What is Life ?

Biological Clock and its Clinical Use

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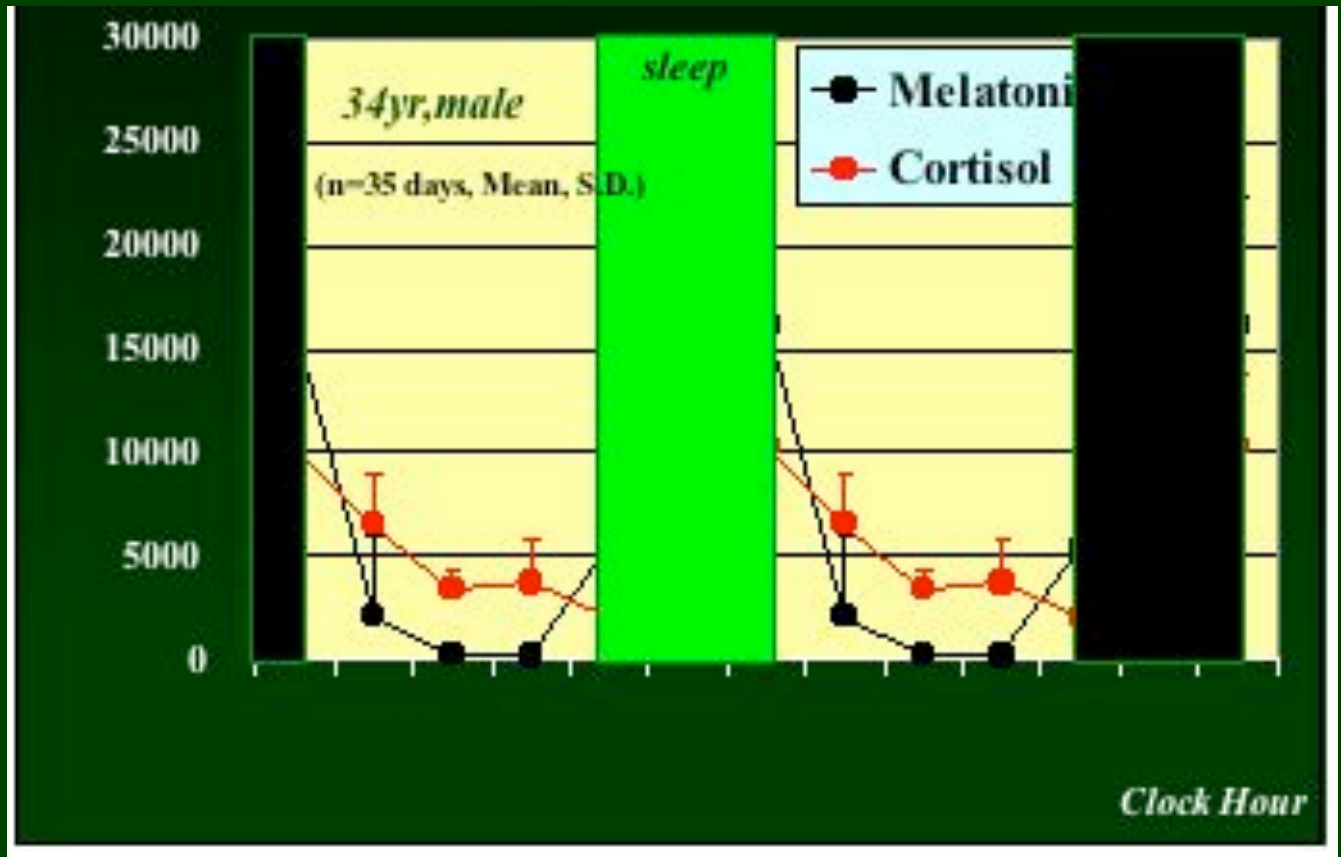
Today' topics are

- ***Recent progress in chronobiology***
- ***Chronomics***
- ***Ecological medicine in the field***
- ***Chronoastobiology***

Most functions of Life, including autonomic nervous, endocrine and immune systems, are not homeostatic, but show circadian fluctuations to coordinate with the natural 24-hourly light/dark cycle

