Data Analysis

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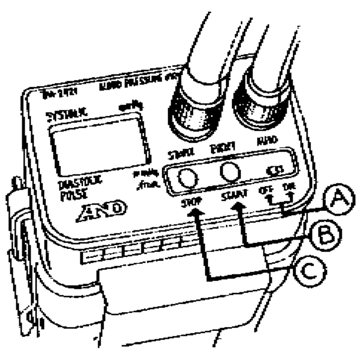
Procedure

- Data are collected at intervals (e.g., 30 min) around the clock for at least 24 hours, preferably for 7 days or longer.

Opportunity

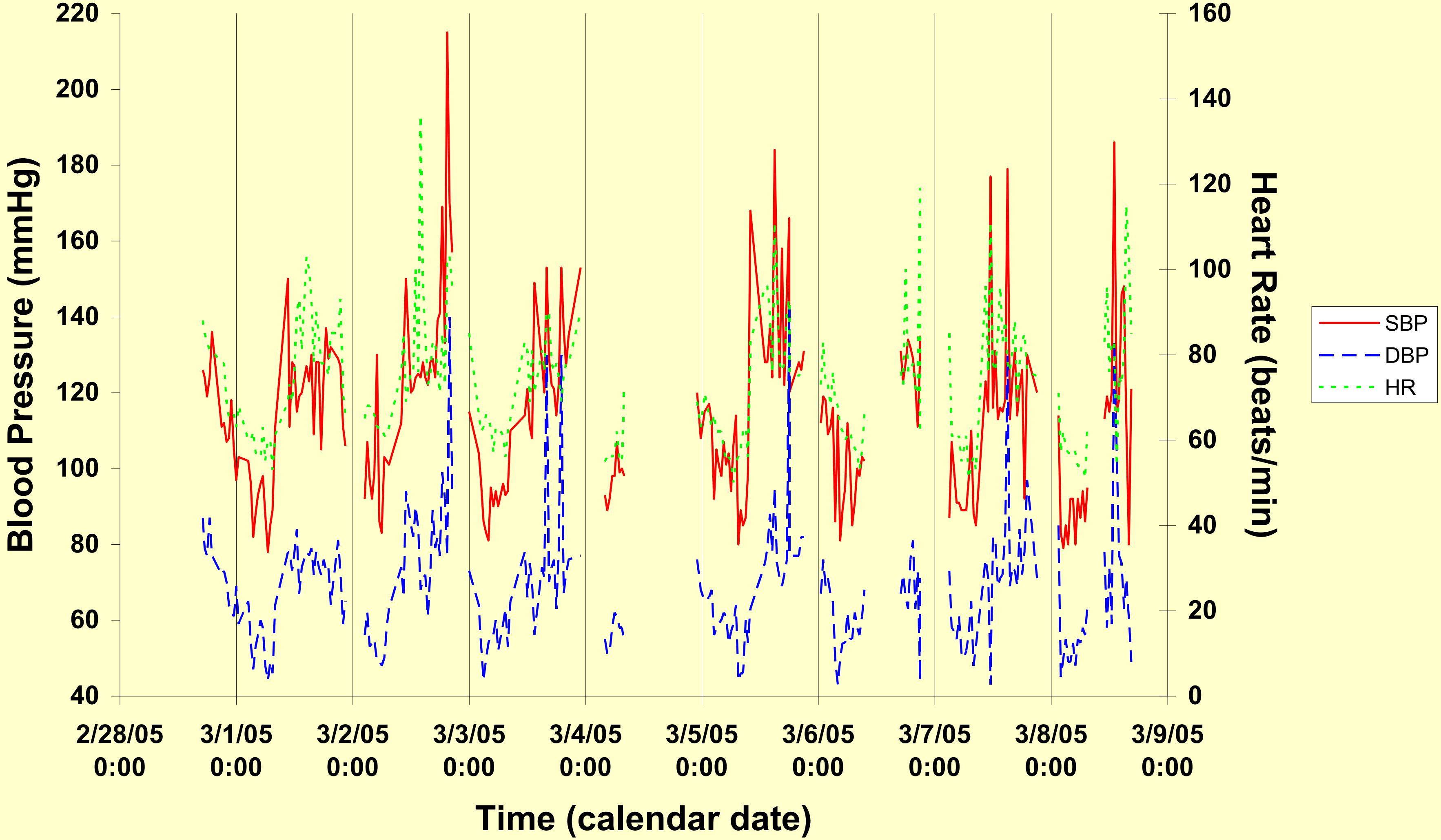


Ambulatory monitors can be obtained with a great reduction in cost with chronobiologic analyses from the University of Minnesota (corne001@umn.edu), with results interpreted in the light of gender- and age-adjusted archived norms in clinical health.

Procedure

- Data are collected at intervals (e.g., 30 min) around the clock for at least 24 hours, preferably for 7 days or longer.
- Data are retrieved from the monitor by means of an interface (RS232 port).

Timeplot of oscillometric readings of #013



Procedure

- Data are collected at intervals (e.g., 30 min) around the clock for at least 24 hours, preferably for 7 days or longer.
- Data are retrieved from the monitor by means of an interface (RS232 port).
- Data are analyzed by cosinor (e.g., least squares fit of cosine curves with periods of 24 and 12 hours) to derive estimates of MESOR, amplitude, and acrophase.

Let us consider first the case of a single component model.

SINGLE COSINOR METHOD

$Y(t) = M + A\cos(2\pi t/\tau + \phi) + e(t)$

Y_i are data collected at times t_i ($i=1, \ldots, N$)

M is the MESOR

(midline estimating statistic of rhythm)

2A is the double amplitude

(a measure of the extent of predictable change within a cycle)

ϕ is the acrophase

(a measure of the timing of overall high values)

τ is the period (duration of one cycle)

e_i is the error term, assumed to be independent, normally distributed with mean zero and unknown constant variance σ^2.

When the period is known, the model can be rewritten as

$$Y(t) = M + \beta X + \gamma Z + e(t)$$

where $\beta = A\cos\phi$ and $\gamma = -A\sin\phi$
and $X = \cos(2\pi t/\tau)$ and $Z = \sin(2\pi t/\tau)$

The model is linear in its parameters
M, β and γ.

The principle of the least squares method is to find values $\widehat{M}$, $\hat{\beta}$ and $\hat{\gamma}$ such that the residual sum of squares

$\Sigma_i\ e^2$

is minimal, or equivalently its first-order derivative is equal to zero.

The estimation procedure consists of:

1. Differentiating $\Sigma_i\ e^2$ with respect to each parameter
2. Equating these derivatives to zero to obtain the "normal equations"
3. Solving the system of equations thus obtained for the parameters M, β and γ.

Let $\omega = 2\pi/\tau$

The normal equations are

$$\Sigma y_i = MN + \beta \Sigma \cos\omega t_i + \gamma \Sigma \sin\omega t_i$$

$$\Sigma y_i \cos\omega t_i = M \Sigma \cos\omega t_i + \beta \Sigma \cos^2\omega t_i + \gamma \Sigma \sin\omega t_i \cos\omega t_i$$

$$\Sigma y_i \sin\omega t_i = M \Sigma \sin\omega t_i + \beta \Sigma \sin\omega t_i \cos\omega t_i + \gamma \Sigma \sin^2\omega t_i$$

In matrix form: $b = S\,x$ or

$$\begin{pmatrix} \Sigma y_i \\ \Sigma y_i \cos\omega t_i \\ \Sigma y_i \sin\omega t_i \end{pmatrix} = \begin{pmatrix} N & \Sigma \cos\omega t_i & \Sigma \sin\omega t_i \\ \Sigma \cos\omega t_i & \Sigma \cos^2\omega t_i & \Sigma \sin\omega t_i \cos\omega t_i \\ \Sigma \sin\omega t_i & \Sigma \sin\omega t_i \cos\omega t_i & \Sigma \sin^2\omega t_i \end{pmatrix} \begin{pmatrix} M \\ \beta \\ \gamma \end{pmatrix}$$

The estimates $\widehat{M}$, $\widehat{\beta}$, and $\widehat{\gamma}$ are obtained by inverting the S matrix

$$x = S^{-1}\, b$$

$$\begin{pmatrix} M \\ \beta \\ \gamma \end{pmatrix} = \begin{pmatrix} N & \Sigma \cos\omega t_i & \Sigma \sin\omega t_i \\ \Sigma \cos\omega t_i & \Sigma \cos^2\omega t_i & \Sigma \sin\omega t_i \cos\omega t_i \\ \Sigma \sin\omega t_i & \Sigma \sin\omega t_i \cos\omega t_i & \Sigma \sin^2\omega t_i \end{pmatrix}^{-1} \begin{pmatrix} \Sigma y_i \\ \Sigma y_i \cos\omega t_i \\ \Sigma y_i \sin\omega t_i \end{pmatrix}$$

Estimates for the amplitude and acrophase are then obtained by

$$\hat{A} = (\hat{\beta}^2 + \hat{\gamma}^2)^{1/2}$$

$$\hat{\phi} = \arctan(-\hat{\gamma}/\hat{\beta}) + K\pi \quad \text{where K is an integer}$$

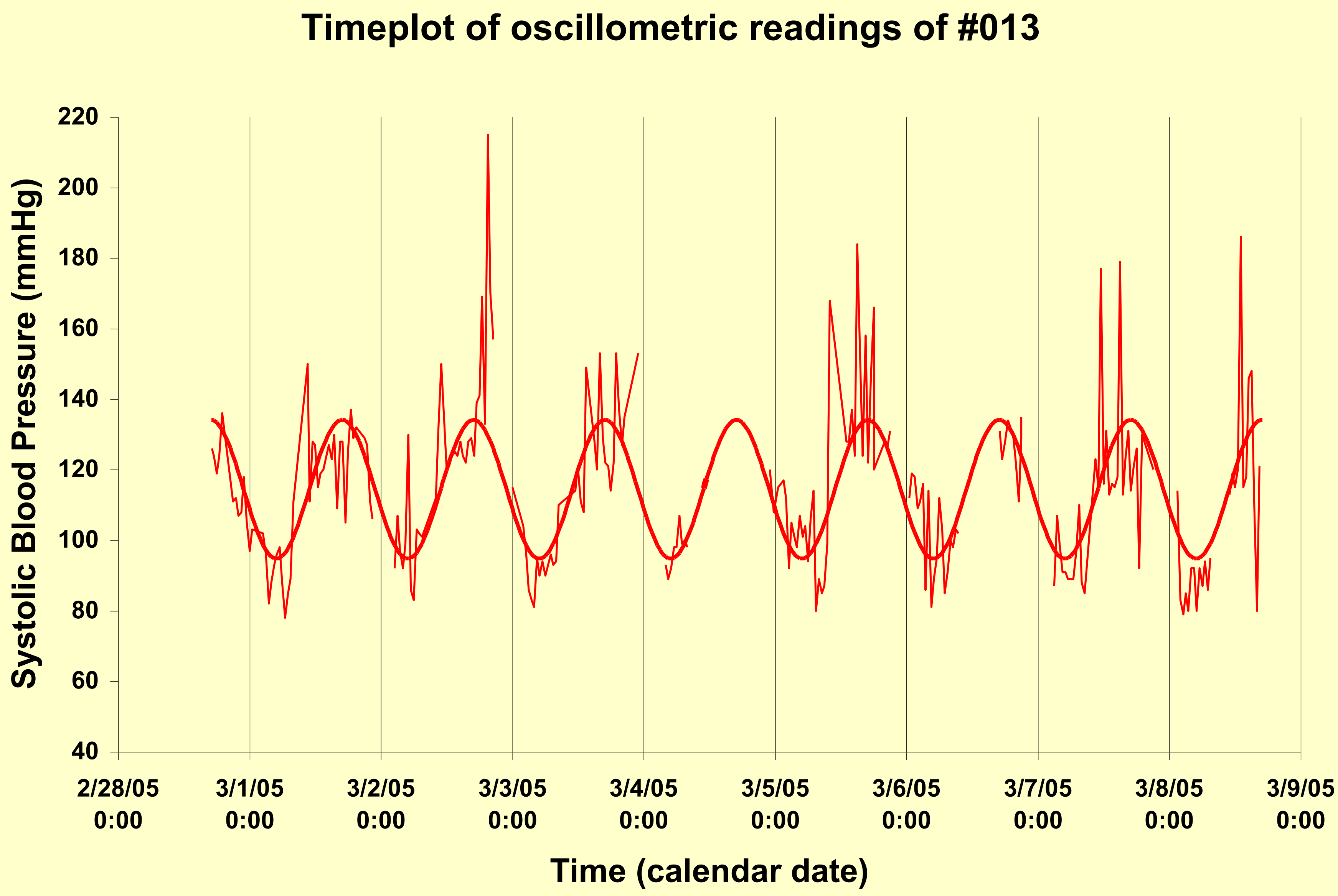
The correct value of ϕ is determined by taking into account the signs of $\hat{\beta}$ and $\hat{\gamma}$.

SBP = Systolic Blood Pressure (mmHg)									
DBP = Diastolic Blood Pressure (mgHg)									
HR = Heart Rate (beats/min)									
MAP = Mean Arterial Pressure (MAP=(SBP+(2*DBP))/3) (mmHg)									
PP = Pulse Pressure (PP=SBP-DBP) (mmHg)									
DP = Double Product (DP=(SBP*HR)/100) (mmHg*bpm%)									
ID	**Date**	**SBP**	**DBP**	**HR**	**MAP**	**PP**	**DP**		
GC013	2/28/05 17:06	126	87	88	100.00	39	110.88		
GC013	2/28/05 17:30	124	79	85	94.00	45	105.40		
GC013	2/28/05 18:00	119	77	83	91.00	42	98.77		
GC013	2/28/05 18:30	124	87	81	99.33	37	100.44		
GC013	2/28/05 19:00	136	77	81	96.67	59	110.16		
GC013	2/28/05 21:00	111	72	78	85.00	39	86.58		
GC013	2/28/05 21:30	112	73	78	86.00	39	87.36		
GC013	2/28/05 22:00	107	70	69	82.33	37	73.83		
GC013	2/28/05 22:30	108	64	65	78.67	44	70.20		
GC013	2/28/05 23:00	118	62	65	80.67	56	76.70		
GC013	2/28/05 23:30	105	61	66	75.67	44	69.30		
GC013	3/1/05 0:00	97	69	63	78.33	28	61.11		
GC013	3/1/05 0:30	103	59	68	73.67	44	70.04		
GC013	3/1/05 2:30	102	65	60	77.33	37	61.20		
GC013	3/1/05 3:00	96	54	60	68.00	42	57.60		
GC013	3/1/05 3:30	82	47	62	58.67	35	50.84		
GC013	3/1/05 4:00	88	53	57	64.67	35	50.16		

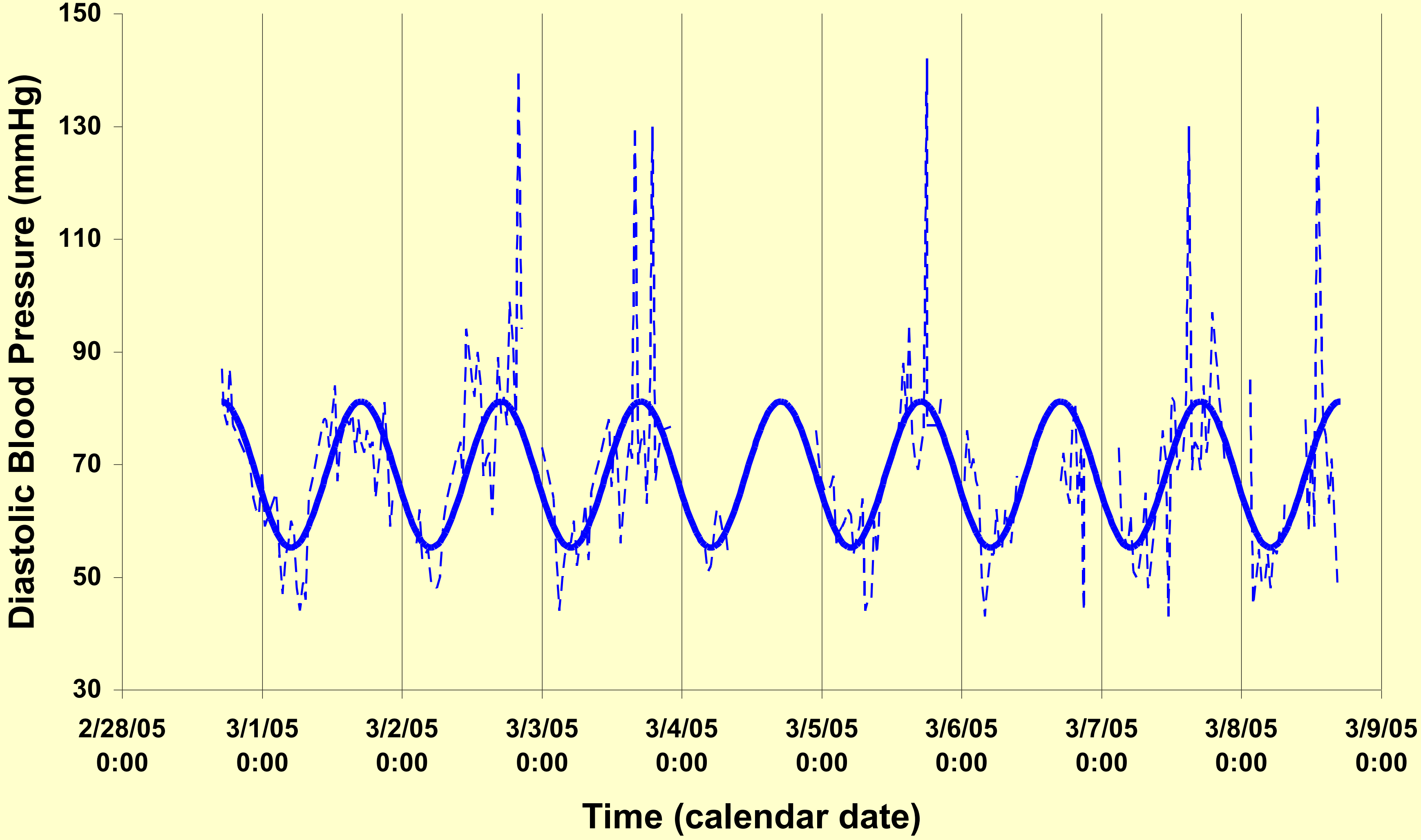
Variable	M	A	ϕ
SBP	114.447	19.667	-254
DBP	68.202	12.975	-255
HR	72.913	13.106	-249

Acrophases are expressed in negative degrees, with 360°≡24 hours and 0° set to local midnight.

