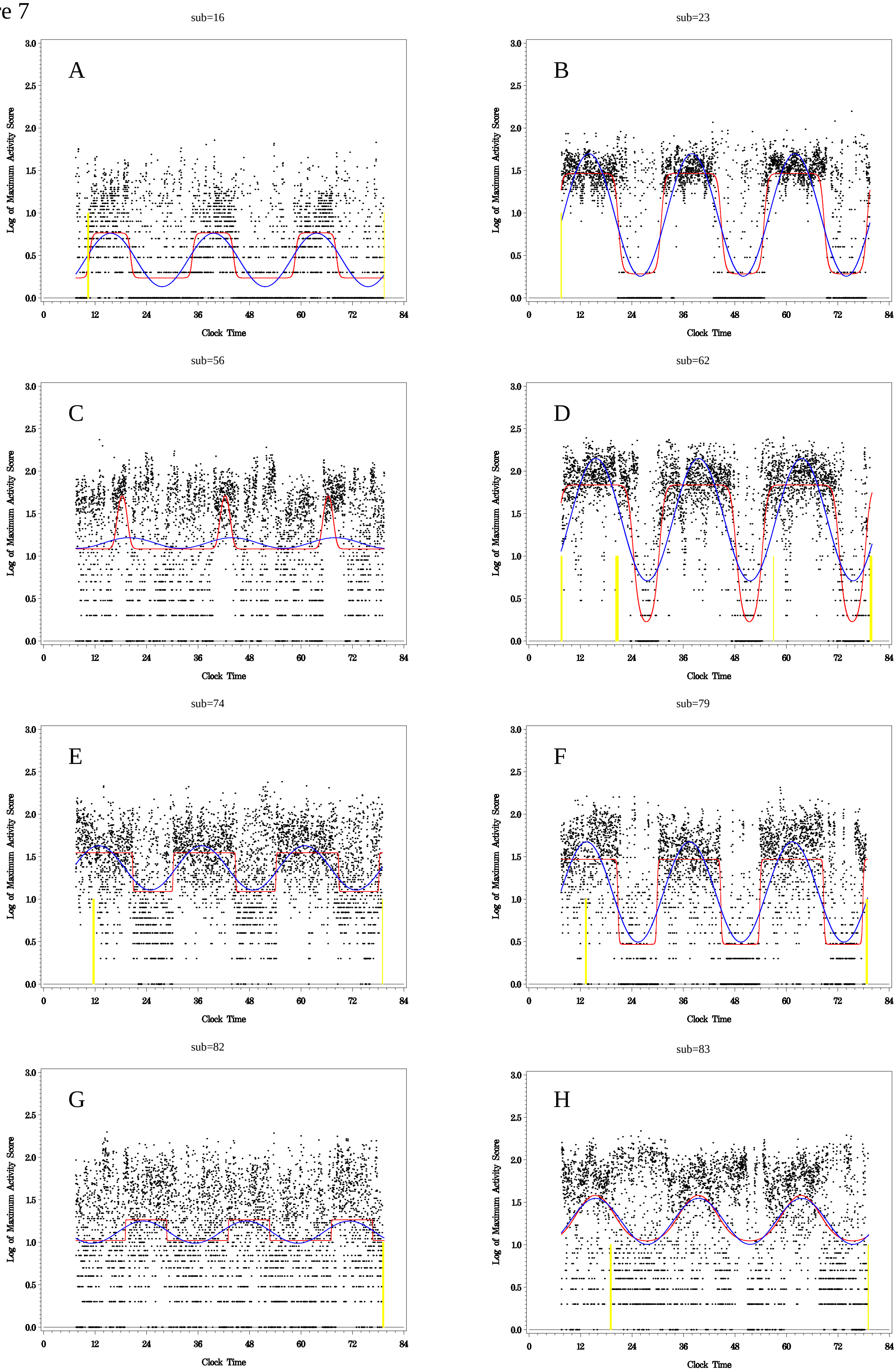
1.5
2.0
2.5
3.0
0
12
24
36
48
60
72
84

Figure 7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Log of Maximum Activity Score
Clock Time
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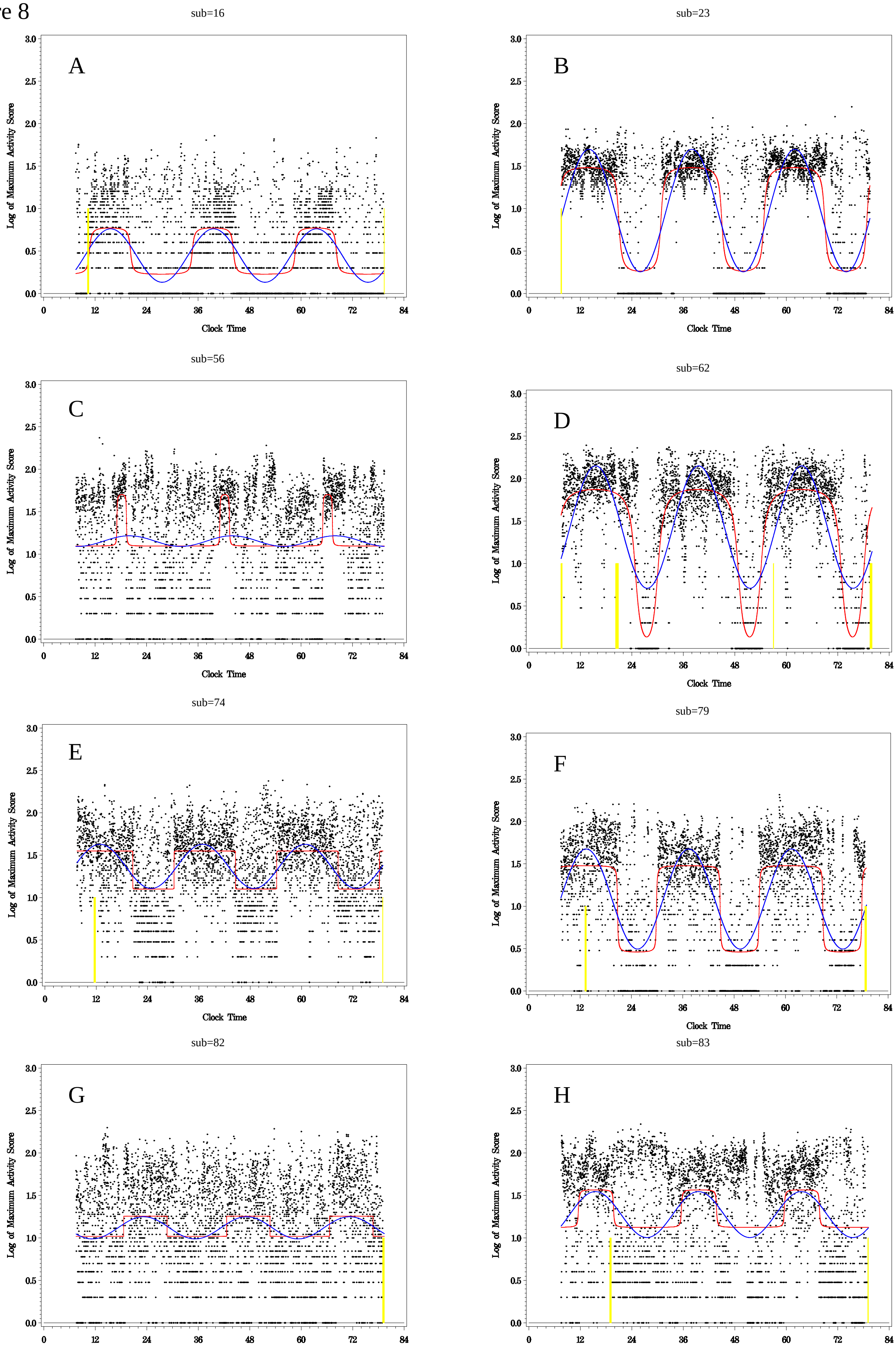
0
12
24
36
48
60
72
84

Figure 8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Log of Maximum Activity Score
Clock Time
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1.0
1.5
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2.5
3.0
0
12
24
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48
60
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