Circadian rhythm of Melatonin and Cortisol in saliva

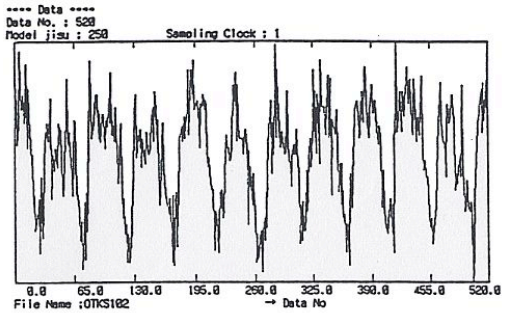


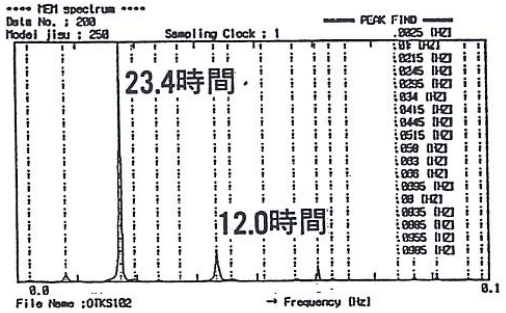
More than 10 days ambulatory BP monitoring disclosed, variation of BP and HR also shows circadian rhythm

Spectral analysis of BP variability

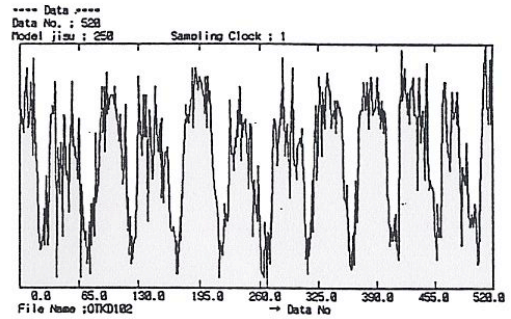
Time-series data | **MEM Power spectrum**