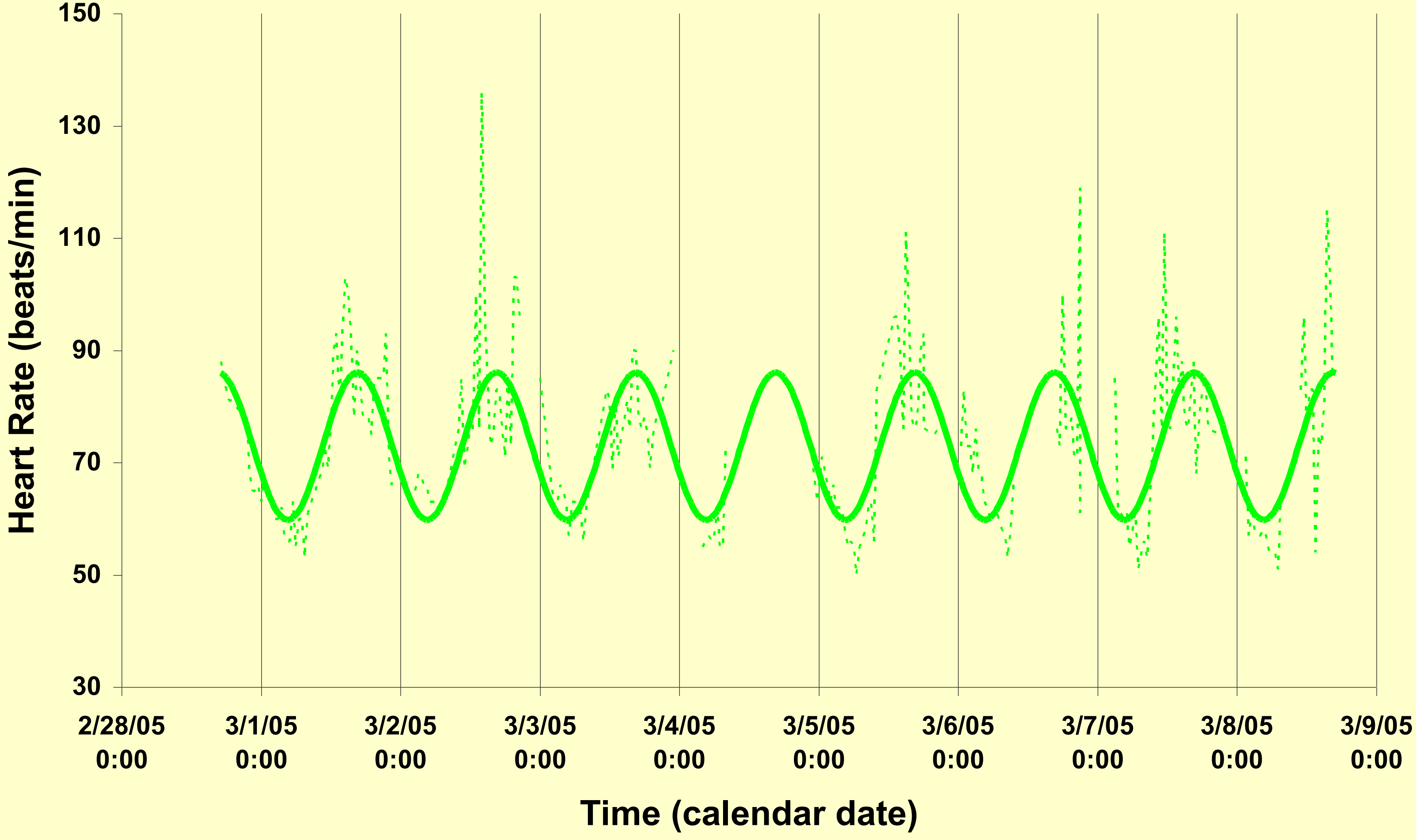
SBP = Systolic Blood Pressure (mmHg)											
DBP = Diastolic Blood Pressure (mgHg)											
HR = Heart Rate (beats/min)											
MAP = Mean Arterial Pressure (MAP=(SBP+(2*DBP))/3) (mmHg)											
PP = Pulse Pressure (PP=SBP-DBP) (mmHg)											
DP = Double Product (DP=(SBP*HR)/100) (mmHg*bpm%)											
ID	**Date**	**SBP**	**DBP**	**HR**	**MAP**	**PP**	**DP**	2/28/05 0:00			
GC013	2/28/05 17:06	126	87	88	100.00	39	110.88	2/28/05 17:00	134.11	81.18	85.95
GC013	2/28/05 17:30	124	79	85	94.00	45	105.40	2/28/05 17:30	133.90	81.07	85.66
GC013	2/28/05 18:00	119	77	83	91.00	42	98.77	2/28/05 18:00	133.35	80.73	85.15
GC013	2/28/05 18:30	124	87	81	99.33	37	100.44	2/28/05 18:30	132.48	80.19	84.43
GC013	2/28/05 19:00	136	77	81	96.67	59	110.16	2/28/05 19:00	131.30	79.44	83.52
GC013	2/28/05 21:00	111	72	78	85.00	39	86.58	2/28/05 19:30	129.84	78.50	82.42
GC013	2/28/05 21:30	112	73	78	86.00	39	87.36	2/28/05 20:00	128.11	77.38	81.16
GC013	2/28/05 22:00	107	70	69	82.33	37	73.83	2/28/05 20:30	126.15	76.10	79.76
GC013	2/28/05 22:30	108	64	65	78.67	44	70.20	2/28/05 21:00	123.98	74.69	78.24
GC013	2/28/05 23:00	118	62	65	80.67	56	76.70	2/28/05 21:30	121.66	73.17	76.64
GC013	2/28/05 23:30	105	61	66	75.67	44	69.30	2/28/05 22:00	119.20	71.56	74.96
GC013	3/1/05 0:00	97	69	63	78.33	28	61.11	2/28/05 22:30	116.67	69.90	73.26
GC013	3/1/05 0:30	103	59	68	73.67	44	70.04	2/28/05 23:00	114.10	68.20	71.54
GC013	3/1/05 2:30	102	65	60	77.33	37	61.20	2/28/05 23:30	111.54	66.51	69.85
GC013	3/1/05 3:00	96	54	60	68.00	42	57.60	3/1/05 0:00	109.03	64.84	68.22
GC013	3/1/05 3:30	82	47	62	58.67	35	50.84	3/1/05 0:30	106.60	63.24	66.66
GC013	3/1/05 4:00	88	53	57	64.67	35	50.16	3/1/05 1:00	104.32	61.71	65.21


Timeplot of oscillometric readings of #013
Systolic Blood Pressure (mmHg)
220
200
180
160
140
120
100
80
60
40
2/28/05 0:00
3/1/05 0:00
3/2/05 0:00
3/3/05 0:00
3/4/05 0:00
3/5/05 0:00
3/6/05 0:00
3/7/05 0:00
3/8/05 0:00
3/9/05 0:00
Time (calendar date)

Timeplot of oscillometric readings of #013



Timeplot of oscillometric readings of #013

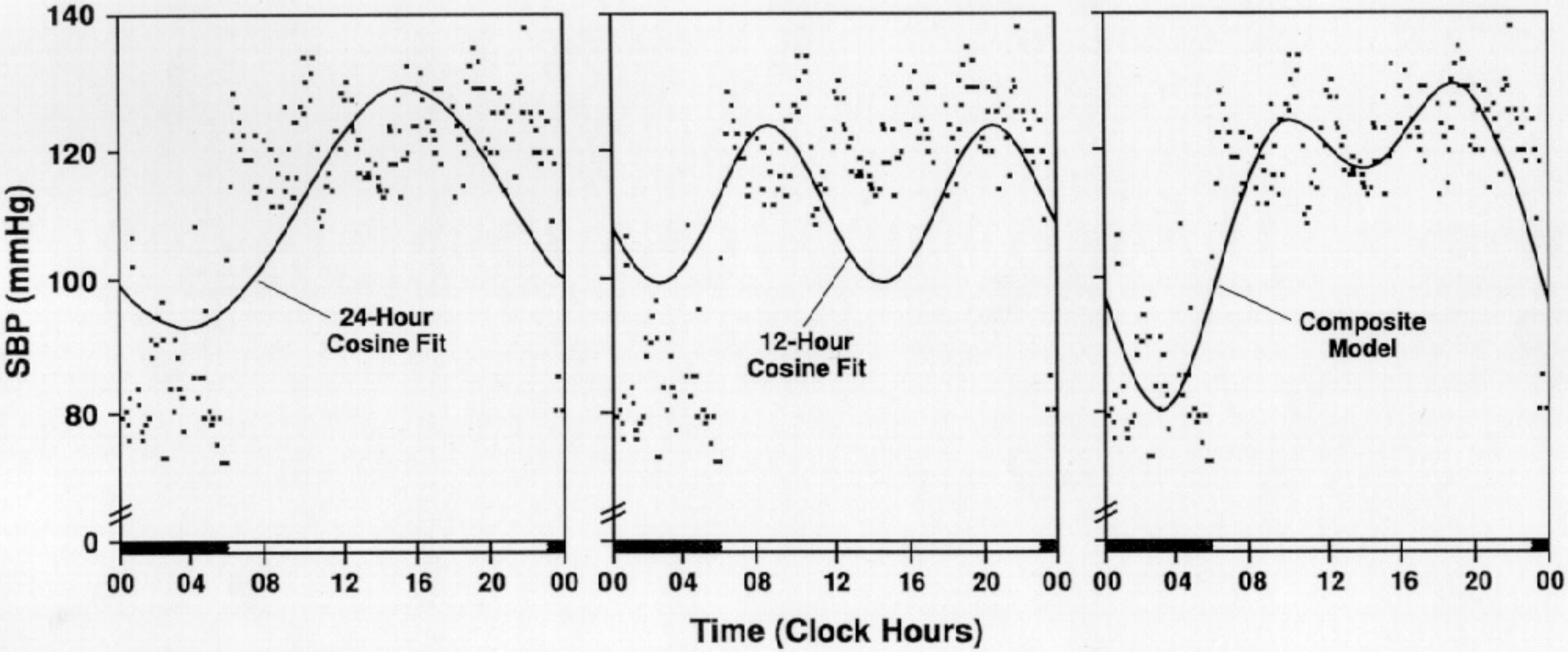


The model is easily extended to include more than a single component:

$$Y(t) = M + \Sigma_i A_i \cos(2\pi t/\tau_i + \phi_i) + e(t) \quad i=1, ..., k$$

A system of 2k+1 normal equations with 2k+1 parameters needs to be resolved in this case. The parameters are M and (A_i, ϕ_i) of cosine curves with periods τ_i, i=1, …, k.
Usually, a 2-component model is considered with periods of 24 and 12 hours.

APPROXIMATION OF CIRCADIAN WAVEFORM BY TWO-COMPONENT MODEL FITTED STEPWISE TO 24-HOUR PROFILE OF SYSTOLIC BLOOD PRESSURE (SBP) OF CLINICALLY HEALTHY MAN, 24 YEARS OF AGE*



* Each dot represents a measurement.

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Variable	M	24h A	24h ϕ	12h A	12h ϕ
SBP	115.641	19.327	-256	4.739	-327.000
DBP	68.912	12.750	-257	2.874	-343.000
HR	73.600	12.699	-252	4.735	-26.000

Acrophases are expressed in negative degrees, with 360°≡24 hours and 0° set to local midnight.

SBP = Systolic Blood Pressure (mmHg)												
DBP = Diastolic Blood Pressure (mgHg)												
HR = Heart Rate (beats/min)												
MAP = Mean Arterial Pressure (MAP=(SBP+(2*DBP))/3) (mmHg)												
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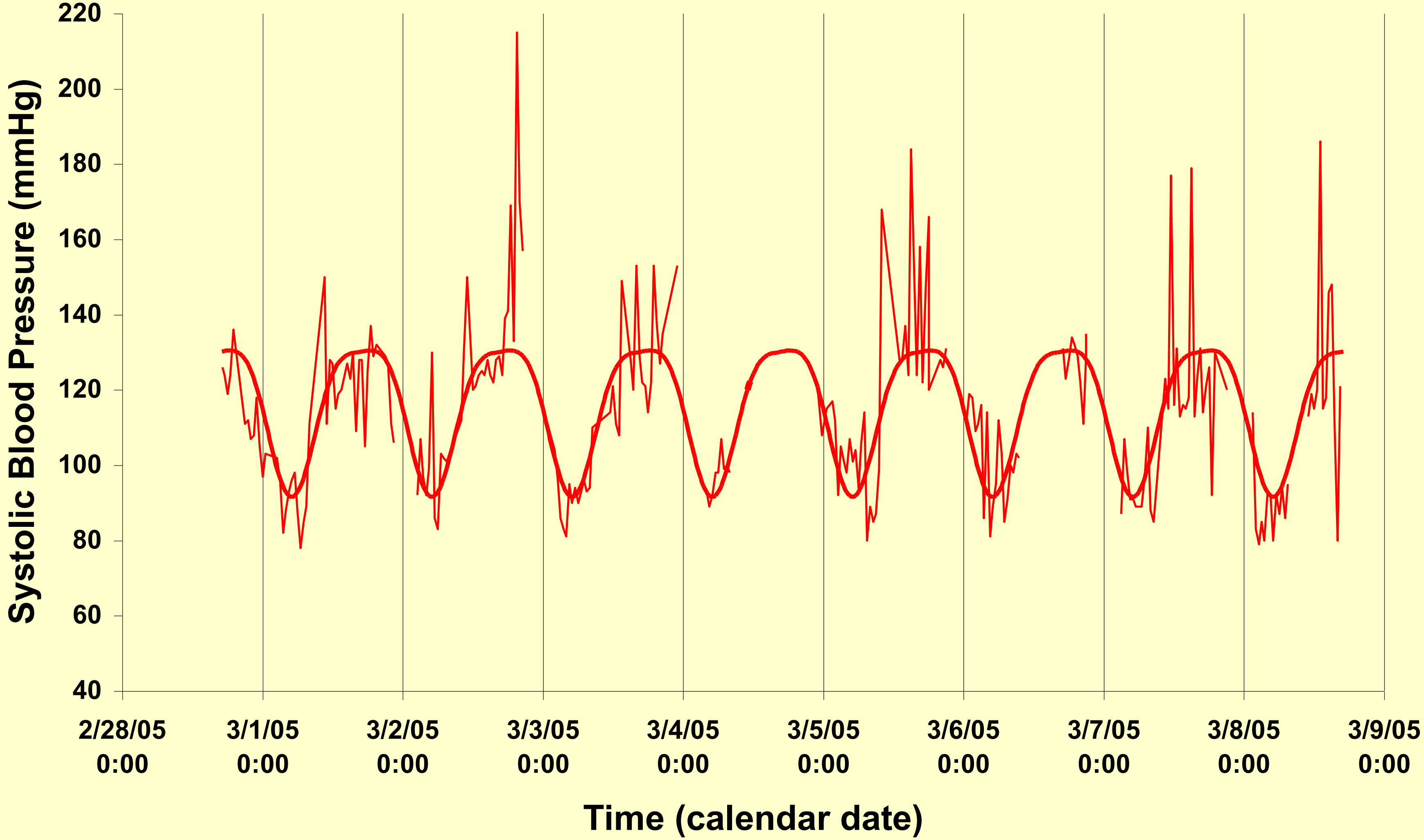
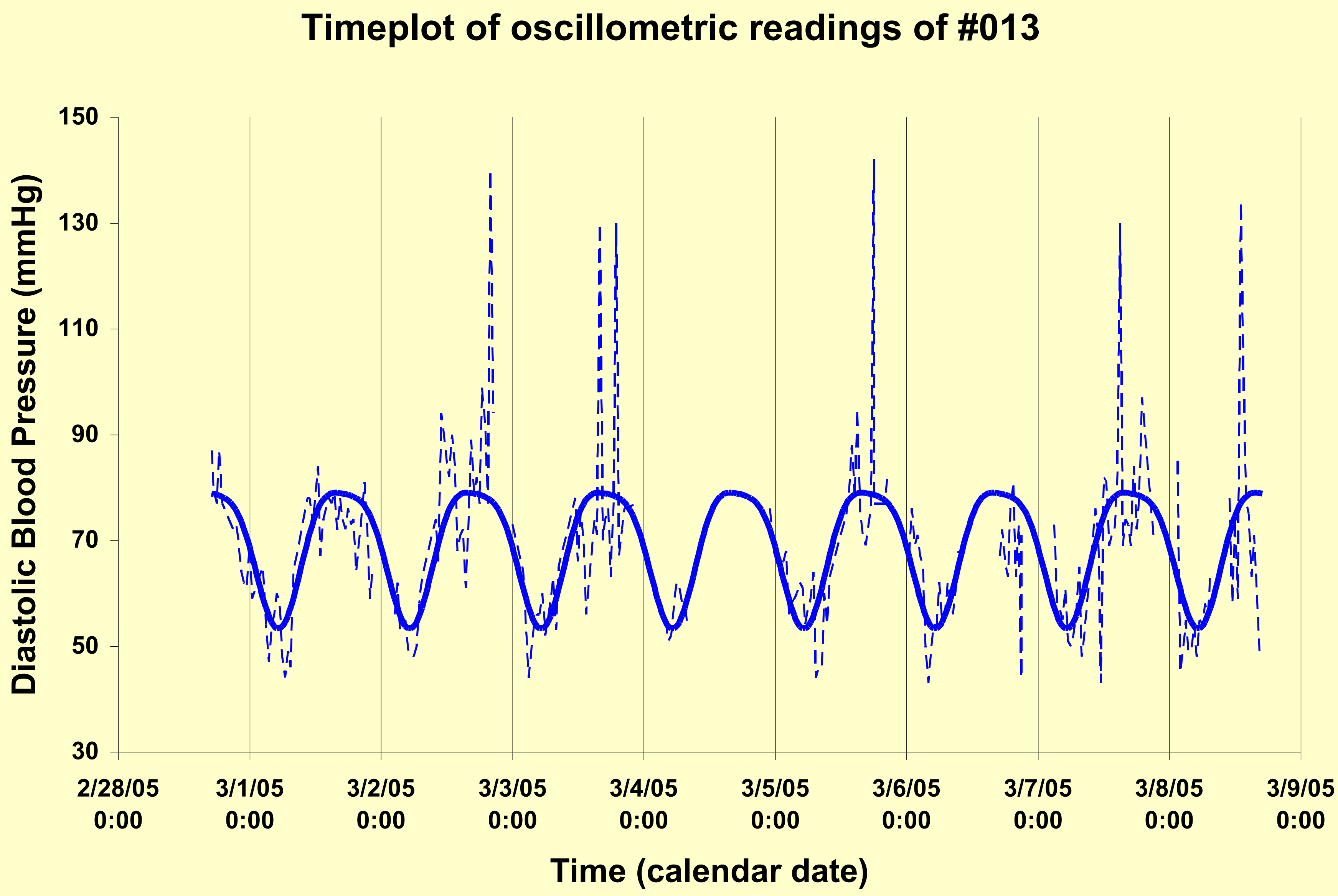
DP = Double Product (DP=(SBP*HR)/100) (mmHg*bpm%)												
ID	**Date**	**SBP**	**DBP**	**HR**	**MAP**	**PP**	**DP**	2/28/05 0:00				
GC013	2/28/05 17:06	126	87	88	100.00	39	110.88	2/28/05 17:00	130.23	78.85	83.64	
GC013	2/28/05 17:30	124	79	85	94.00	45	105.40	2/28/05 17:30	130.34	78.73	82.52	
GC013	2/28/05 18:00	119	77	83	91.00	42	98.77	2/28/05 18:00	130.42	78.59	81.43	
GC013	2/28/05 18:30	124	87	81	99.33	37	100.44	2/28/05 18:30	130.45	78.42	80.42	
GC013	2/28/05 19:00	136	77	81	96.67	59	110.16	2/28/05 19:00	130.39	78.21	79.54	
GC013	2/28/05 21:00	111	72	78	85.00	39	86.58	2/28/05 19:30	130.19	77.94	78.79	
GC013	2/28/05 21:30	112	73	78	86.00	39	87.36	2/28/05 20:00	129.79	77.59	78.18	
GC013	2/28/05 22:00	107	70	69	82.33	37	73.83	2/28/05 20:30	129.14	77.12	77.70	
GC013	2/28/05 22:30	108	64	65	78.67	44	70.20	2/28/05 21:00	128.18	76.51	77.30	
GC013	2/28/05 23:00	118	62	65	80.67	56	76.70	2/28/05 21:30	126.87	75.72	76.95	
GC013	2/28/05 23:30	105	61	66	75.67	44	69.30	2/28/05 22:00	125.19	74.74	76.58	
GC013	3/1/05 0:00	97	69	63	78.33	28	61.11	2/28/05 22:30	123.13	73.55	76.15	
GC013	3/1/05 0:30	103	59	68	73.67	44	70.04	2/28/05 23:00	120.71	72.16	75.59	
GC013	3/1/05 2:30	102	65	60	77.33	37	61.20	2/28/05 23:30	117.96	70.56	74.87	
GC013	3/1/05 3:00	96	54	60	68.00	42	57.60	3/1/05 0:00	114.94	68.79	73.94	
GC013	3/1/05 3:30	82	47	62	58.67	35	50.84	3/1/05 0:30	111.73	66.88	72.79	
GC013	3/1/05 4:00	88	53	57	64.67	35	50.16	3/1/05 1:00	108.42	64.89	71.42	

