Modelling Time as a Circular Scale

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Chronobiology Definition and Time

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Chronobiology is a discipline whose principles consider **time** as an essential dimension of biological phenomena.

Time

- Biological time may be linear (chronological time) and cyclical (period time).

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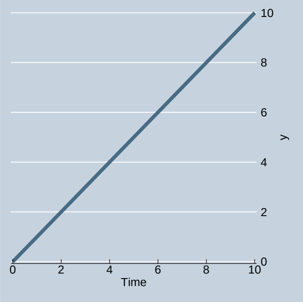

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- GLM: Rates, persons time at risk (Family Poisson, offset: time at risk and link log).

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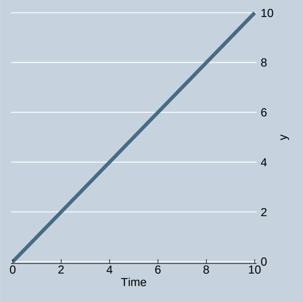

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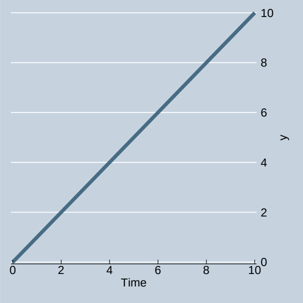

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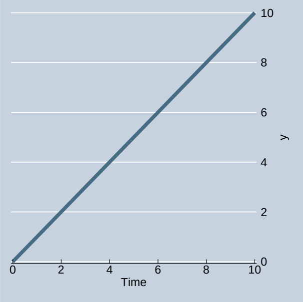

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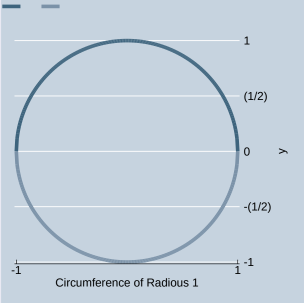

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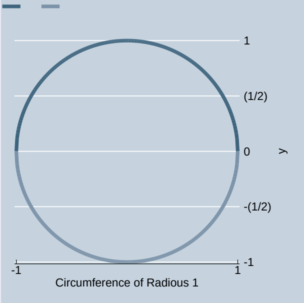

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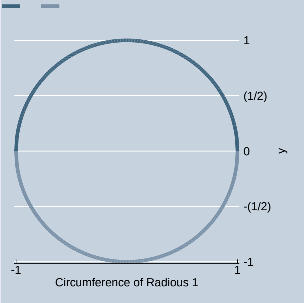

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Circular time modeling assumptions

Sinusoidal pattern

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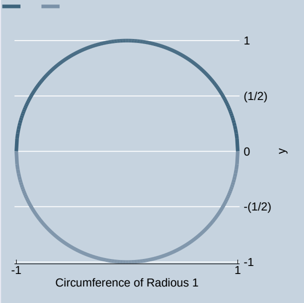

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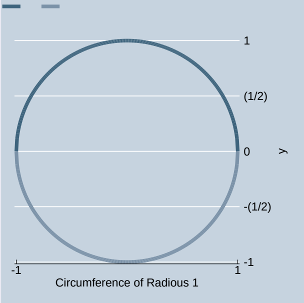

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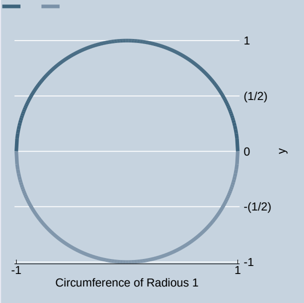

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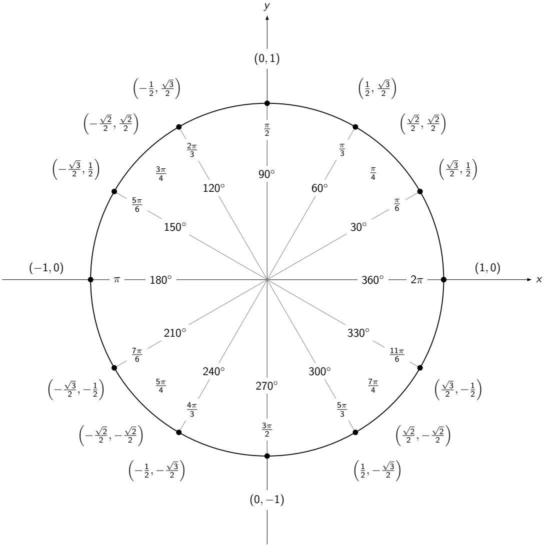
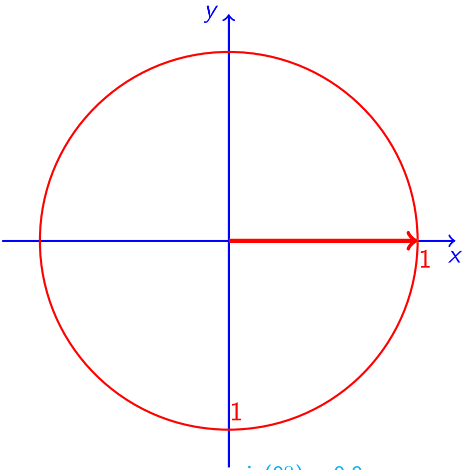
The trigonometric circle