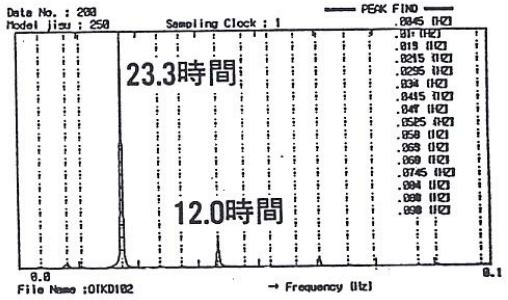
Syst. BP



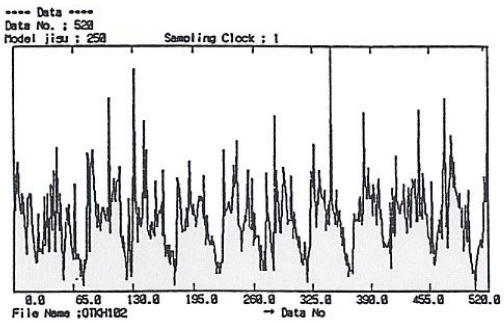


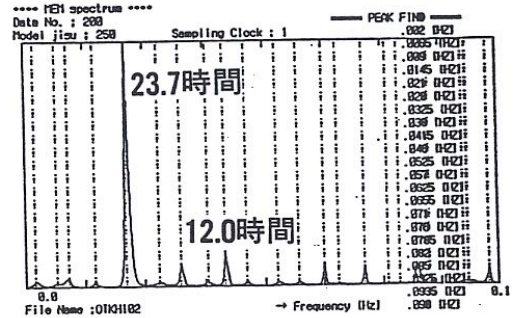
Diast. BP





Heart Rate

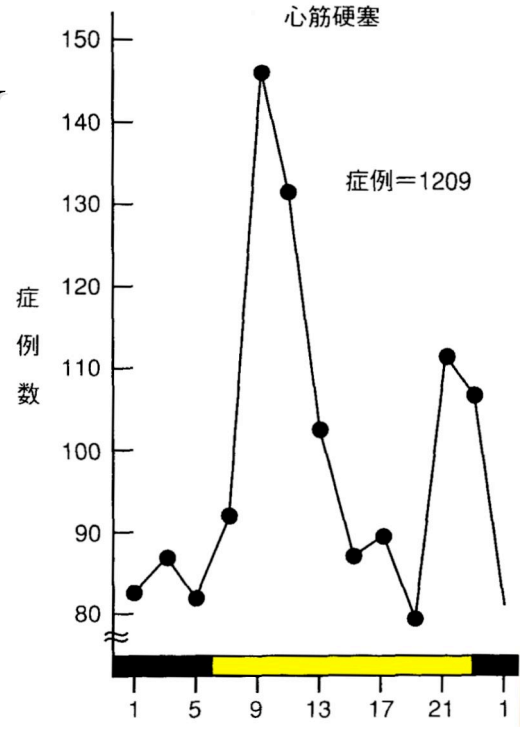




Onset of the disease also shows circadian rhythm

病気の発症には“魔の時間帯”がある

MI



Clock Hour

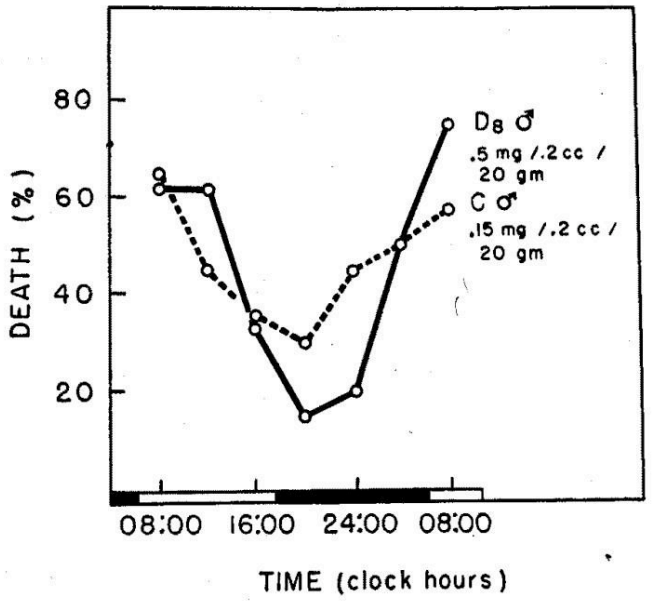
心筋梗塞の発症は、
朝に多い

Myocardial Infarction (MI) is
frequent in the “**morning**”.

By 1959, a susceptibility rhythm to ouabain was shown in mice of two stocks.

Halberg F, Stephens AN. ***Susceptibility to ouabain and physiologic circadian periodicity.*** Proc Minn Acad Sci 1959; 27, 139-143.)

"Chronobiology" as a science in its own right was proposed in 1950 by Franz Halberg, who found a genetic basis for a 24-hour variation in counts of circulating eosinophil cells in five different strains of inbred mice, and officially introduced this term and "circadian" to a nomenclature committee in Stockholm for the first time in 1955, but first published "circadian" in 1959.