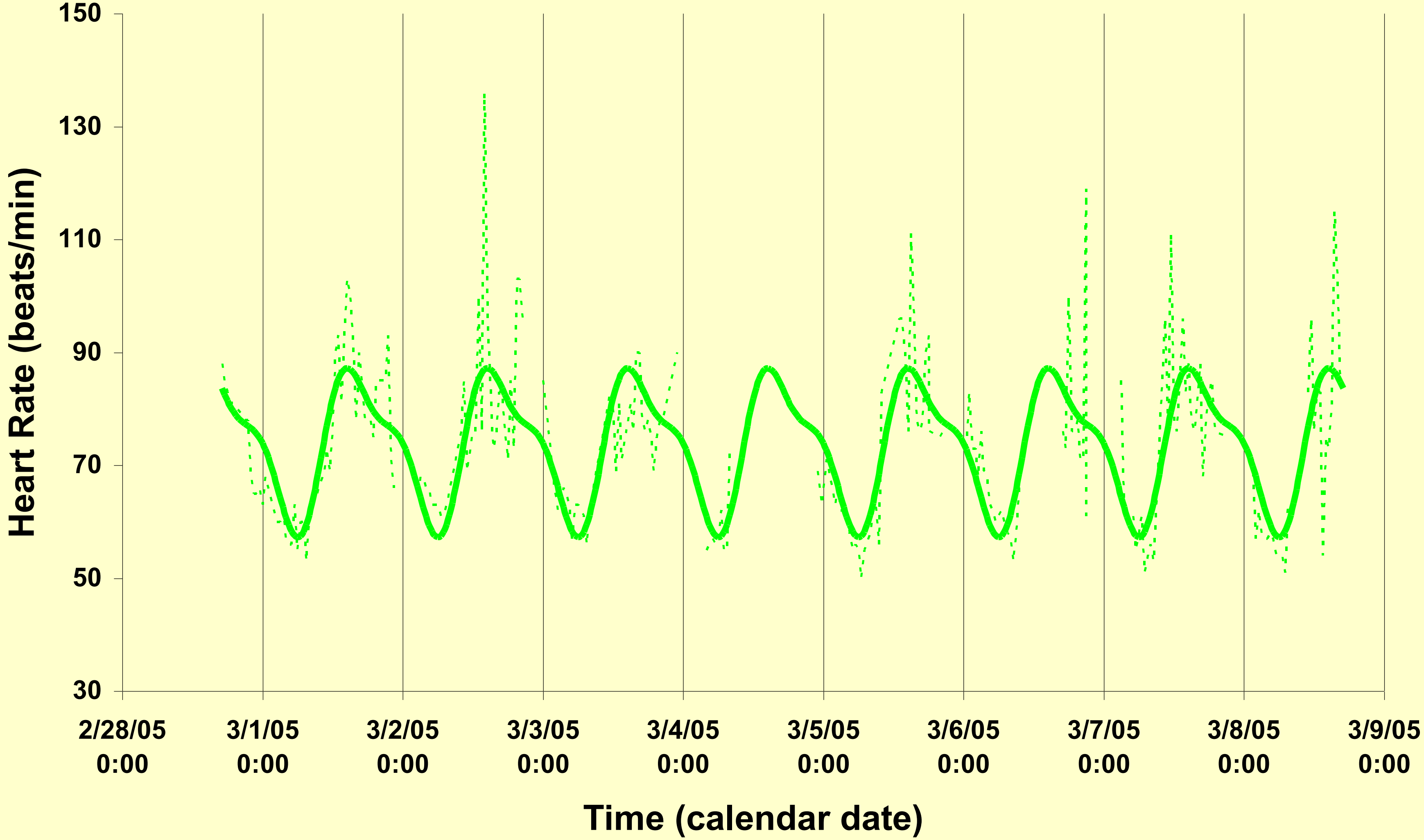
Timeplot of oscillometric readings of #013





Timeplot of oscillometric readings of #013
Diastolic Blood Pressure (mmHg)
150
130
110
90
70
50
30
2/28/05 0:00
3/1/05 0:00
3/2/05 0:00
3/3/05 0:00
3/4/05 0:00
3/5/05 0:00
3/6/05 0:00
3/7/05 0:00
3/8/05 0:00
3/9/05 0:00
Time (calendar date)

Timeplot of oscillometric readings of #013



Statistical significance of the model and 95% confidence intervals for the parameters can be derived by an analysis of variance. The total variance of the data around the arithmetic mean can be partitioned between the variance accounted for by the model and the residual variance.

$$\Sigma (Y_i - \bar{Y}_i)^2 = \Sigma (Y_i - \hat{Y}_i + \hat{Y}_i - \bar{Y}_i)^2$$
$$= \Sigma (Y_i - \hat{Y}_i)^2 + \Sigma (\hat{Y}_i - \bar{Y}_i)^2$$
$$= \text{RSS} \qquad + \text{MSS}$$

H_0: A=0 is rejected at $P<\alpha$ (e.g., α =5%) if

$F = (MSS/(k-1))/(RSS/(N-k)) > F_{1-\alpha}(k-1,N-k)$

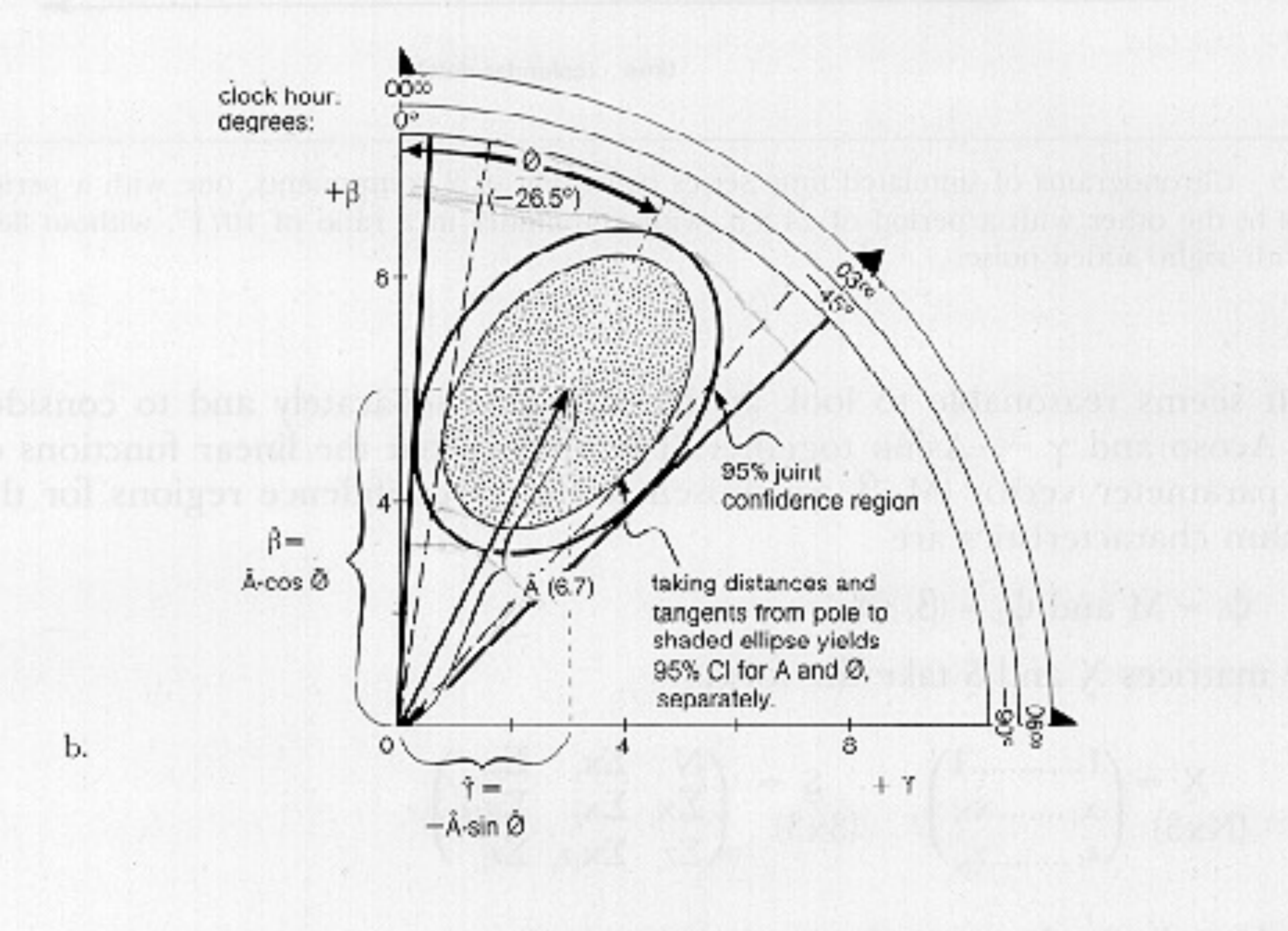
where α is the probability level.

Variable	PR	P	MESOR	S.E.	Amplitude	S.E.	(95.0 %CI)		Acrophase phi	SE	(95.0 %CI)	Hour
1 SBP	49	< .001	114.447	1.026	19.667	1.402	17.12,	22.21	-254	5	(-245,-264)	1658
2 DBP	41	< .001	68.202	0.804	12.975	1.094	10.98,	14.97	-255	5	(-244,-267)	1702
3 HR	53	< .001	72.913	0.636	13.106	0.888	11.52,	14.69	-249	4	(-241,-258)	1638

Variable	Period	MESOR ±	S.E.	PR	P	Amplitude	S.E.	(95.0 %CI)		Acrophase phi	SE	(95.0 %CI)
1 SBP		115.641	1.081									
	24.00			48	< .001	19.327	1.369	16.64,	22.01	-256	5	(-247,-266)
	12.00			3	0.009	4.739	1.428	1.94,	7.54	-327	19	(-291, -4)
	overall			51	< .001							
2 DBP		68.912	0.854									
	24.00			40	< .001	12.750	1.077	10.64,	14.86	-257	6	(-246,-268)
	12.00			2	0.057	2.874	1.144	0.63,	5.12	-343	24	(-296, -30)
	overall			42	< .001							
3 HR		73.600	0.643									
	24.00			51	< .001	12.699	0.829	11.07,	14.32	-252	4	(-244,-260)
	12.00			7	< .001	4.735	0.907	2.96,	6.51	-26	10	(-6, -46)
	overall			58	< .001							

PR = MSS/(MSS+RSS) = R^2.

When F is evaluated at $A = \hat{A}$ instead of at A=0, the equation obtained is that of an ellipse representing the confidence region for (β, γ) or equivalently for (A, ϕ). Conservative confidence intervals for A and ϕ can be derived by computing the minimal and maximal distances from the pole to the error ellipse and by drawing the tangents from the pole to the error ellipse, respectively.


clock hour:
degrees:
00⁰⁰
0°
Ø
+β
(−26.5°)
03⁰⁰
45°
6
4
95% joint
confidence region
β̂ =
Â·cos Ø̂
Â (6.7)
taking distances and
tangents from pole to
shaded ellipse yields
95% CI for A and Ø,
separately.
b.
0
4
8
−90°
06⁰⁰
γ̂ =
−Â·sin Ø̂
+ γ

Results from the parametric approach are reported in the sphygmochron where they are compared with 90% prediction limits from healthy peers matched by gender and age.

SPHYGMOCHRON-TM

Monitoring Profile over Time;
Computer Comparison with Peer Group Limits

Blood Pressure (BP) and Related Cardiovascular Summary.

Name:---------------------
Age: 55
Monitoring From: 2/28/2005 17:06
Comments:

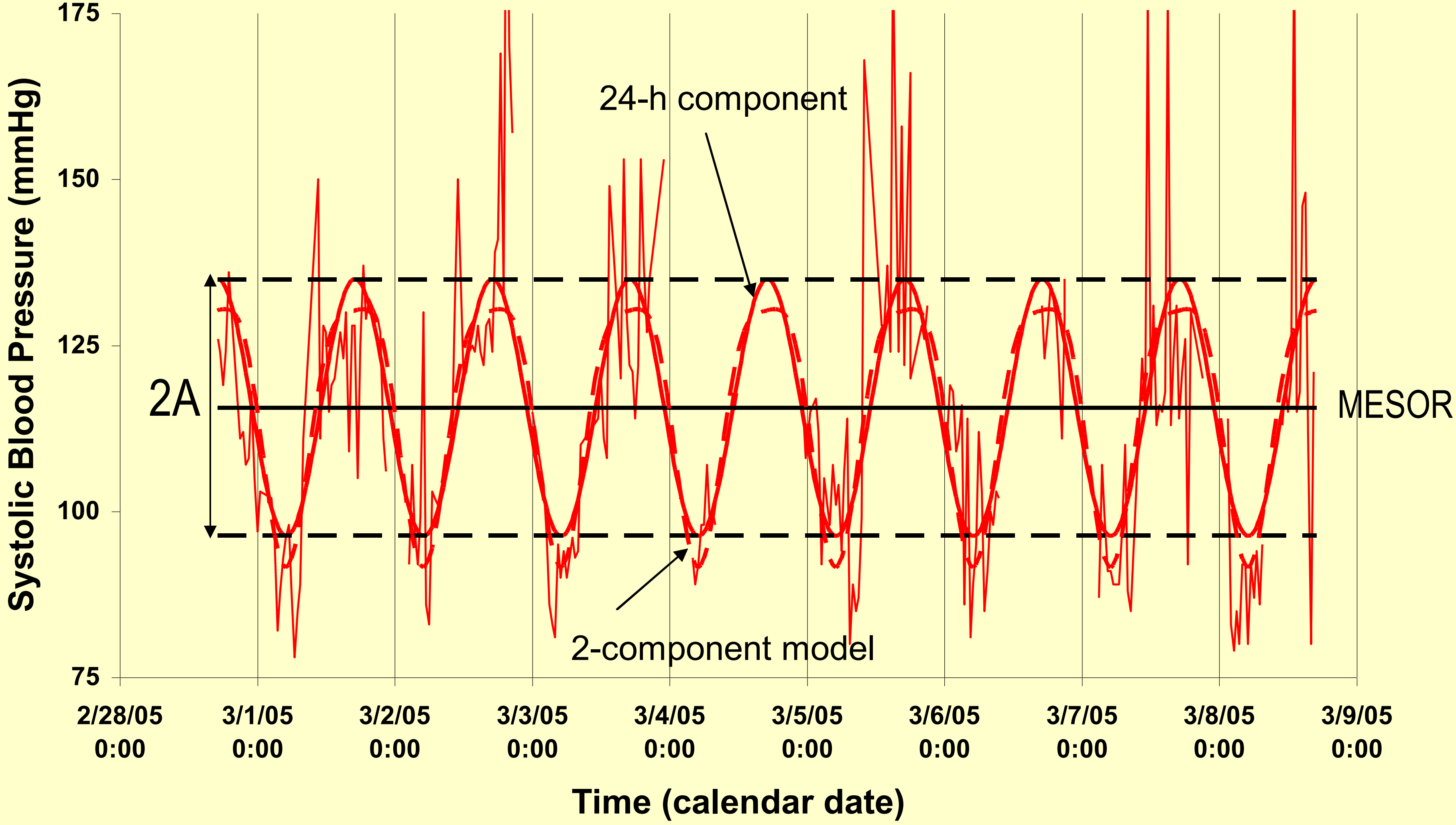
Patient #: GCor013
Sex: F
To: 3/8/2005 16:30

CHRONOBIOLOGIC CHARACTERISTICS

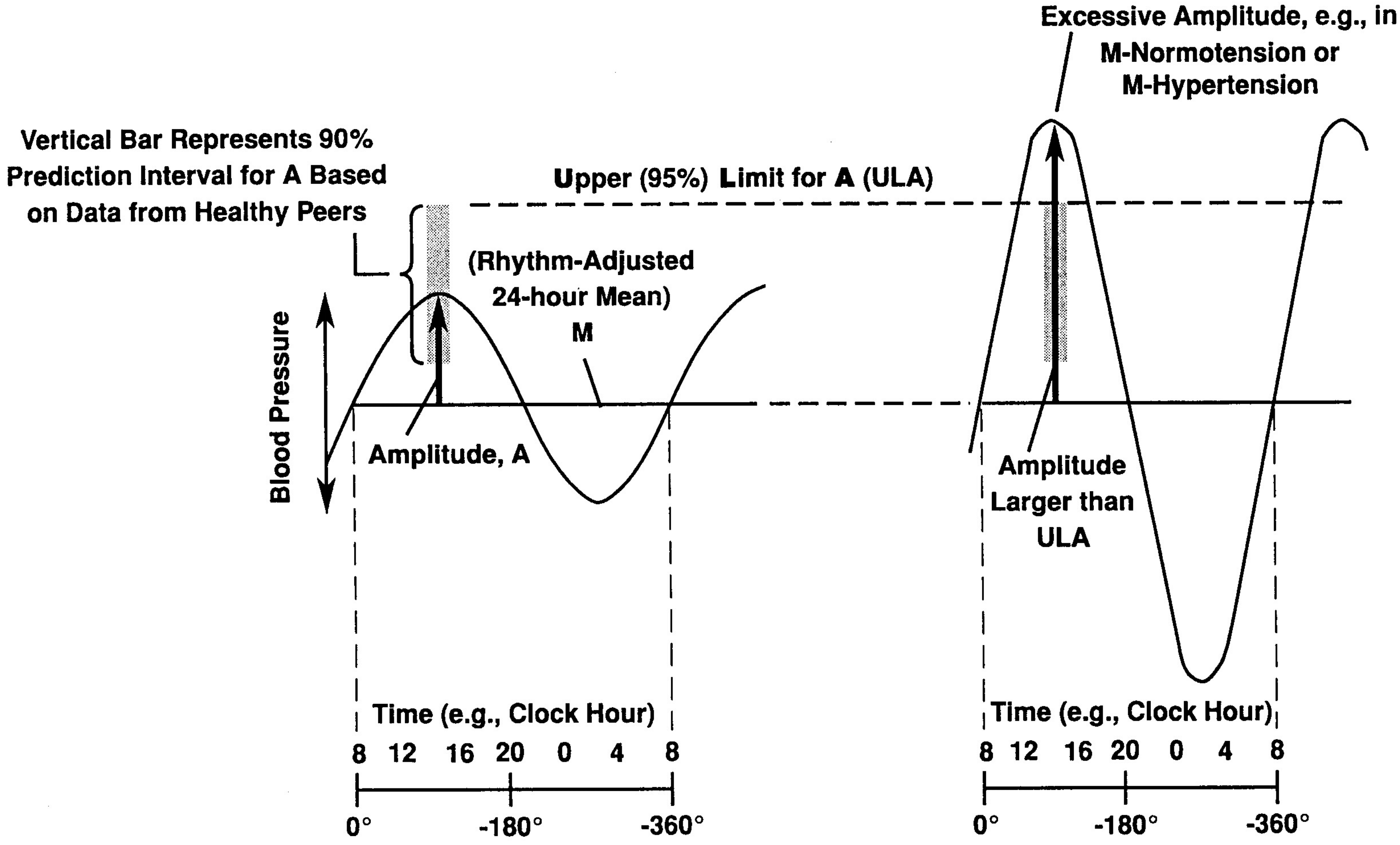
	SYSTOLIC BP (mmHg)		DIASTOLIC BP (mmHg)		HEART RATE (bpm)	
	Patient Value	Peer Group Reference Limits	Patient Value	Peer Group Reference Limits	Patient Value	Peer Group Reference Limits
ADJUSTED 24-h MEAN (MESOR)	115.6	102.2-138.6 Range	68.9	67.4-86.5 Range	73.6	65.3-86.3 Range
PREDICTABLE CHANGE (DOUBLE AMPLITUDE)	**38.65**	3.27-37.15 Range	25.50	4.01-26.50 Range	25.40	3.07-28.70 Range
TIMING OF OVERALL HIGH VALUES (ACROPHASE) (hr:min)	17:05	10:46-18:46 Range	17:09	10:45-17:26 Range	16:48	8:52-19:09 Range

The double amplitude of systolic blood pressure is above the upper 95% prediction limit: systolic CHAT is diagnosed.