$\sin(0^{o}) = 0.0$

$\cos(0^{o}) = 1.0$

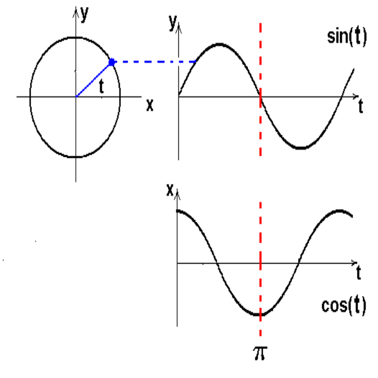
Circular Time

Trigonometric Functions

Link: Sum of Sine and Cosine

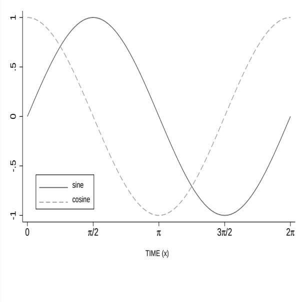
- Together the cosine and sine functions *can represent any point on the curve and the circle*.
- They are called *Trigonometric Functions*.
- The *rate of change* in cos(x) is given by sin(x) and vice versa.
- $\frac{d}{dx}cos(x) = -sin(x)$
- $\frac{d}{dx}sin(x) = cos(x)$

Sum of Sine and Cosine functions



Sine and Cosine Functions

One cycle per 2π units of time



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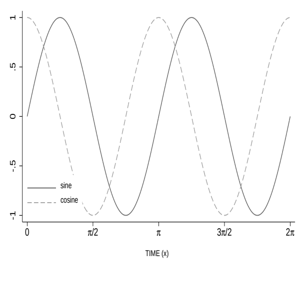

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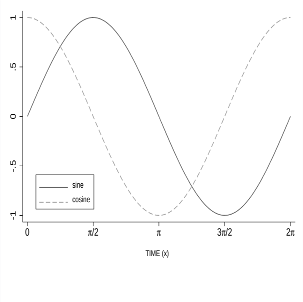

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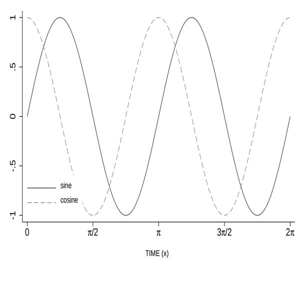

2 Assessing a circular pattern

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The examples used in this presentation: Work in progress

Modeling Vitamin D Serum Concentrations in a population of pregnant women.

- Data were drawn from an observational multicentric nested case-control study of 2,583 pregnant women using existing data and banked serum samples in the USA.
- Objective: To test the presence of a seasonal variation of 25OHD serum concentrations.
- We model maternal individual measurements of 25OHD serum concentrations (not repeat measurement within individuals).

Modeling the time of onset of Preterm Delivery

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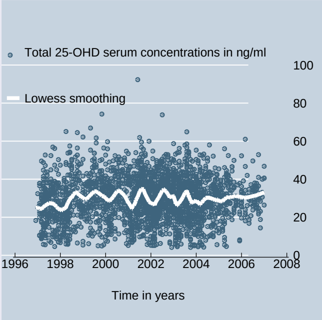
Assessing Seasonality

25OHD serum concentrations over 1996-2008: Lowess Smoothing, n= 2,583.