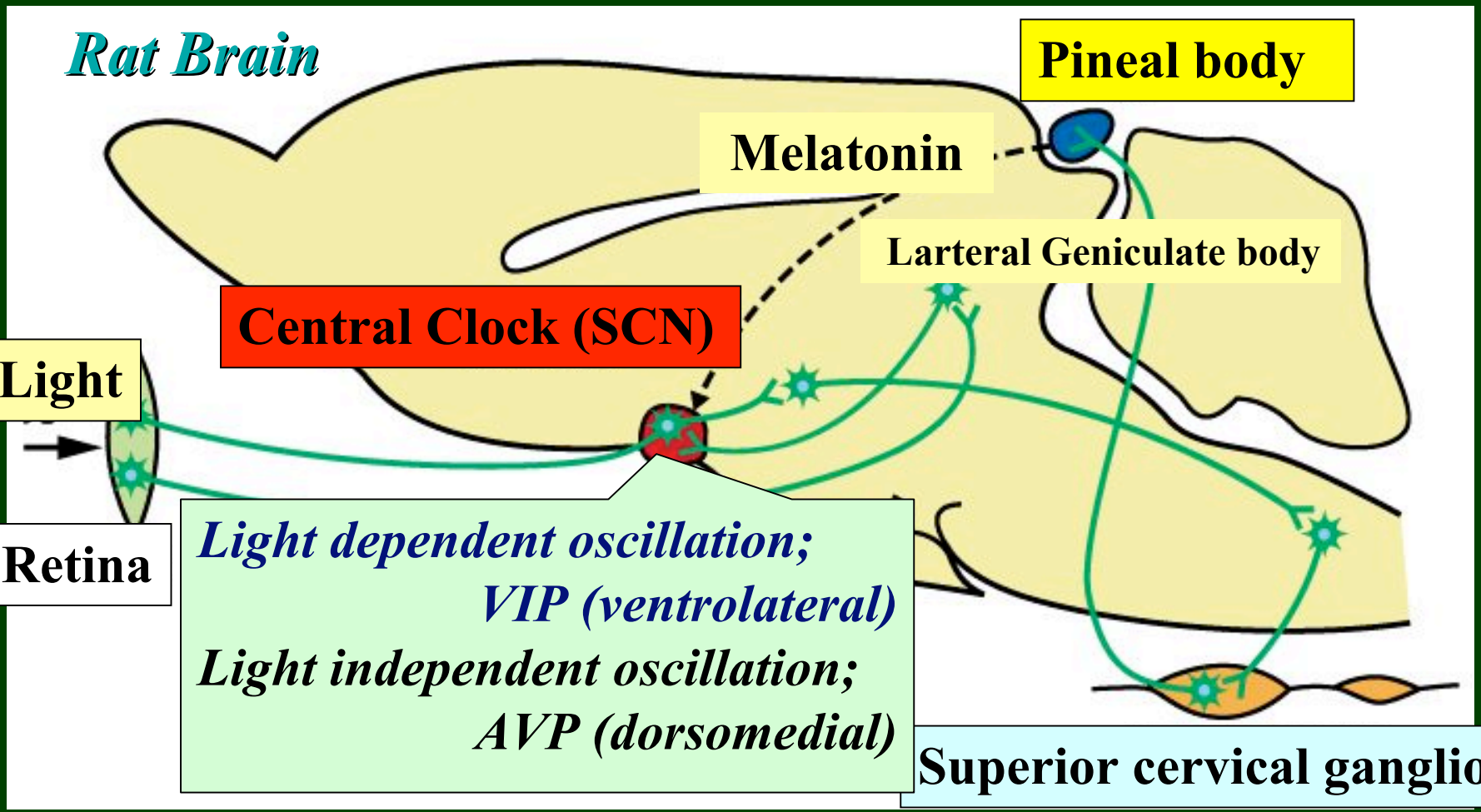
Astrobiology and Chronomedicine

Prof. Franz Halberg in 1989

Circadian rhythms
and
Clinical chronobiology

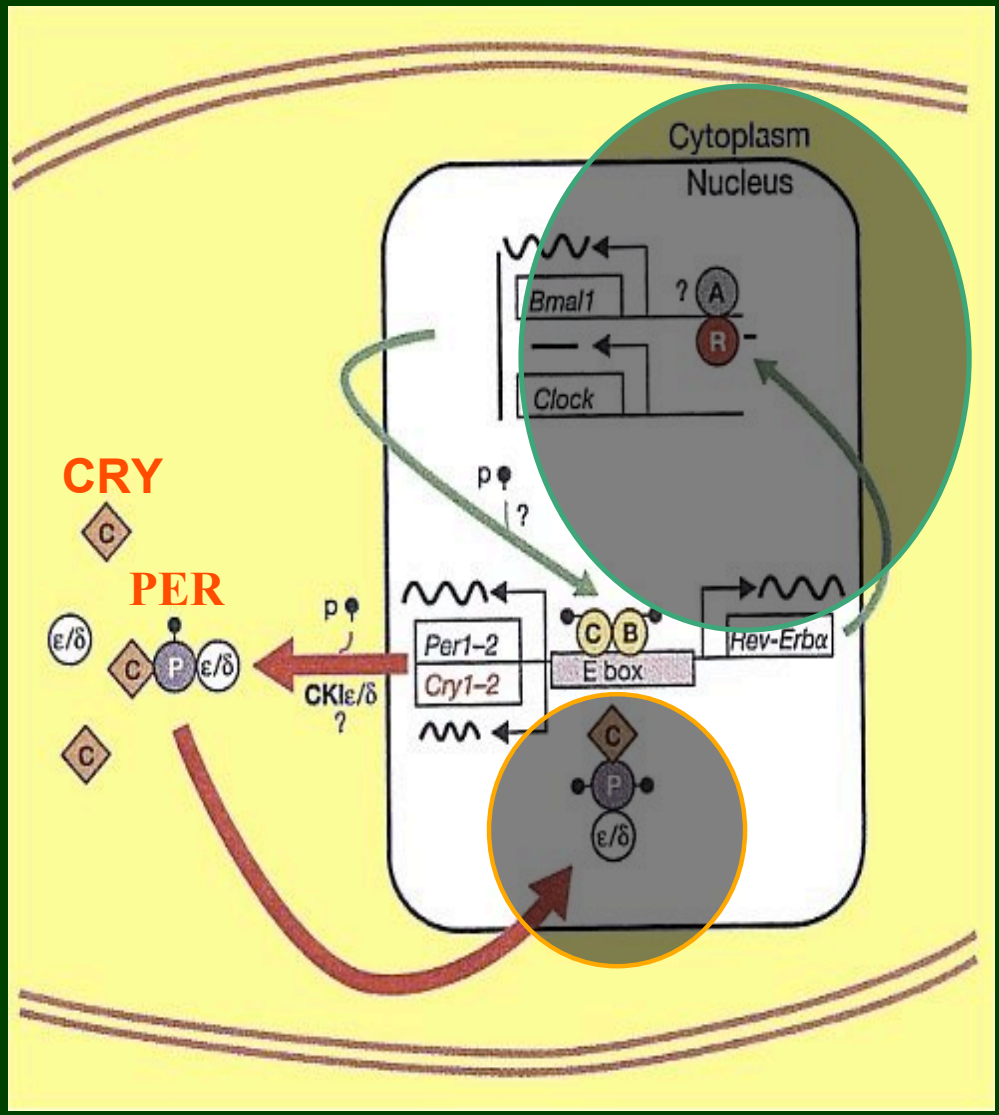
Most organisms, from cyanobacteria to mammals, are known to use circadian mechanisms to coordinate their activities with the natural 24-hourly light/dark cycle and/or interacting socio-ecologic schedules.

Central Circadian Clock ; Supra Chiasmatic Nuclei (SCN) of the hypothalamus in mammals



Mammalian Circadian Clockwork Model
細胞内 概日時計 機構

- ***Negative transcription feedback loops***
  - When the human clock gene was disclosed and mapped to chromosome in 1997, it was surprising to see that the clock gene was very similar in all earthly life.



Recent several papers showed Clock gene mutant animals develop Metabolic syndrome along with growing up

Obesity and Metabolic Syndrome in Circadian *Clock* Mutant Mice
Science, Vol 308, 1043-1045, 2005