Timeplot of oscillometric readings of #013



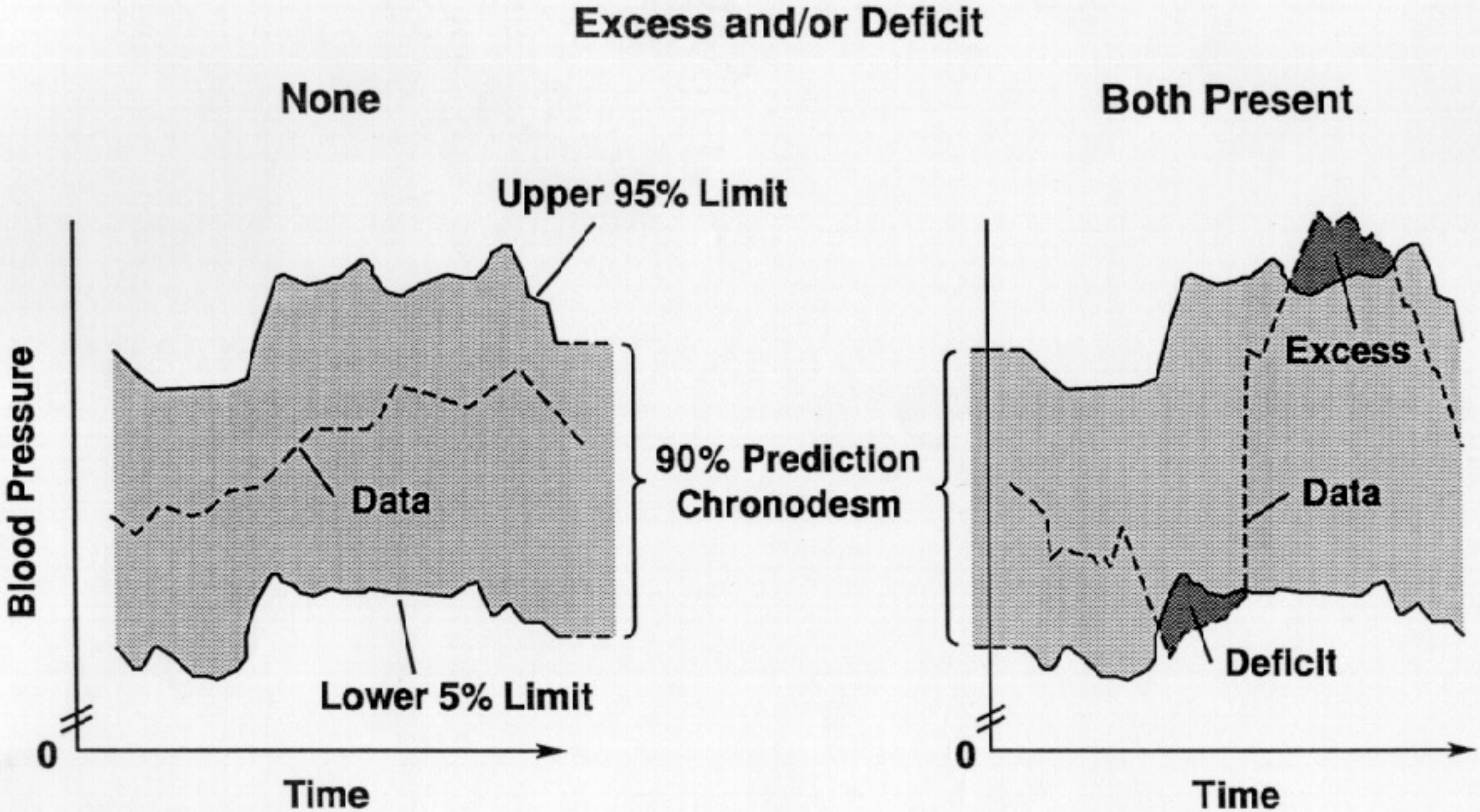
Excessive Amplitude: Amplitude Deviating Above Reference Limit

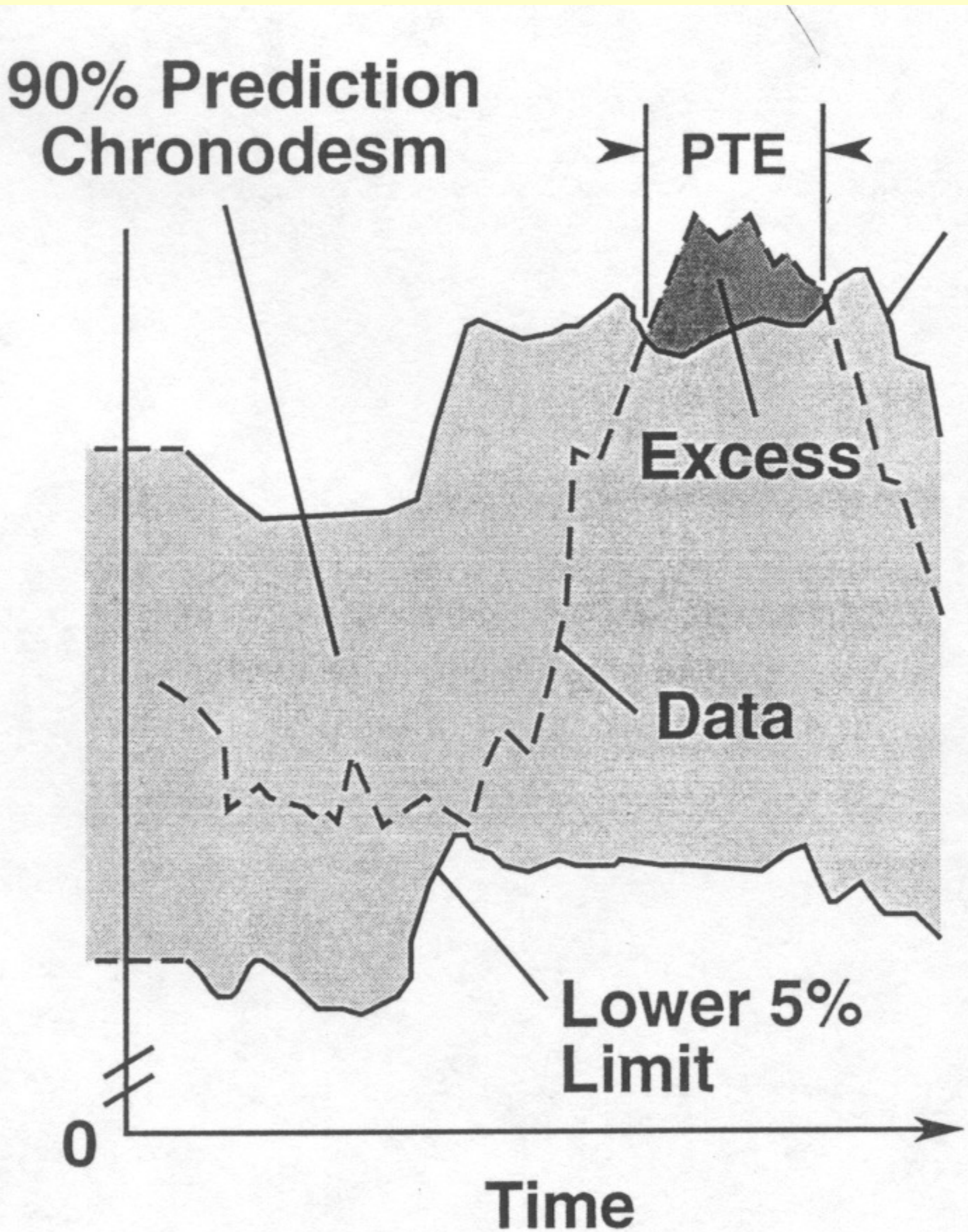


Procedure

- Data are collected at intervals (e.g., 30 min) around the clock for at least 24 hours, preferable for 7 days or longer.
- Data are retrieved from the monitor by means of an interface (RS232 port).
- Data are analyzed by cosinor (e.g., least squares fit of cosine curves with periods of 24 and 12 hours) to derive estimates of MESOR, amplitude, and acrophase.
- Data are analyzed non-parametrically.

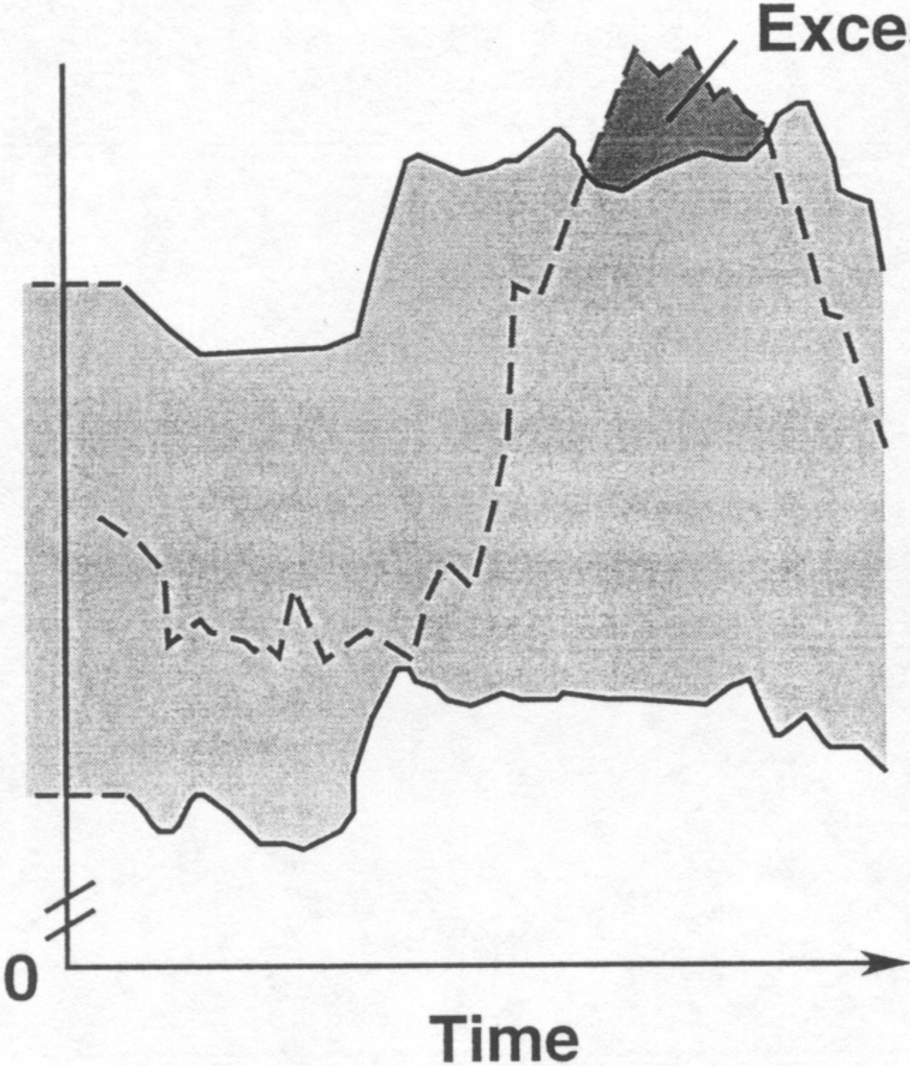
NONPARAMETRIC APPROACH TO DEVIANT BLOOD PRESSURE





Percent Time Elevation (PTE)

Timespan of BP elevation above time-varying threshold, expressed as a percentage of 24 h (unless otherwise specified)



Hyperbaric Index (HBI)

Measure of excess load exerted upon the arterial walls; area of BP readings above time-varying threshold

Time-Specified Reference Limits (Chronodesms)

Derived as 90% prediction limits for given timepoint (or short – e.g., 30-min interval) using data from healthy peers matched by gender and age.

Let $Y_1, \ldots, Y_n$ be a sample randomly drawn from a normal population with mean μ and variance σ^2. A tolerance interval containing a proportion p of the population is defined by

$\mu \pm z_{\alpha/2}\,\sigma$ where $z_{\alpha/2}$ is the upper $(1-\alpha/2)$ fractile of the standard normal curve (e.g., 1.96 for $\alpha = 0.05$). This interval covers a fraction $(1-\alpha)$ of the population.

Time-Specified Reference Limits (Chronodesms)

In practice, μ and σ are not known and need to be estimated from the sample:

$$\widehat{\mu} = \overline{Y} = 1/n \,.\, \Sigma_j \, Y_j$$

$$\hat{\sigma}^2 = s^2 = 1/(n-1) \,.\, \Sigma_j \, (Y_j - \overline{Y})^2$$

Using these estimates to derive a tolerance interval will generally not cover an exact fraction $(1-\alpha)$ of the population (because the mean and variance are not known), but it will do so *on the average*.

$\overline{Y} \pm t_{\alpha/2;\,(n-1)}\, s\, [(n+1)/n]^{1/2}$ (t = Student distribution).

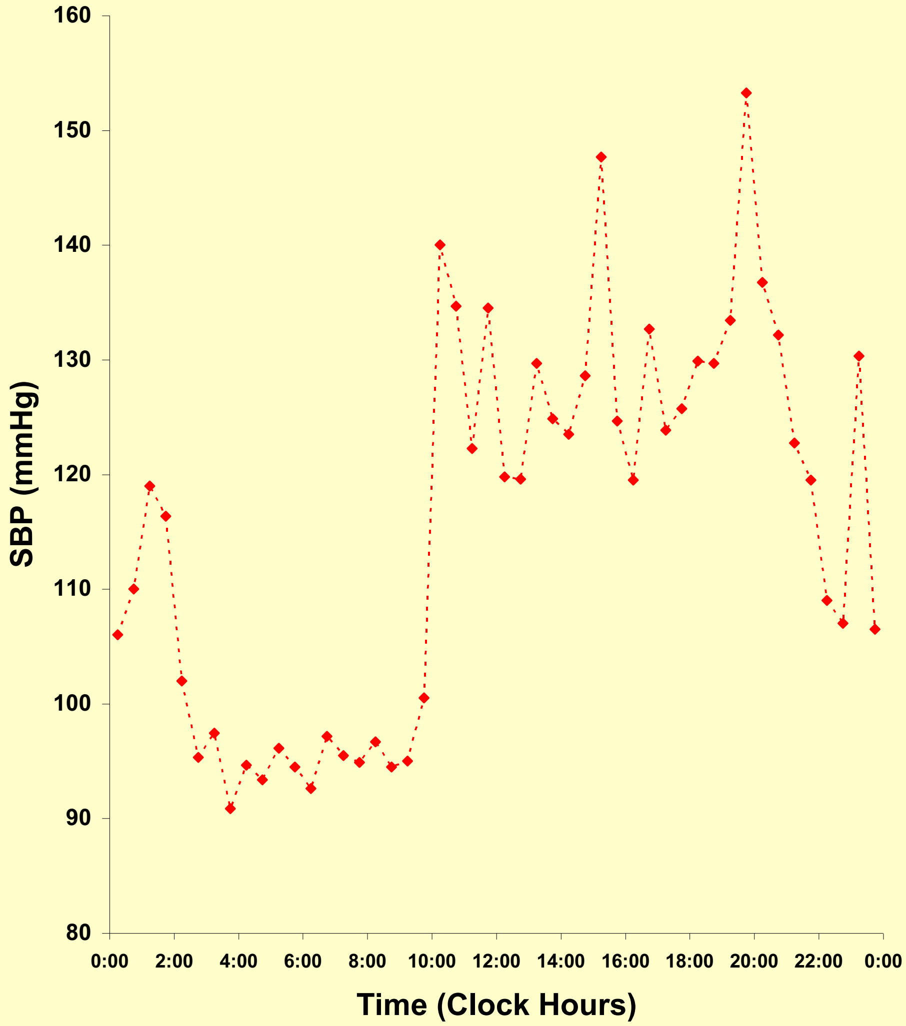
Time-Specified Reference Limits (Chronodesms)

This interval may also be interpreted as having probability (1-α) of including any single additional observation from the same population. In this sense, the interval is a *prediction interval* or a *tolerance interval of β-expectation*.

Nonparametric endpoints

The data are stacked over a single 24-hour span (all data collected at or around 00:00 are averaged, as are all data collected at or around 00:30, …, and at or around 23:30). Practically, averages are computed over consecutive 30-min intervals after the data from different days have been stacked.