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Assumptions

Assessing seasonality: First, Stationarity Time Series and Second a Sinusoidal or cyclic pattern (if modelled with a cosinor approach, it has to be symetric)

Fourier Time Series: Periodogram

Number of cycles in 2π time

- The periodogram $\mathrm{I}(w_j)$ is always positive, and it will be larger at frequencies that are strongly represented in the data.
- Therefore the number of time points needed to complete a cycle of 2π could be computed as the inverse of the Fourier frequency using:

$$1/f_j = \frac{2\pi}{w_j}$$

Formulae

$$I(w_j) = \frac{2}{n}(\hat{C}^2 + \hat{S}^2) \quad j = 1, \ldots n/2$$

$$\hat{C}^2 = 2\sum_{t=1}^{n} y_t \, cos(w_j t)/n,$$

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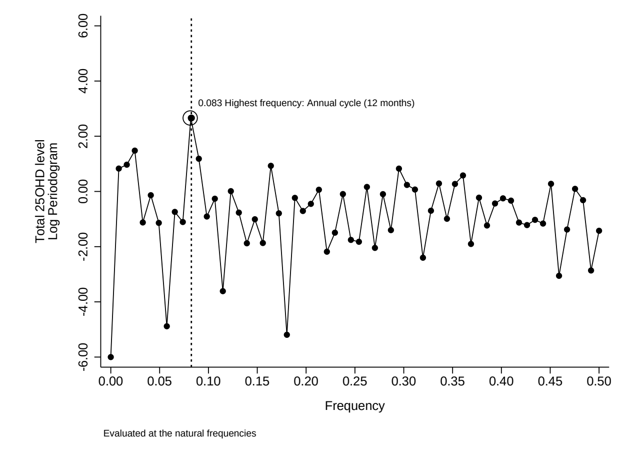
Example

Periodogram of 25OHD serum concentrations and highest frequency



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3 Describing Circadian and Seasonal Patterns

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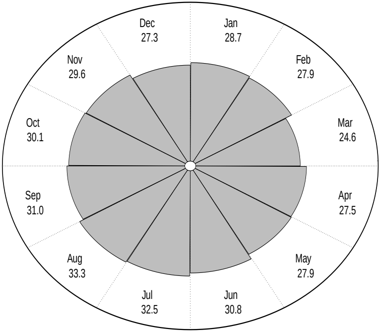
Data reduction

- Data reduction is one of the simplest methods for investigating a circadian, seasonal or annual pattern.
- A common method of data reduction is to group the data into 24 hours, 12 months, seasons, etc.
- Care needs to be taken when interpreting estimates, as they represent the average rates in each stratum.

Example:Circular Plot 25OHD serum concentrations



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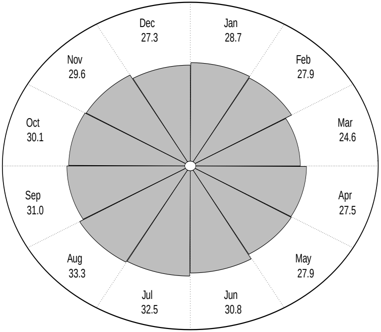

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Grouping Data example

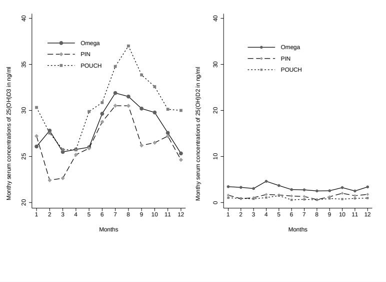
Grouping: tabular data

Mean and standard deviation of 25OHD serum concentrations by seasons, site and race, (n= 2,583).

	Black $\mu(\sigma^2)$,(n=649)			White $\mu(\sigma^2)$,(n=1934)		
	Omega(n=27)	Pin(n=350)	Pouch(n=272)	Omega(n=727)	Pin(n=642)	Pouch(n=565)
Winter	24.6(6.9)	17.5(8.6)	17.7(9.2)	29.7(8.4)	29.4(9.9)	34.6(10.9)
Spring	27.6(6.7)	18.0(8.8)	18.5(8.2)	29.4(8.9)	30.8(9.4)	33.5(10.3)
Summer	36.5(4.5)	21.6(8.5)	24.8(10.4)	33.4(8.6)	35.0(10.8)	39.3(9.5)
Fall	22.5(6.6)	19.4(9.8)	22.5(8.9)	31.9(7.7)	33.0(8.8)	36.7(10.6)
Annual	26.8(7.3)	19.0(9.0)	20.9(9.6)	31.2(8.6)	31.9(9.9)	36.1(10.5)

Grouping: Figure

Observed monthly means of 25OHD2 and D3 serum concentrations by site, (n= 2,583)



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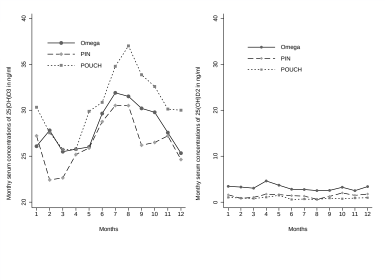

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3 Modelling Stationary Circadian an Seasonal Patterns

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Generalized Linear Models

GLM specification

$$y_i = \beta_0 + \beta_1 x_i \quad \text{where} \quad E(y) = \mu \quad \text{and} \quad \mu = X\beta$$

$$y_i \sim N(\mu_i, \sigma_i^2)$$

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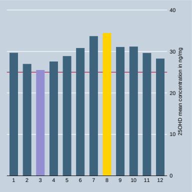
GLM Example

Observed monthly means, standard deviation and differences of 25OHD serum concentrations, (n= 2,583).