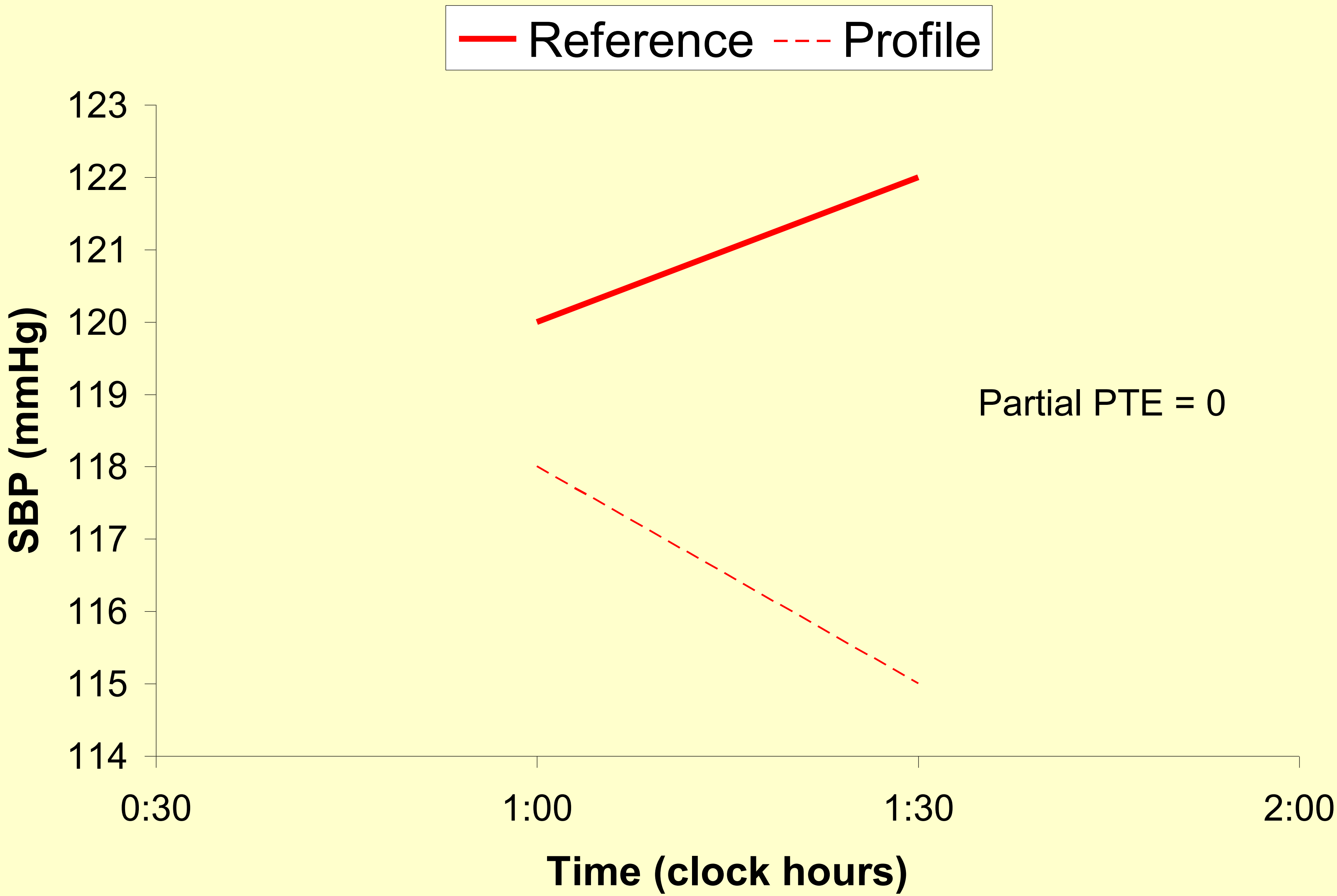
Circadian Pattern of SBP
(#013, F, 55y)

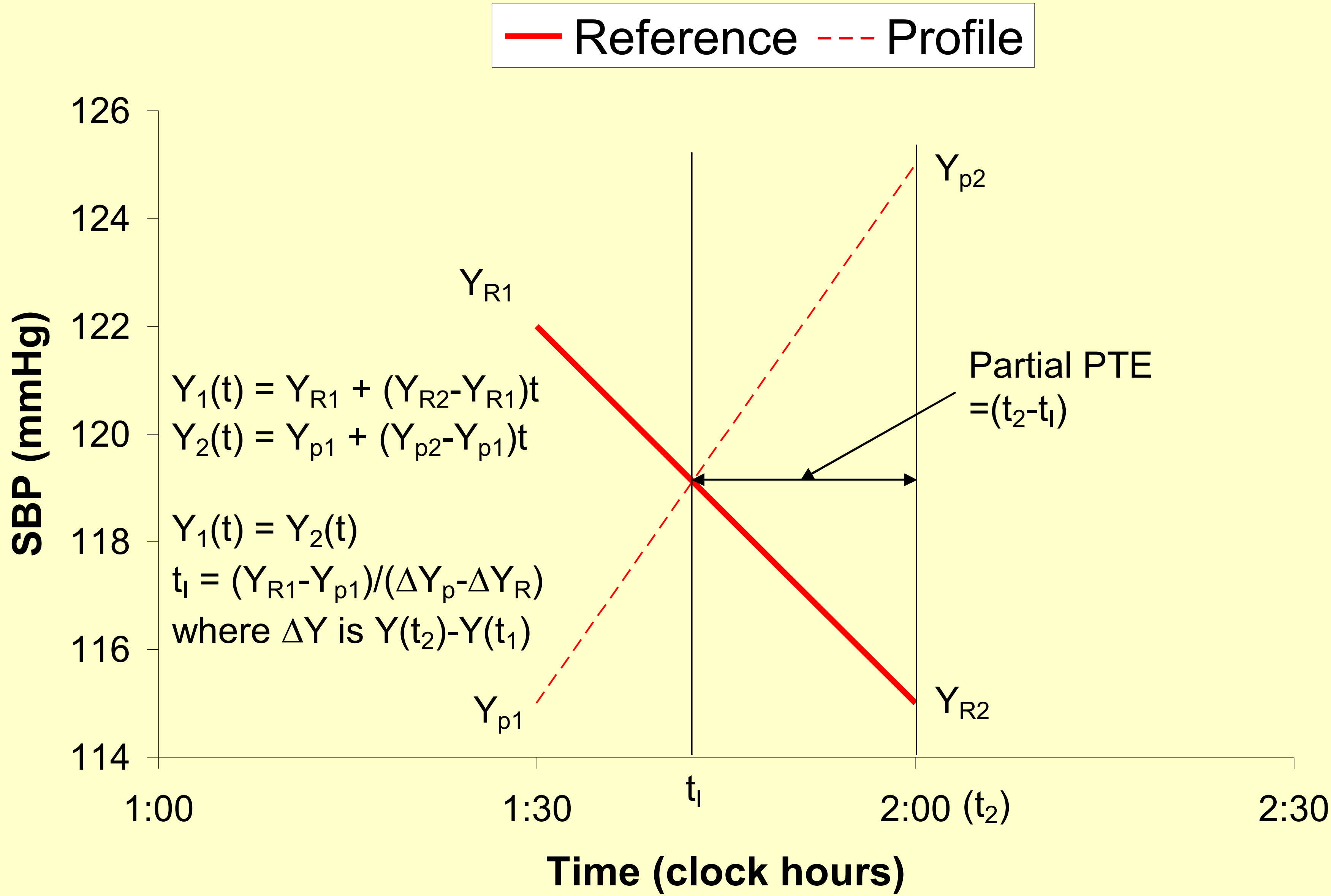


Nonparametric endpoints

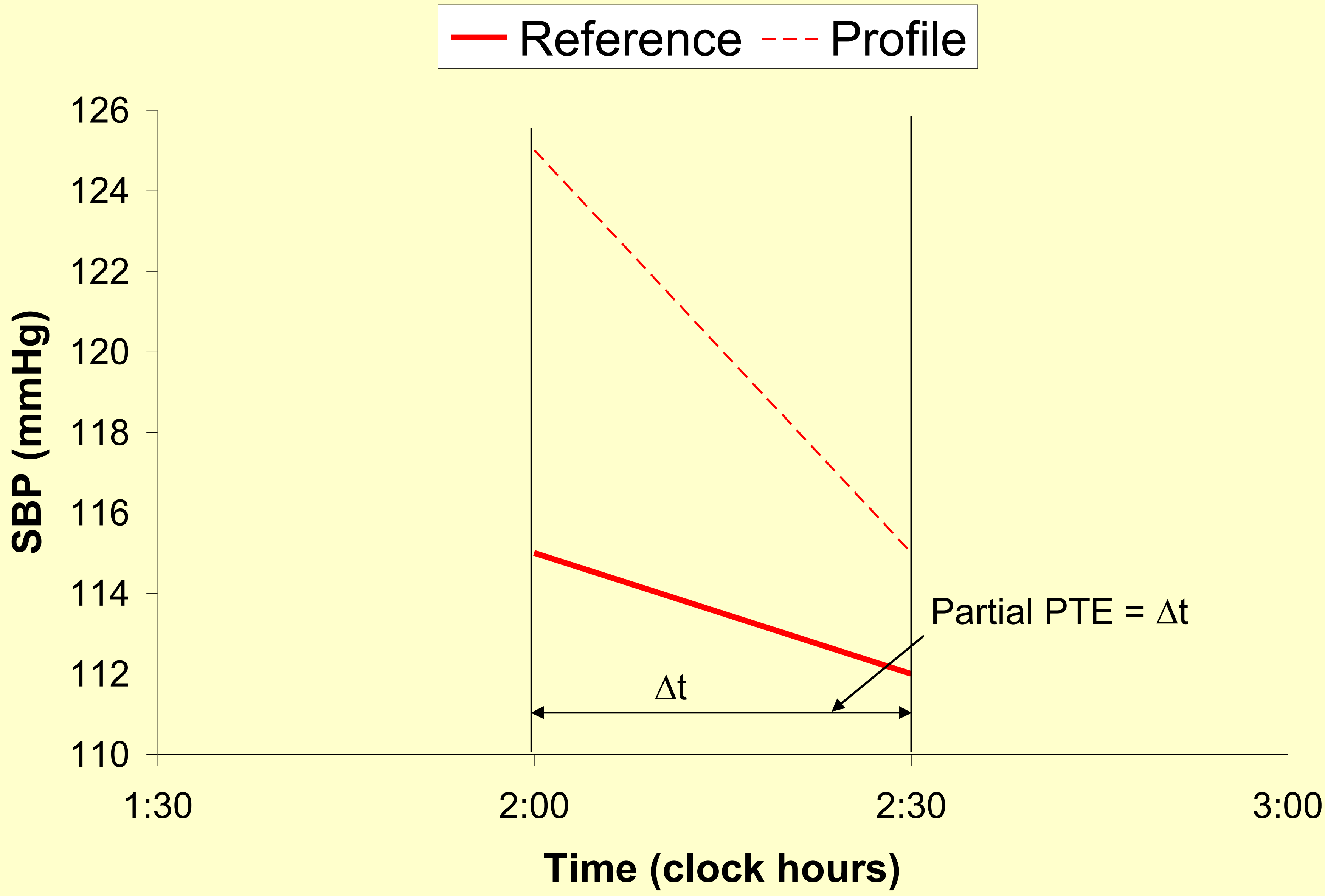
A scan from 00:00 to 24:00 is conducted to determine whether the profile at that time is within the prediction interval or whether it is above the upper 95% prediction limit. If so, using linear interpolation, the amount of time the profile was excessive is estimated and summed over the 24-hour span. The total is divided by 24 hours to yield the percentage time elevation (PTE).

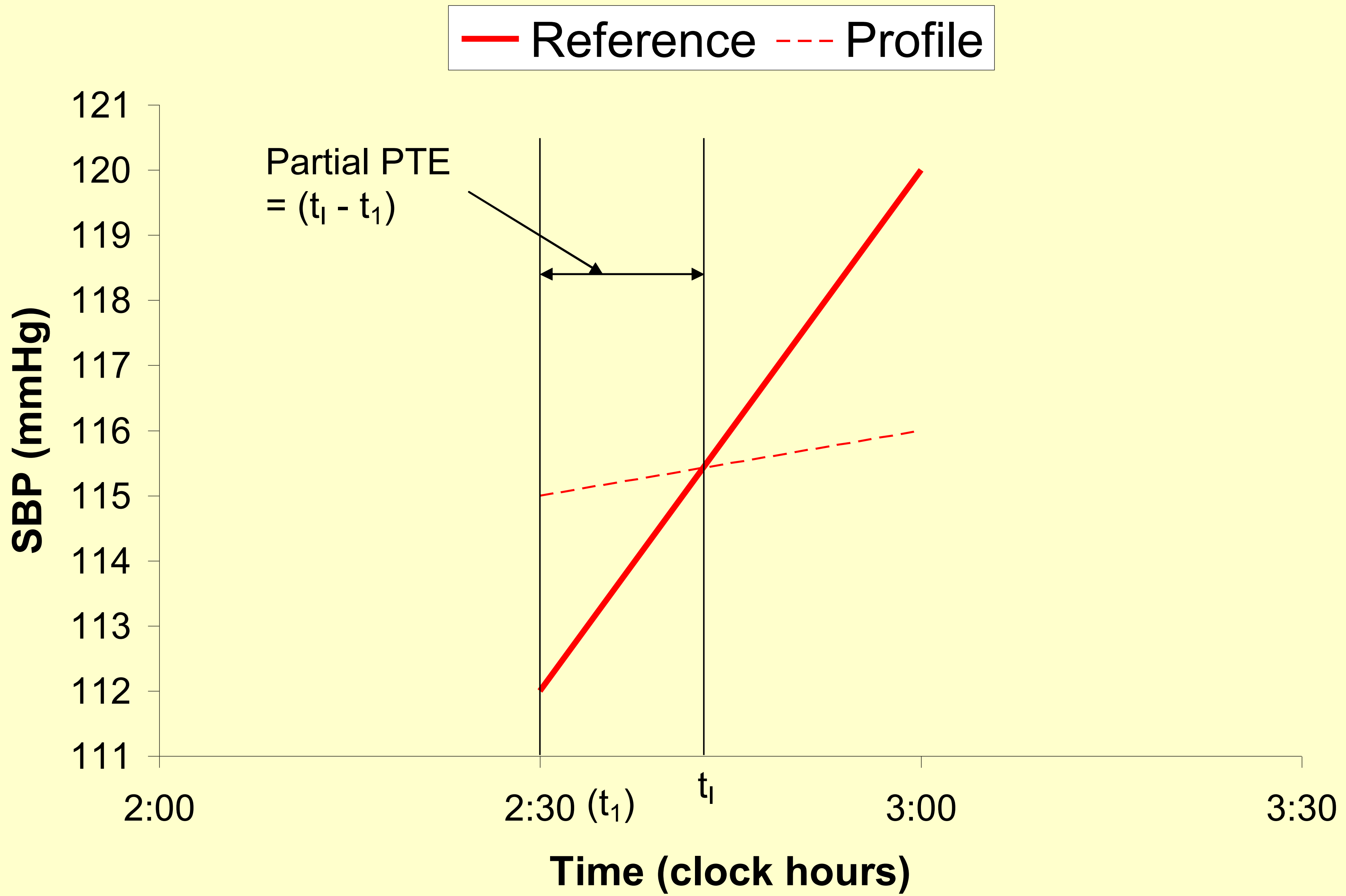
For each (e.g., 30-min) interval, there are 4 different possibilities.


Reference
Profile
123
122
121
120
119
118
117
116
115
114
SBP (mmHg)
Partial PTE = 0
0:30
1:00
1:30
2:00
Time (clock hours)



Reference
Profile
126
124
122
120
118
116
114
SBP (mmHg)
Y_{R1}
Y_{p2}
Y_{p1}
Y_{R2}
$Y_1(t) = Y_{R1} + (Y_{R2}-Y_{R1})t$
$Y_2(t) = Y_{p1} + (Y_{p2}-Y_{p1})t$
$Y_1(t) = Y_2(t)$
$t_I = (Y_{R1}-Y_{p1})/(\Delta Y_p-\Delta Y_R)$
where ΔY is $Y(t_2)-Y(t_1)$
Partial PTE
$=(t_2-t_I)$
1:00
1:30
t_I
2:00 (t_2)
2:30
Time (clock hours)


Reference
Profile
126
124
122
120
118
116
114
112
110
SBP (mmHg)
Partial PTE = Δt
Δt
1:30
2:00
2:30
3:00
Time (clock hours)

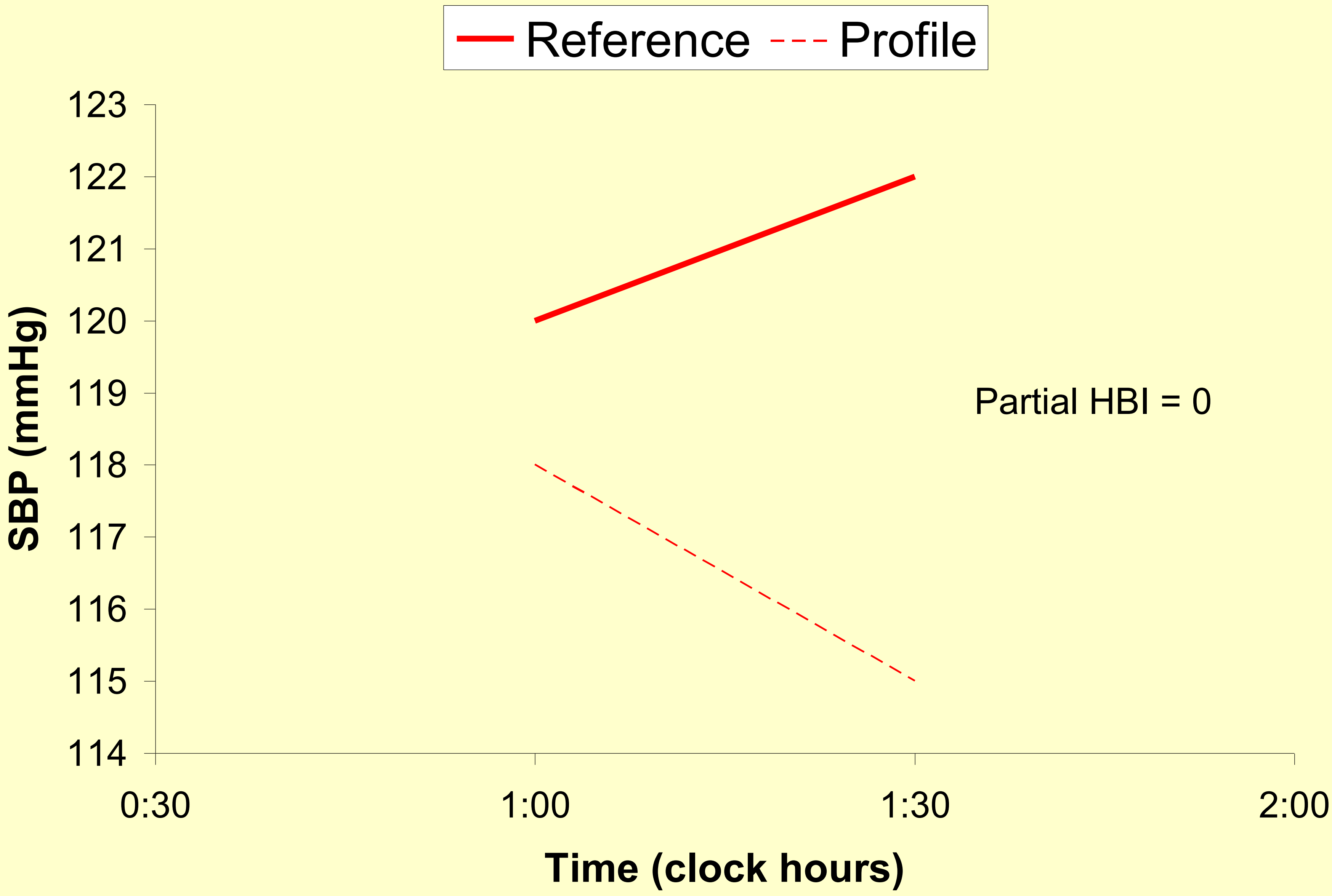


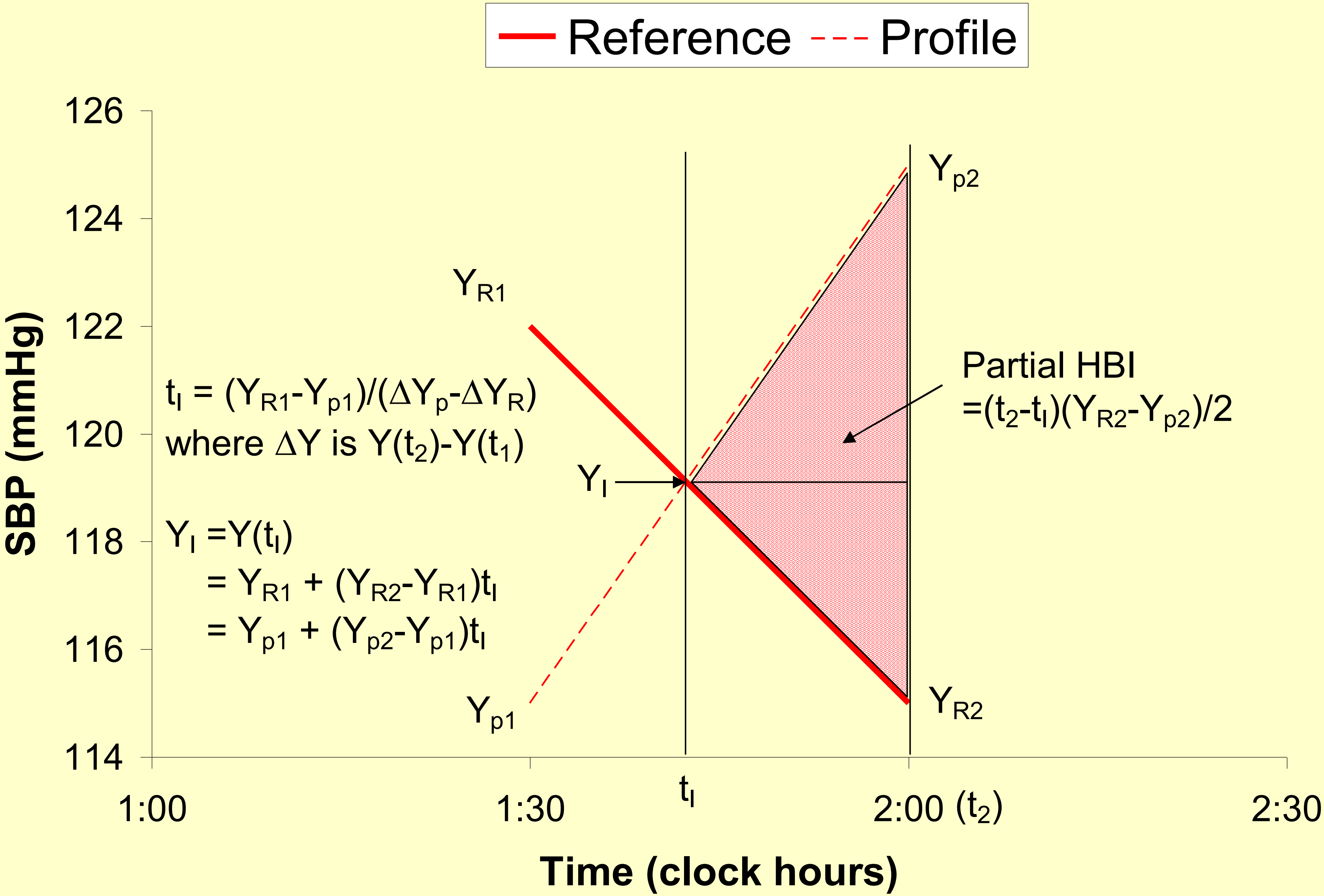
Reference
Profile
Partial PTE
= (t_l - t_1)
SBP (mmHg)
121
120
119
118
117
116
115
114
113
112
111
2:00
2:30 (t_1)
t_l
3:00
3:30
Time (clock hours)

Nonparametric endpoints

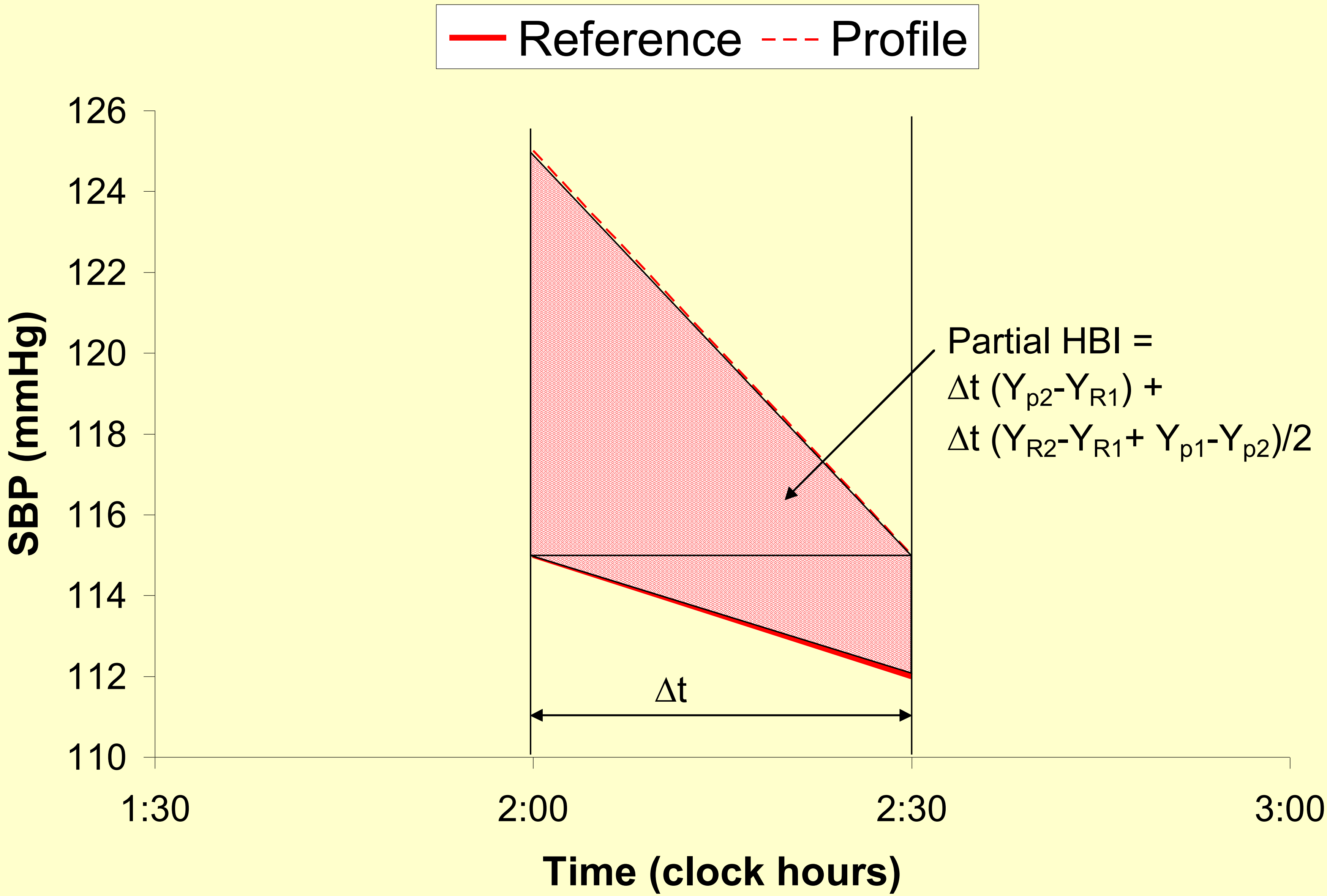
The amount of excess (BP: hyperbaric index or HBI; HR: tachycardic index or TCI) is calculated by numerical integration in a way similar to the calculation of the PTE.

Again, there are 4 possibilities depending on whether the profile is completely below or above the limit or whether it rises above or drops below the limit.

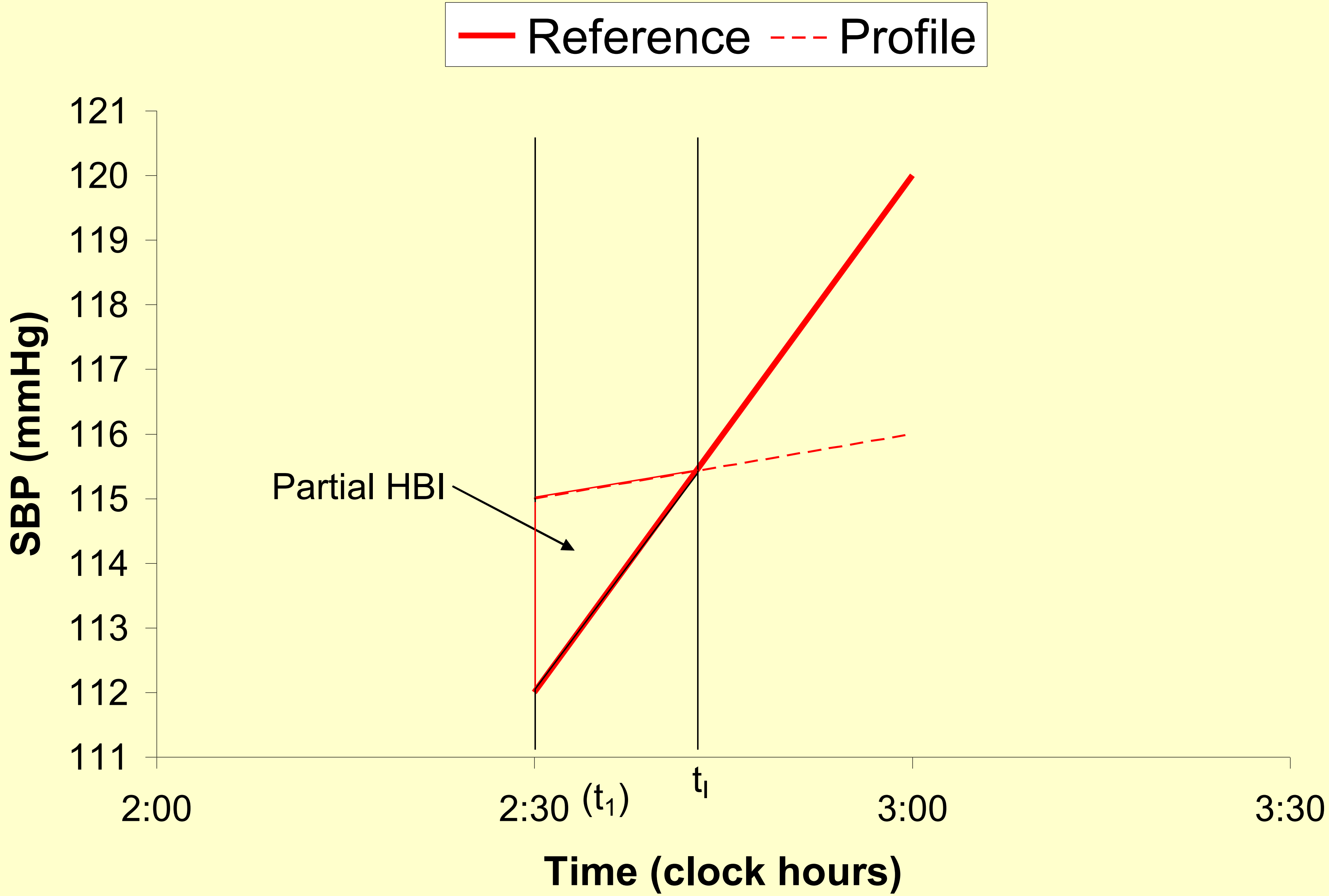

Reference
Profile
123
122
121
120
119
118
117
116
115
114
SBP (mmHg)
Partial HBI = 0
0:30
1:00
1:30
2:00
Time (clock hours)



Reference
Profile
126
124
122
120
118
116
114
SBP (mmHg)
1:00
1:30
t_I
2:00 (t_2)
2:30
Time (clock hours)
Y_{p2}
Y_{R1}
Partial HBI
$=(t_2-t_I)(Y_{R2}-Y_{p2})/2$
$t_I = (Y_{R1}-Y_{p1})/(\Delta Y_p-\Delta Y_R)$
where ΔY is $Y(t_2)-Y(t_1)$
Y_I
$Y_I = Y(t_I)$
$= Y_{R1} + (Y_{R2}-Y_{R1})t_I$
$= Y_{p1} + (Y_{p2}-Y_{p1})t_I$
Y_{p1}
Y_{R2}



Reference
Profile
126
124
122
120
118
116
114
112
110
SBP (mmHg)
Partial HBI =
Δt (Y_p2-Y_R1) +
Δt (Y_R2-Y_R1+ Y_p1-Y_p2)/2
Δt
1:30
2:00
2:30
3:00
Time (clock hours)



Reference
Profile
121
120
119
118
117
116
115
114
113
112
111
SBP (mmHg)
Partial HBI
2:00
2:30 (t1)
tI
3:00
3:30
Time (clock hours)

Nonparametric endpoints

The timing of excess is calculated as the "center of gravity" of the area of excess:

$t_E = \arctan(s/c)$ where

$s = \Sigma_j \, hbi_j \sin \varphi_j \, / \, \Sigma_j \, hbi_j$

$c = \Sigma_j \, hbi_j \cos \varphi_j \, / \, \Sigma_j \, hbi_j$

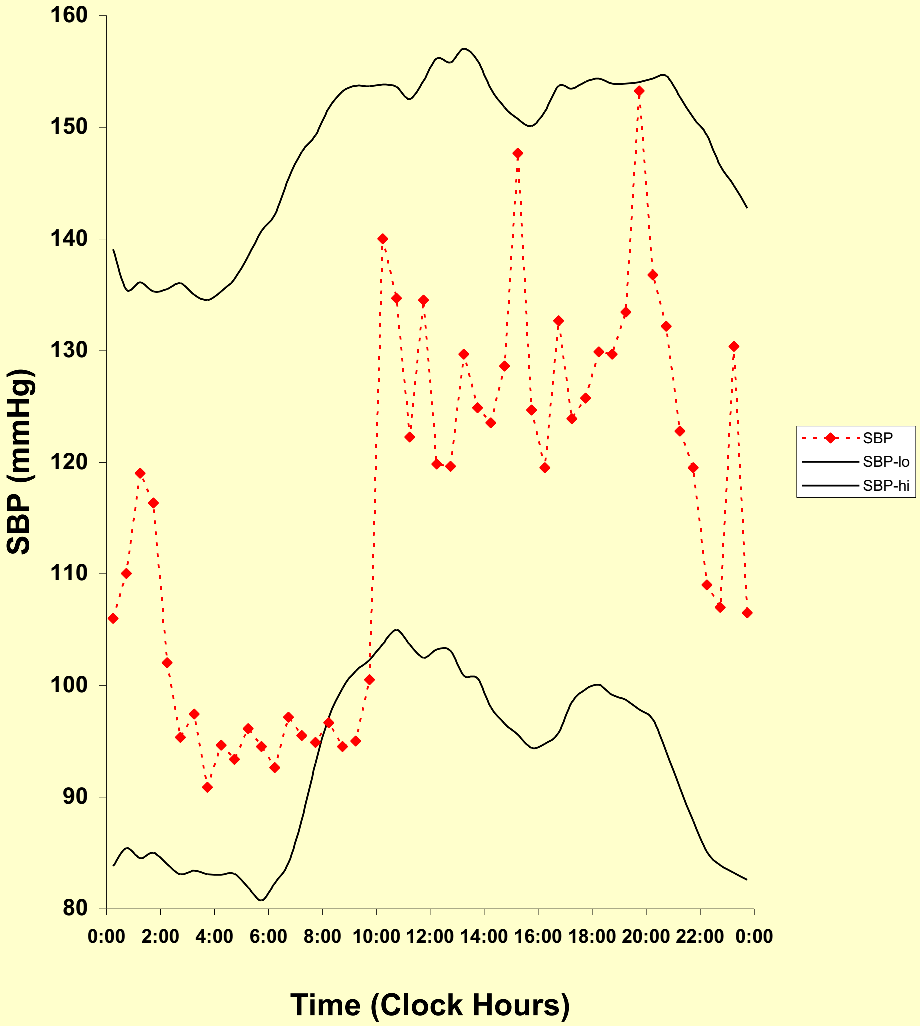
$\varphi_j = -\omega t_j$

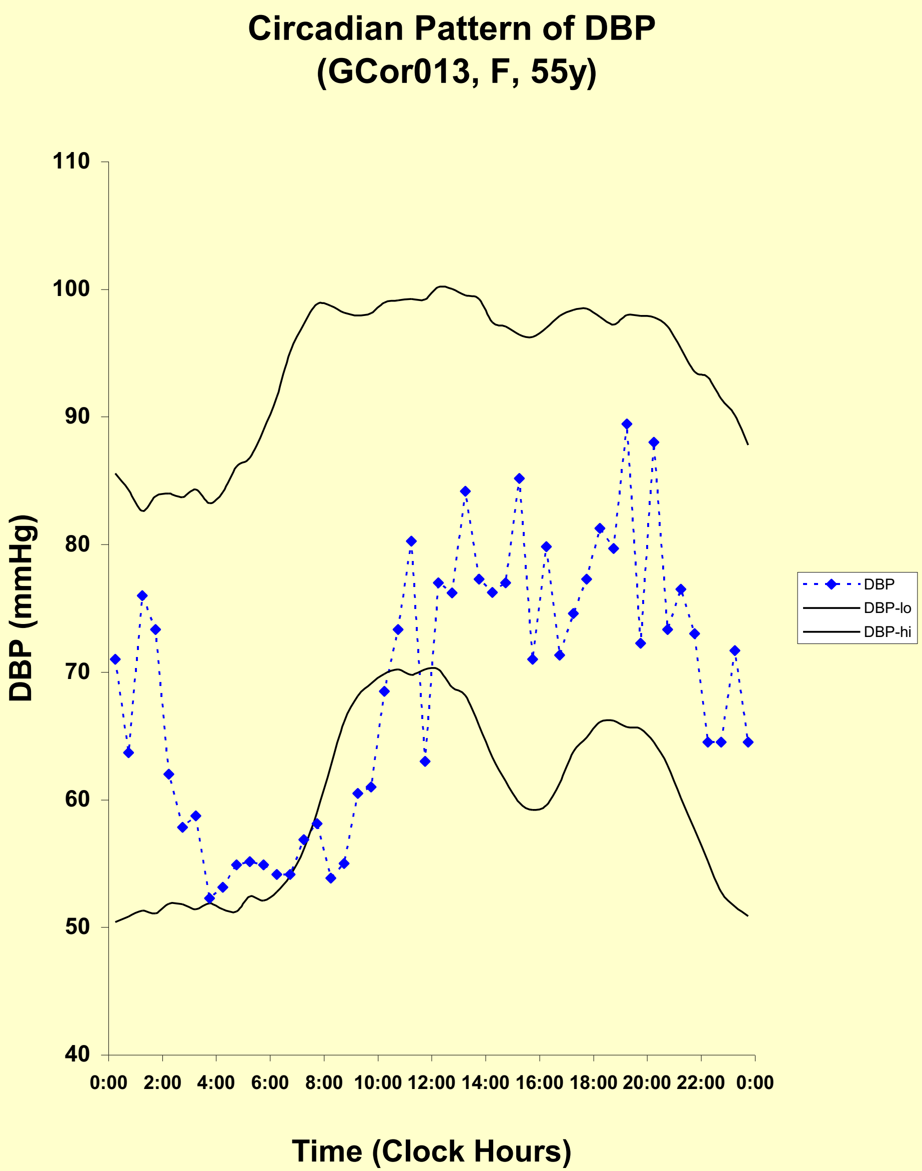
where hbi_j are the partial HBIs and t_j are the (e.g., 30-min) intervals' midpoints.