Month	Number of women tested	25(OH)D Mean	25(OH)D Std. Dev.	Absolute difference and 95%CI	Relative difference in percentage (%)
January	221	29.6	11.0	Ref.	Ref.
February	202	26.9	11.5	-2.68[(-4.83) to (-0.54)]	-9.1
March	233	25.5	10.8	-4.17[(-6.17) to (-2.16)]	-14.1
April	270	27.5	11.1	-2.11[(-4.07) to (-0.14)]	-7.1
May	241	28.8	10.7	-0.80[(-2.79) to 1.18]	-2.7
June	207	30.8	11.3	1.14 [(-0.97) to 3.25]	3.9
July	191	33.6	10.9	4.01 (1.89 to 6.13)	13.5
August	215	34.4	11.1	4.76 (2.68 to 6.84)	16.1
September	197	31.0	10.2	1.40 [(-0.63) to 3.44]	4.7
October	232	31.1	11.3	1.49 [(-0.57) to 3.54]	5.0
November	202	29.6	10.4	-0.04[(-2.08) to 1.99]	-0.1
December	172	28.2	11.0	-1.41[(-3.60) to 0.77]	-4.8

Figure. Observed monthly means of 25OHD serum concentrations, (n= 2,583)



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Cosinor Model

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The Cosinor model:

$$Y_t = c\,cos(w_t) + s\,sin(w_t)$$

t=1,...,n.

If we are interested in an annual seasonal cycle based on monthly data, then we would compute w_t as follow:

$$w_t = 2\pi\, f_t \quad \text{where}\,, \; f_t = \frac{month_t - 1}{12}$$

Amplitude and Phase

Where the Amplitude is:

$$A = \sqrt{c^2 + s^2}\,, \; (A \geq 0)$$

and the Phase [P(ϕ)]:

$$P = \begin{cases} arctan(s/c)\,, & c \geq 0, \\ arctan(s/c) + \pi\,, & c < 0\,, s \geq 0, \\ arctan(s/c) - \pi\,, & c < 0\,, s > 0. \end{cases}$$

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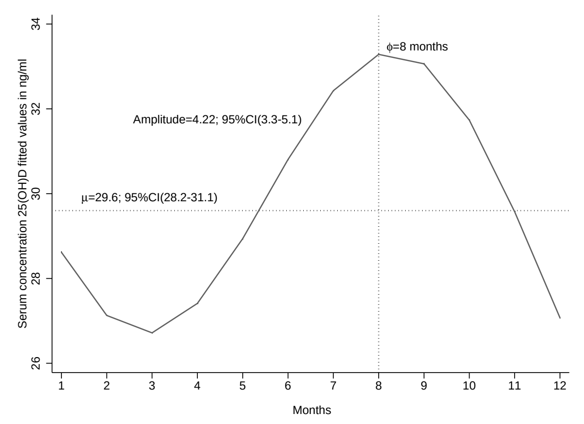
Cosinor Modelling Example

Fitted Means: Univariate example

Modelled distribution of 25OHD serum concentrations, n=2,583



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Cosinor Inference Example

Crude and Adjusted Annual Means of 25OHD and Mean Peak-Trough Difference in 25OHD (n= 2,583)

Variables		Crude 25(OH)D Annual Mean, ng/mL	95%CI	Adjusted 25(OH)D Annual Mean, ng/mL[b]	95%CI	25(OH)D Mean Peak-Trough difference, ng/mL	95%CI
Maternal Age							
	15-24	27.7	27.1, 28.4	28.2	27.4, 28.9	5.9	4.9, 7.0
	25-34	29.9	29.4, 30.3	30.4	29.9, 30.9	8.2	6.8, 9.6
	$\geq$35	31.9	31.2, 32.8	29.7	28.9, 30.5	7.5	5.9, 9.0
	P for difference	<0.001		0.003		0.005	
Race							
	Black	20.2	19.5, 21.0	19.6	18.9, 20.4	5.9	4.9, 7.0
	White	32.8	32.4, 33,2	33.0	32.6, 33.5	7.1	5.6, 8.6
	P for difference	<0.001		<0.001		<0.001	
Site							
	Omega (Seattle)	30.8	30.0, 31.6	30.9	30.3, 31.5	5.7	4.7, 6.7
	Pin (North Carolina)	27.5	26.8, 28.2	27.5	26.8, 28.1	2.3	0.9, 3.7
	Pouch (Michigan)	31.2	30.4, 31.9	31.2	30.5, 31.8	6.0	4.6, 7.4
	P for difference	0.372		0.236		0.001	
Gestational week							
	I Trimester	27.3	25.7, 28.8	26.8	28.8, 27.9	5.9	4.9, 7.0
	II Trimester	29.8	29.4, 30.3	29.8	29.5, 30.3	8.9	7.4, 10.5
	P for difference	0.002		<0.001		0.001	
Maternal Education							
	Highschool or less	26.7	26.0, 27.5	28.0	27.2, 28.8	5.9	4.9, 7.0
	Post Highschool	30.9	30.4, 31.5	30.4	29.9, 30.9	8.3	6.9, 9.7
	P for difference	<0.001		<0.001		0.001	
Pre-pregnancy BMI in kg/m^2							
	<25	31.4	30.8, 31.9	30.9	30.4, 31.4	5.9	4.9, 7.0
	25-30	29.4	28.5, 30.3	29.4	28.6, 30.3	4.5	3.1, 6.0
	>30	25.1	24.2, 26.0	26.5	25.6, 27.3	1.6	0.1, 3.0
	P for difference	<0.001		<0.001		<0.001	

[a] Models were adjusted for the main effect of maternal age, gestational weeks, race and study site.
[b] Annual means were centered to reflect study population values for maternal age, gestational weeks, race and study site.

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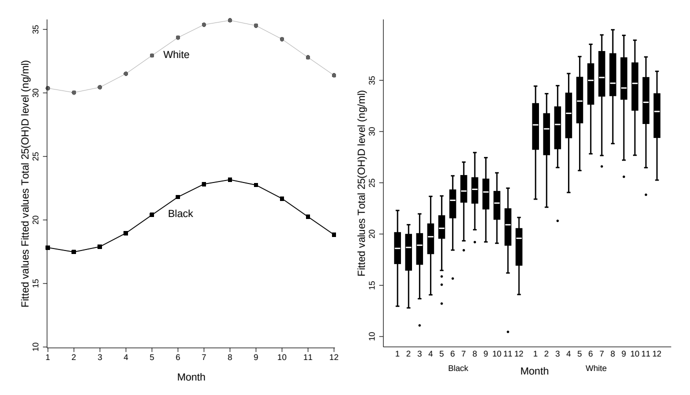
Cosinor Modelling Example

Fitted Means: Bivariate example

Distribution of 25OHD serum concentrations modelled with a bivariate Stationary Cosinor Model by race (n= 2,583)



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Cubic Splines

A cubic spline function with K knots is given by:

$$f(x) = \sum_{j=0}^{3} \beta_{0j} x^j + \sum_{l=1}^{k} \beta_i (x - t_l)^3 +,$$

where $t_l, l = 1, ..., k$ are the k knots. And x is related with the outcome as:

$$y_i = f(x_i) + \epsilon_i$$

Number of knots

Choosing the knots

- Knots are usually placed at quantiles of the data or at regularly spaced intervals.
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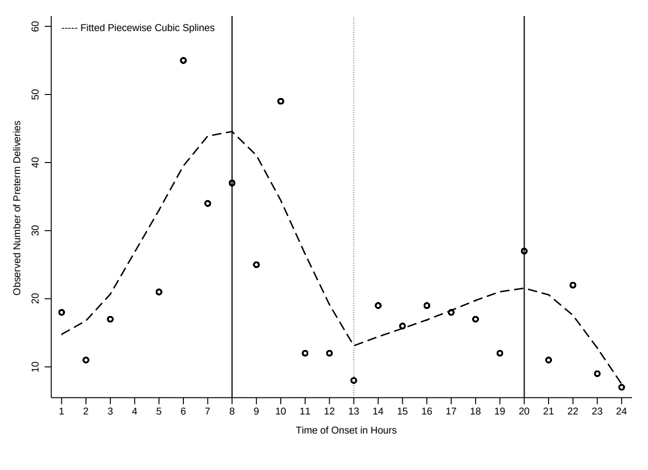
Cubic Spline Example

Modelling the Onset of labor in a sample of Preterm Delivery infants, n= 476



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