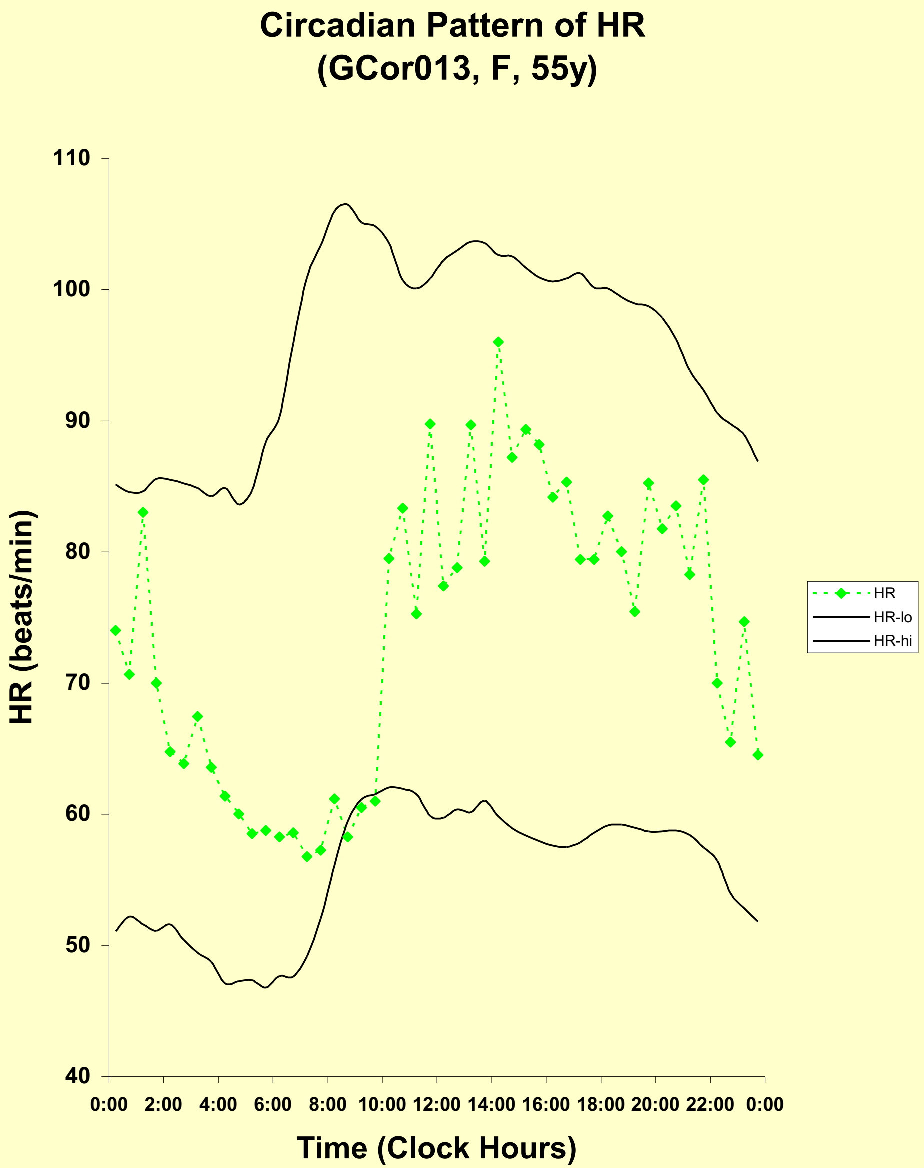
Nonparametric endpoints

Because the excess does not necessarily occur during a single daily episode, the ‘center of gravity’ may not invariably correspond to a reliable estimate of the timing of excess. In order to check on this possibility, fractionated HBI and TCI are also computed over consecutive intervals of 1 or 3 hours. Information about the timing of excess is useful for treatment scheduling.

Circadian Pattern of SBP
(GCor013, F, 55y)




Circadian Pattern of DBP
(GCor013, F, 55y)
110
100
90
80
70
60
50
40
DBP (mmHg)
0:00
2:00
4:00
6:00
8:00
10:00
12:00
14:00
16:00
18:00
20:00
22:00
0:00
Time (Clock Hours)
DBP
DBP-lo
DBP-hi



Circadian Pattern of HR
(GCor013, F, 55y)
110
100
90
80
70
60
50
40
HR (beats/min)
0:00
2:00
4:00
6:00
8:00
10:00
12:00
14:00
16:00
18:00
20:00
22:00
0:00
Time (Clock Hours)
HR
HR-lo
HR-hi

	STD (MIN; MAX)*	STD (MIN; MAX)*	STD (MIN; MAX)*
PERCENT TIME OF ELEVATION	0.0%	0.0%	0.0%
TIMING OF EXCESS	0:00 (hr:min)	0:00 (hr:min)	0:00 (hr:min)
EXTENT OF EXCESS DURING 24 HOURS HBI*	0 (mmHg x hour)	0 (mmHg x hour)	0 (mmHg x hour)
10-YEAR CUMULATIVE EXCESS	0 (mmHg x hour)(in 1,000's units)	0 (mmHg x hour)(in 1,000's units)	0 (mmHg x hour)(in 1,000's units)

Individualized bounded indices: (STD = Standard)(Min = Minimum)(Max = Maximum)(HBI = Hyperbanic Index)

INTERVENTION NEEDED

No

Yes Drug Non-Drug

MORE MONITORING NEEDED

Annually

As soon as possible

Other specify___________________________

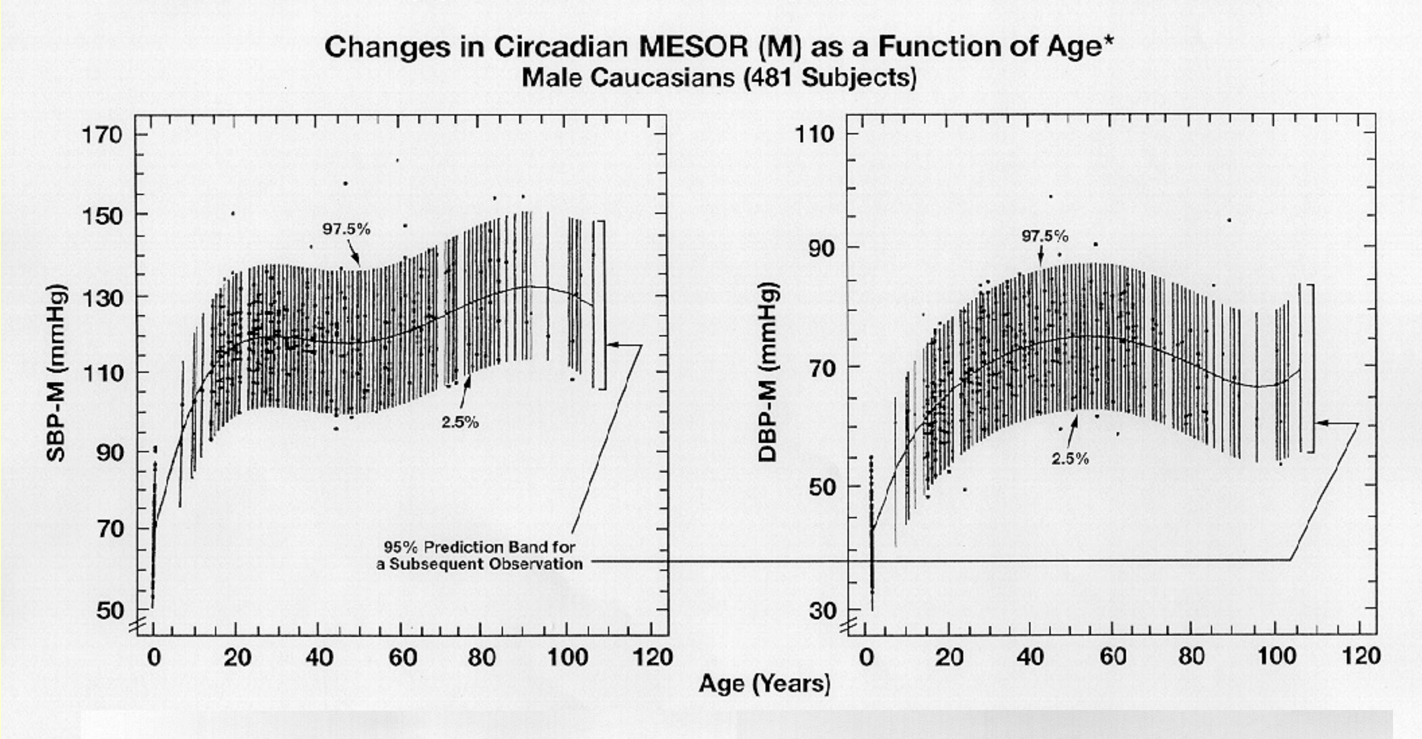
Prepared By____ Date____/____/________

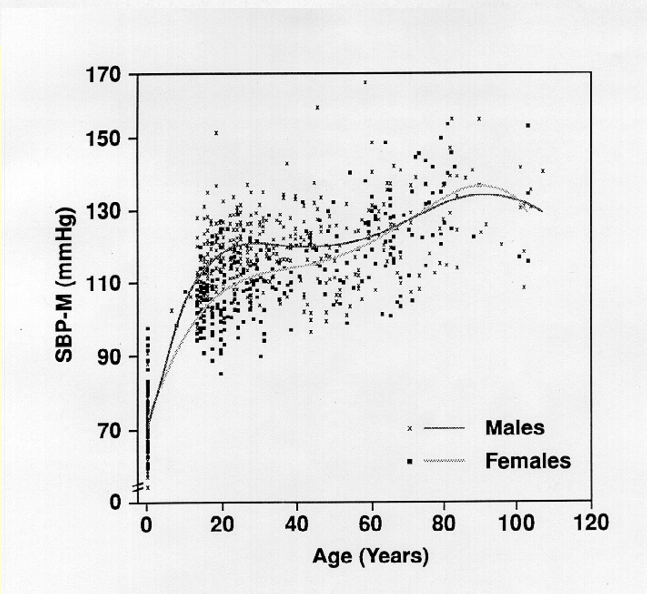
1) Unusually long standing or lying down during waking: unusual activity, such as exercise, emotional loads, or schedule changes, e.g. shiftwork; etc.; 2) Salt, calories, kind and amount, other, etc.

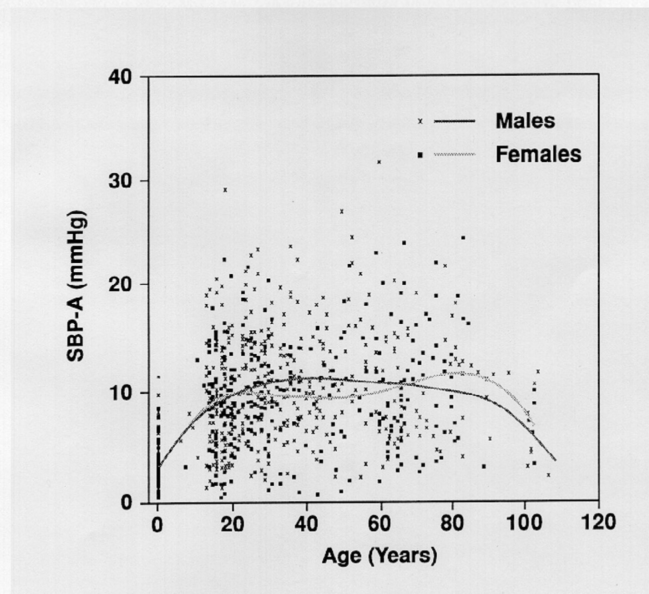
For questions, call F. Halberg or G. Cornelissen at 612-624-6976.

Comments

- Reference values are now computed in terms of clock hours. It would be preferable to compute them in relation to the usual rest-activity schedule of each individual. Hence the merit of a diary.
- Reference values are now computed for a finite number of groups specified by gender and age with a special set of reference values for pregnant women. It would be preferable to determine overall trends with age for women, men and pregnant women in terms of the MESOR and circadian amplitude and acrophase to have a continuum of values.

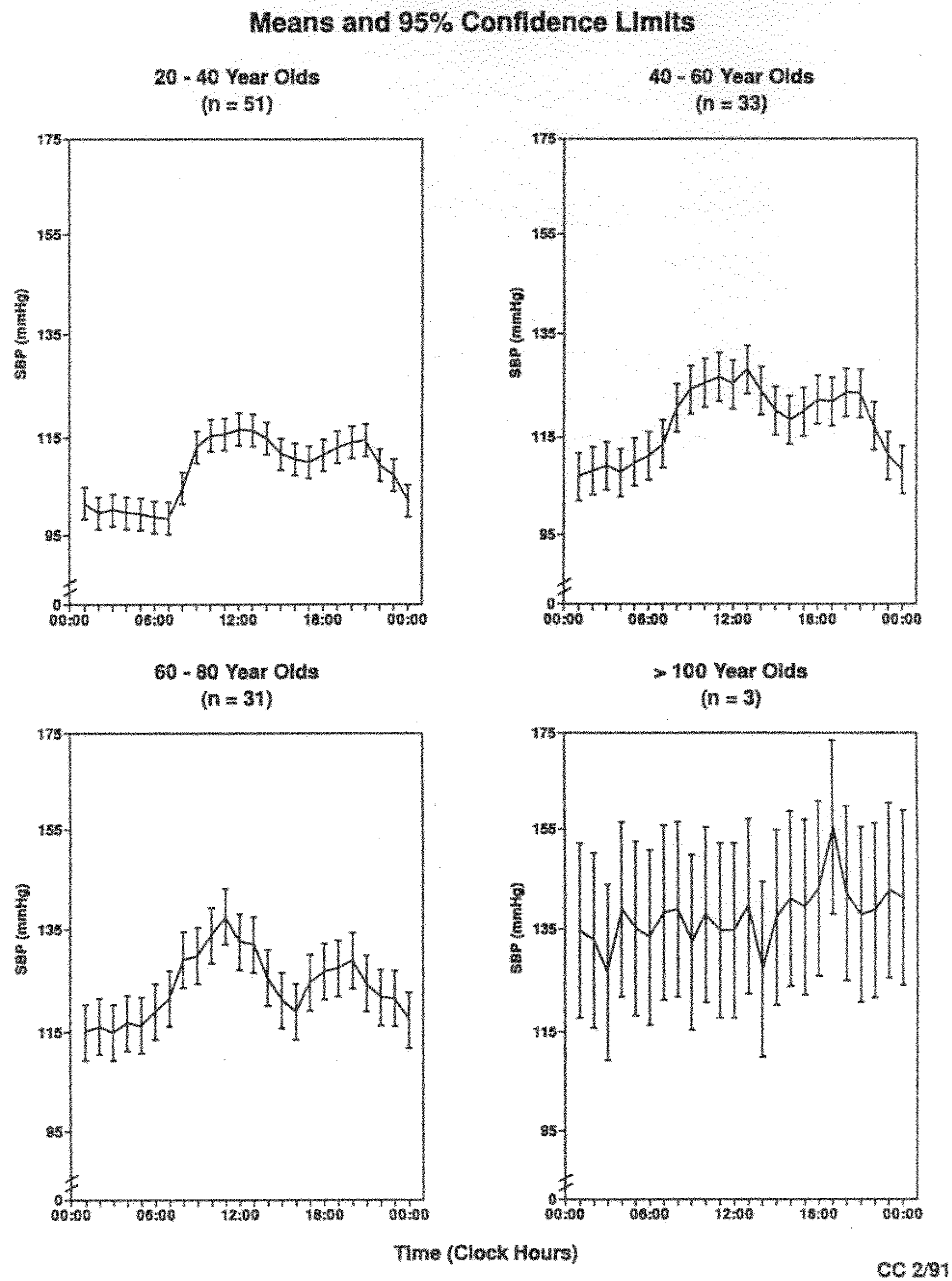

Changes in Circadian MESOR (M) as a Function of Age*
Male Caucasians (481 Subjects)
SBP-M (mmHg)
DBP-M (mmHg)
97.5%
2.5%
95% Prediction Band for
a Subsequent Observation
Age (Years)


SBP-M (mmHg)
Males
Females
Age (Years)


SBP-A (mmHg)
Males
Females
Age (Years)

EXAMPLE:

SBP
in healthy
women



Comments

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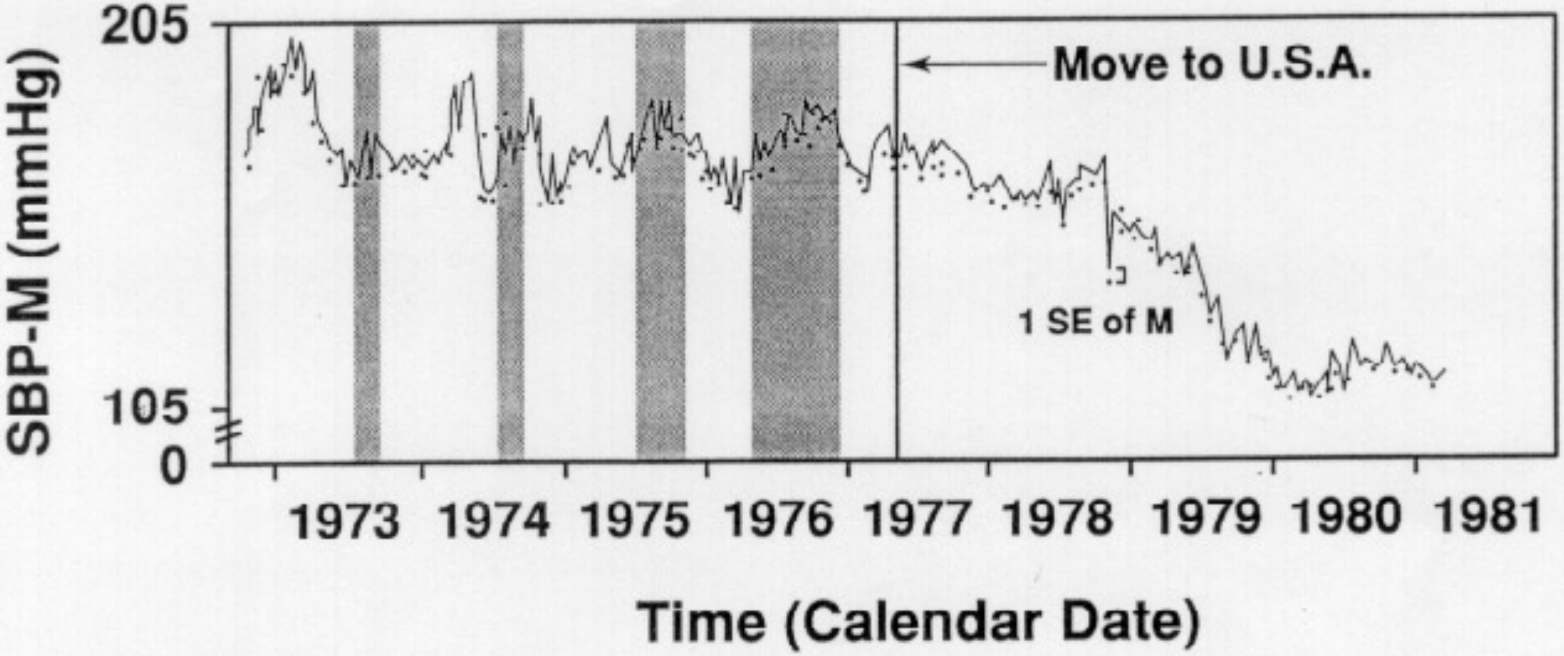
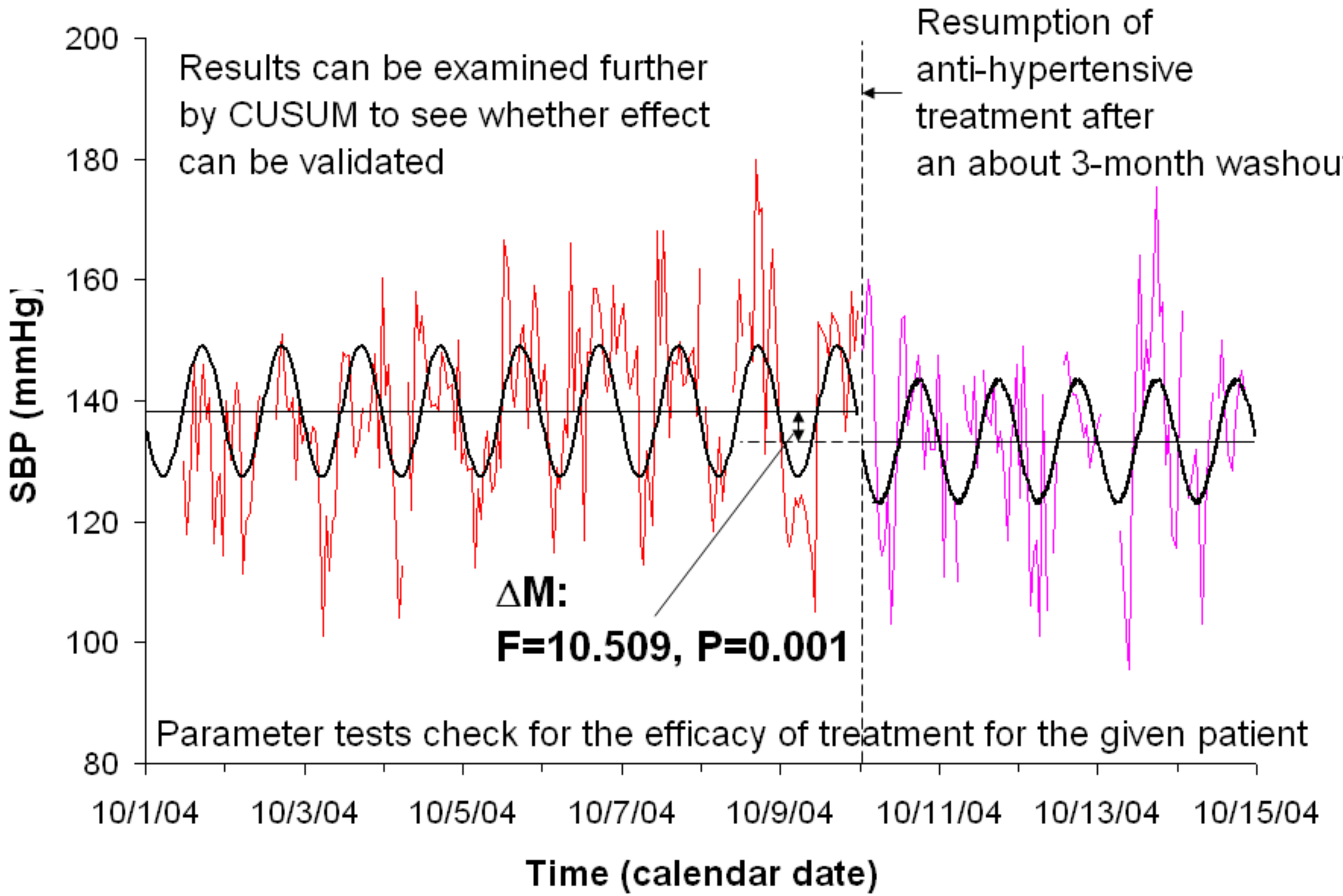
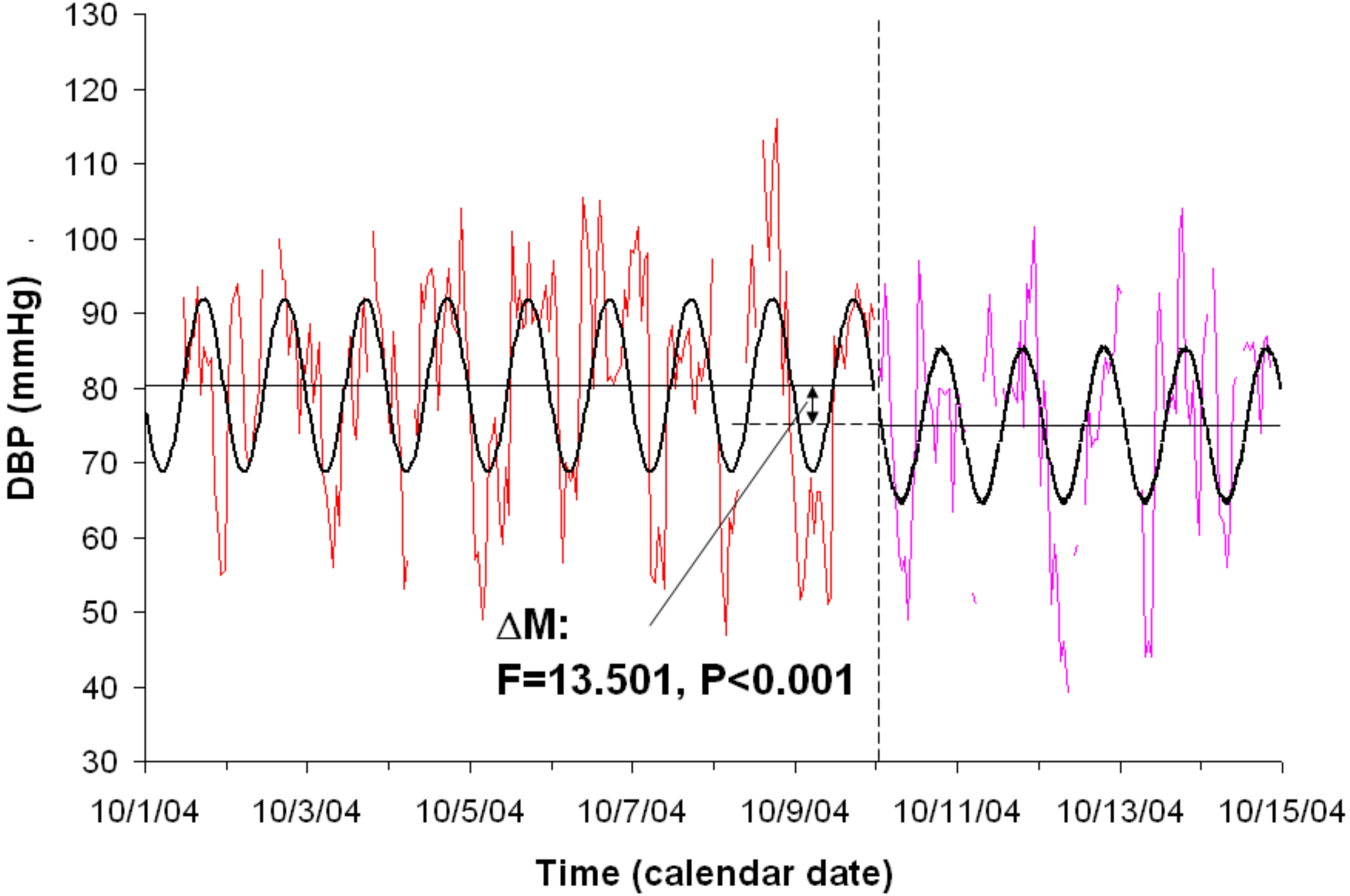
- Reference values are now computed for a finite number of groups specified by gender and age with a special set of reference values for pregnant women. It would be preferable to determine overall trends with age for women, men and pregnant women in terms of the MESOR and circadian amplitude and acrophase to have a continuum of values.
- When repeated profiles are obtained for the same person, additional methods are available such as parameter tests and cumulative sums (CUSUMs) that can assess any changes in rhythm characteristics as a function of time (e.g., in relation to a given intervention such as medication).

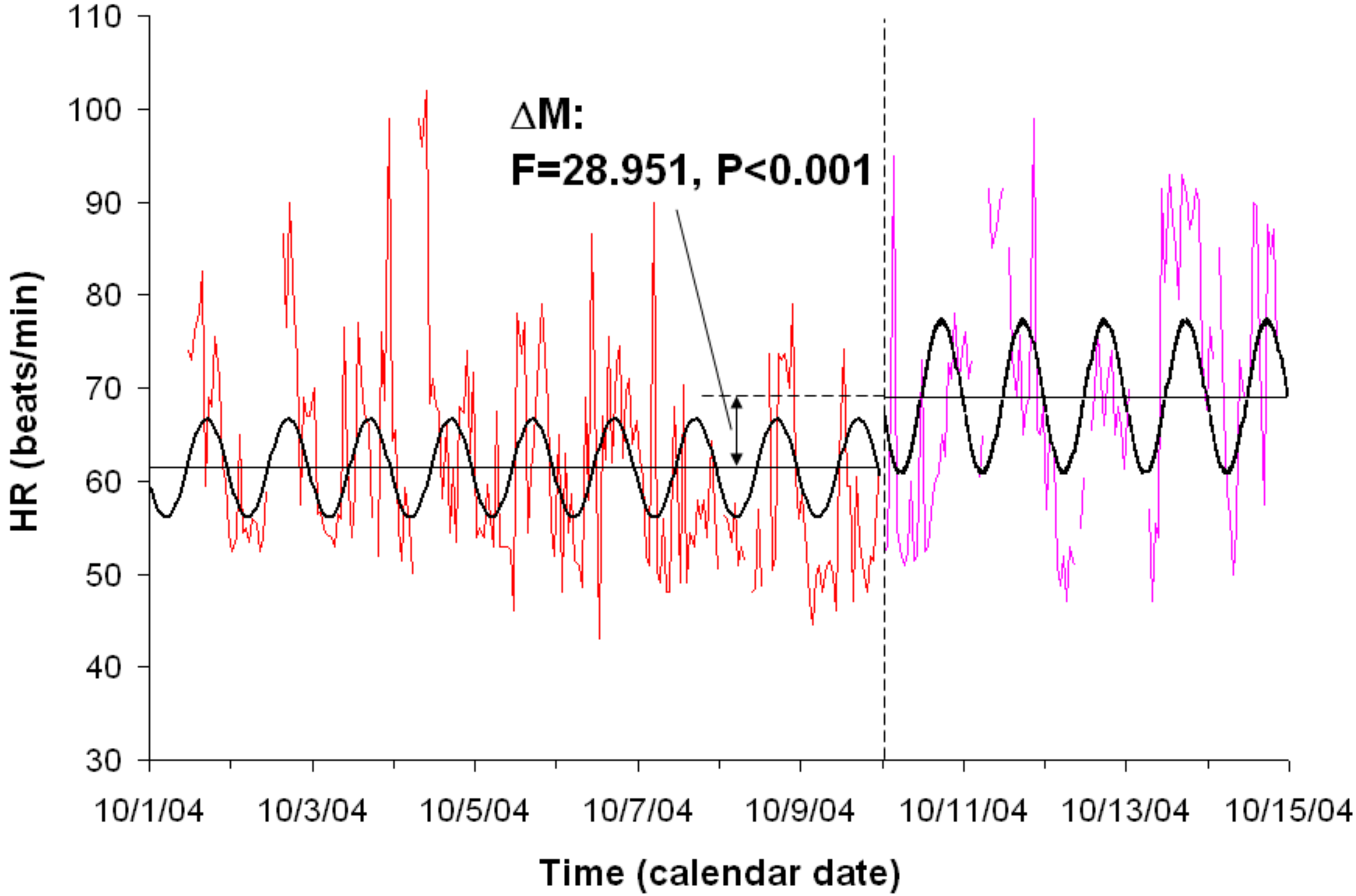
MESOR (M)

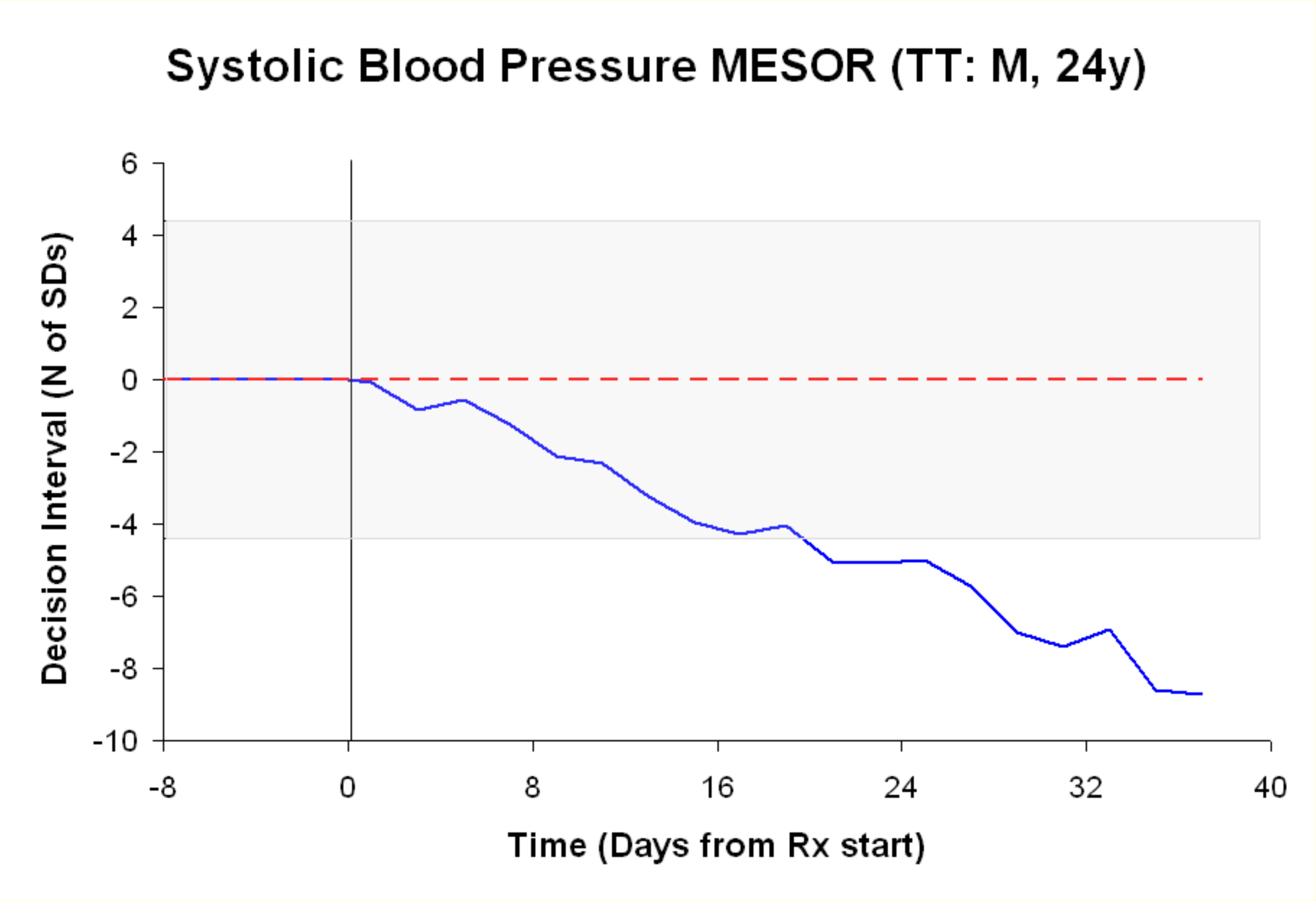


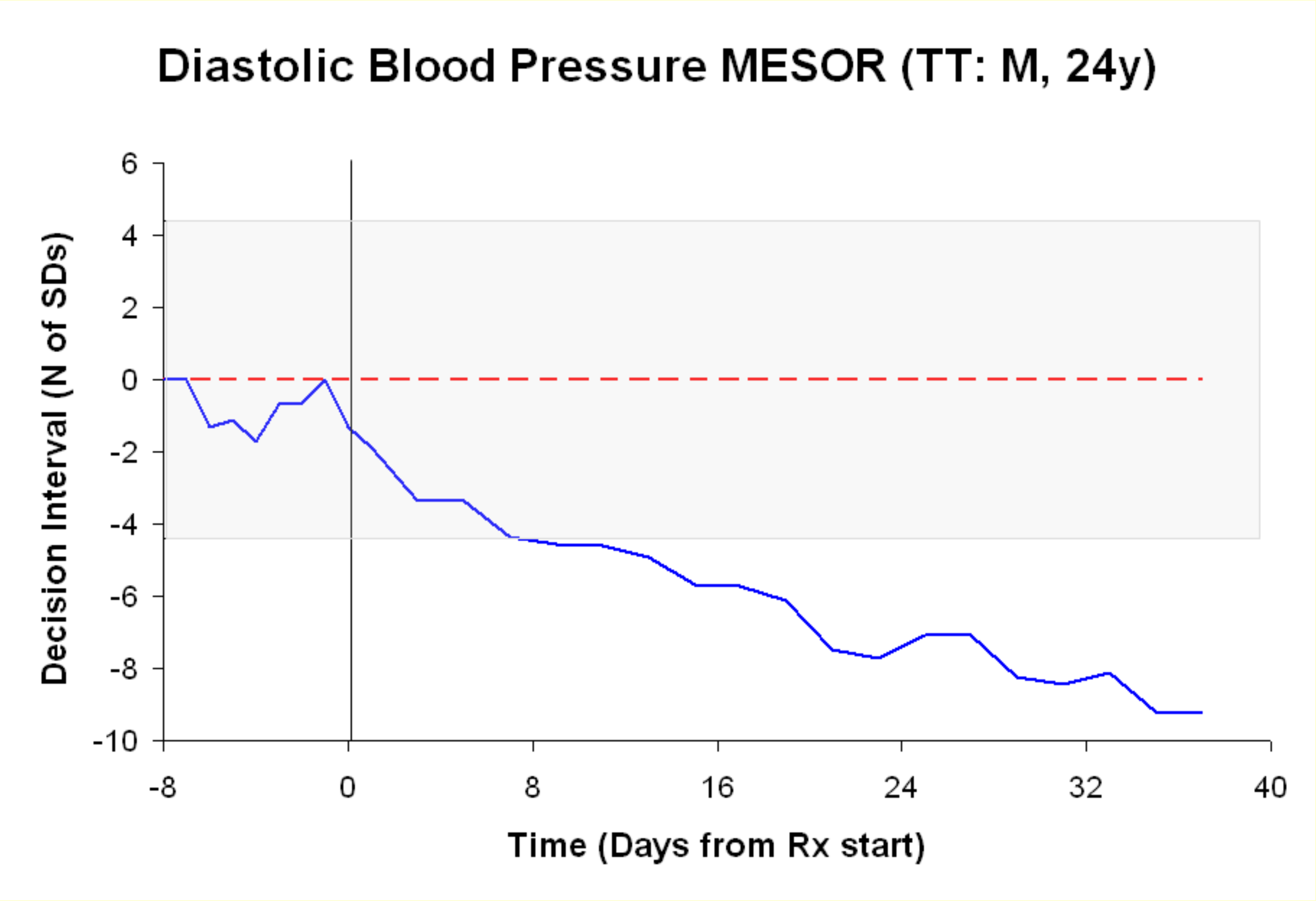
* 14,046 SBP measurements; serial section at trial period of 24 hours over non-overlapping 168-hour intervals. Transmeridian flights over 7 time zones are shaded; antihypertensive medication up to 1978


Resumption of
anti-hypertensive
treatment after
an about 3-month washout
Results can be examined further
by CUSUM to see whether effect
can be validated
ΔM:
F=10.509, P=0.001
Parameter tests check for the efficacy of treatment for the given patient
SBP (mmHg)
200
180
160
140
120
100
80
10/1/04
10/3/04
10/5/04
10/7/04
10/9/04
10/11/04
10/13/04
10/15/04
Time (calendar date)


DBP (mmHg)
130
120
110
100
90
80
70
60
50
40
30
ΔM:
F=13.501, P<0.001
10/1/04
10/3/04
10/5/04
10/7/04
10/9/04
10/11/04
10/13/04
10/15/04
Time (calendar date)


ΔM:
F=28.951, P<0.001
HR (beats/min)
110
100
90
80
70
60
50
40
30
10/1/04
10/3/04
10/5/04
10/7/04
10/9/04
10/11/04
10/13/04
10/15/04
Time (calendar date)


Systolic Blood Pressure MESOR (TT: M, 24y)
Decision Interval (N of SDs)
6
4
2
0
-2
-4
-6
-8
-10
-8
0
8
16
24
32
40
Time (Days from Rx start)


Diastolic Blood Pressure MESOR (TT: M, 24y)
Decision Interval (N of SDs)
6
4
2
0
-2
-4
-6
-8
-10
-8
0
8
16
24
32
40
Time (Days from Rx start)