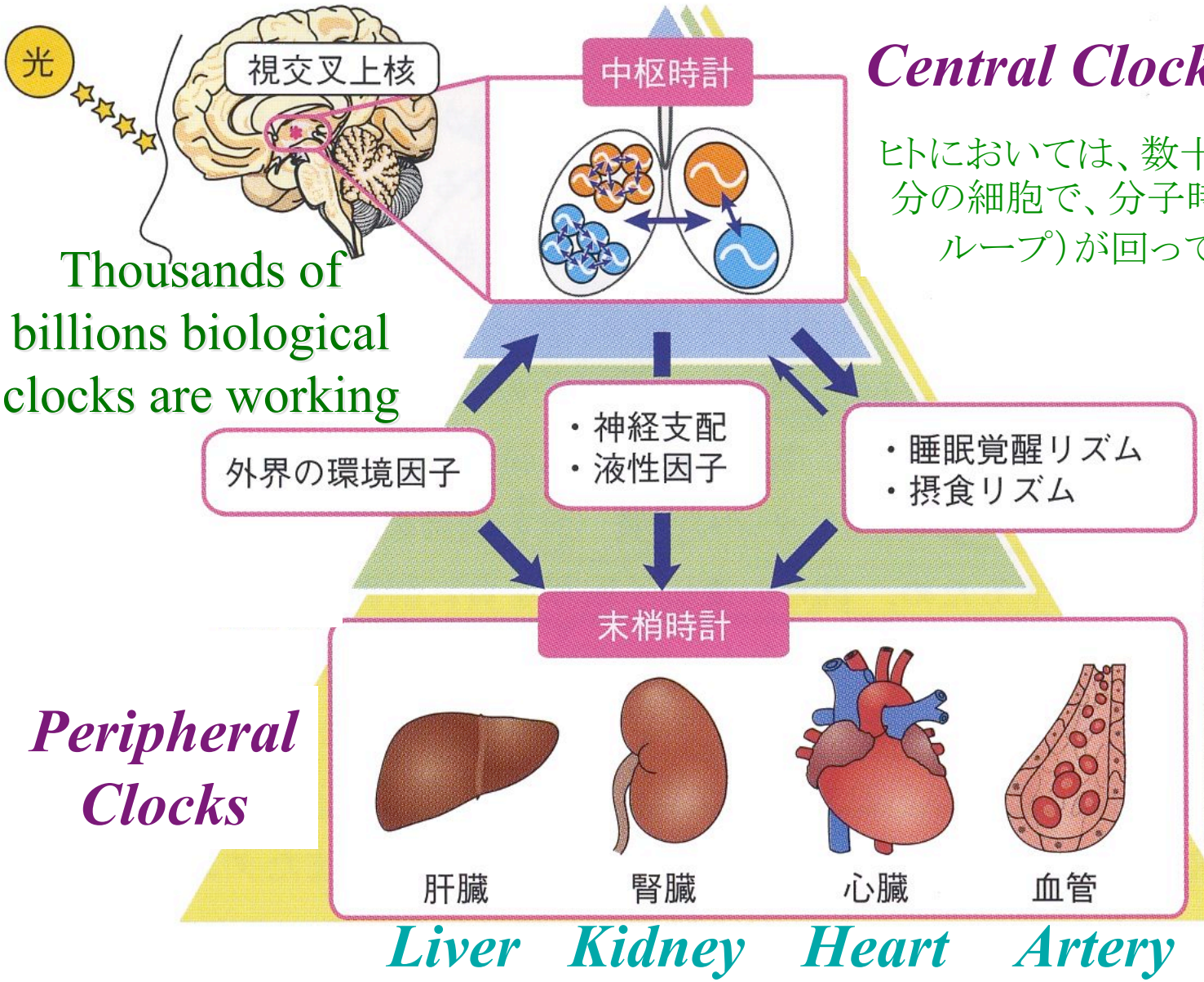
Table 1. Metabolic parameters in WT and *Clock* mutant mice. Serum triglyceride, cholesterol, glucose, insulin, and leptin concentrations were determined in 7- to 8-month-old WT and *Clock* mutant mice fed a regular diet ad libitum (n = 4 to 8 mice per group). For measurement of glucose, insulin, and leptin, blood was collected at 4-hour intervals over a 24-hour time period via an indwelling catheter (40 µl per blood sample), and the data were pooled to provide an overall mean (±SEM) value. For triglyceride and cholesterol measurement, a single blood sample (160 µl) was collected at zeitgeber time 0.

Metabolic parameter		WT	*Clock*	*P* value
Triglyceride (mg/dl)	中性脂肪	136 ± 8	164 ± 8	<0.05
Cholesterol (mg/dl)	コレステロール	141 ± 9	163 ± 6	<0.05
Glucose (mg/dl)	血糖	130 ± 5	161 ± 7	<0.01
Insulin (ng/ml)		1.7 ± 0.3	1.1 ± 0.1	n.s.
Leptin (ng/ml)		3.4 ± 0.4	4.6 ± 0.3	<0.05

時計遺伝子異常のマウスはメタボリック症候群（肥満・血圧高値・血糖異常・中性脂肪高値）になる

壮大な”階層的時計機構”：中枢時計と末梢時計

Hierarchy System of Clock Work in Human



Central Clock

ヒトにおいては、数十兆の大部分の細胞で、分子時計（コア-ループ）が回っている。

Thousands of billions biological clocks are working

Peripheral Clocks

Liver Kidney Heart Artery

Common Diseases, such as HT, HL, MI and Atherosclerosis; Clock-related

Thus, it is now discussing how circadian function is associated with not only QOL, but also with ***morbidity***, ***mortality*** and ***longevity***.

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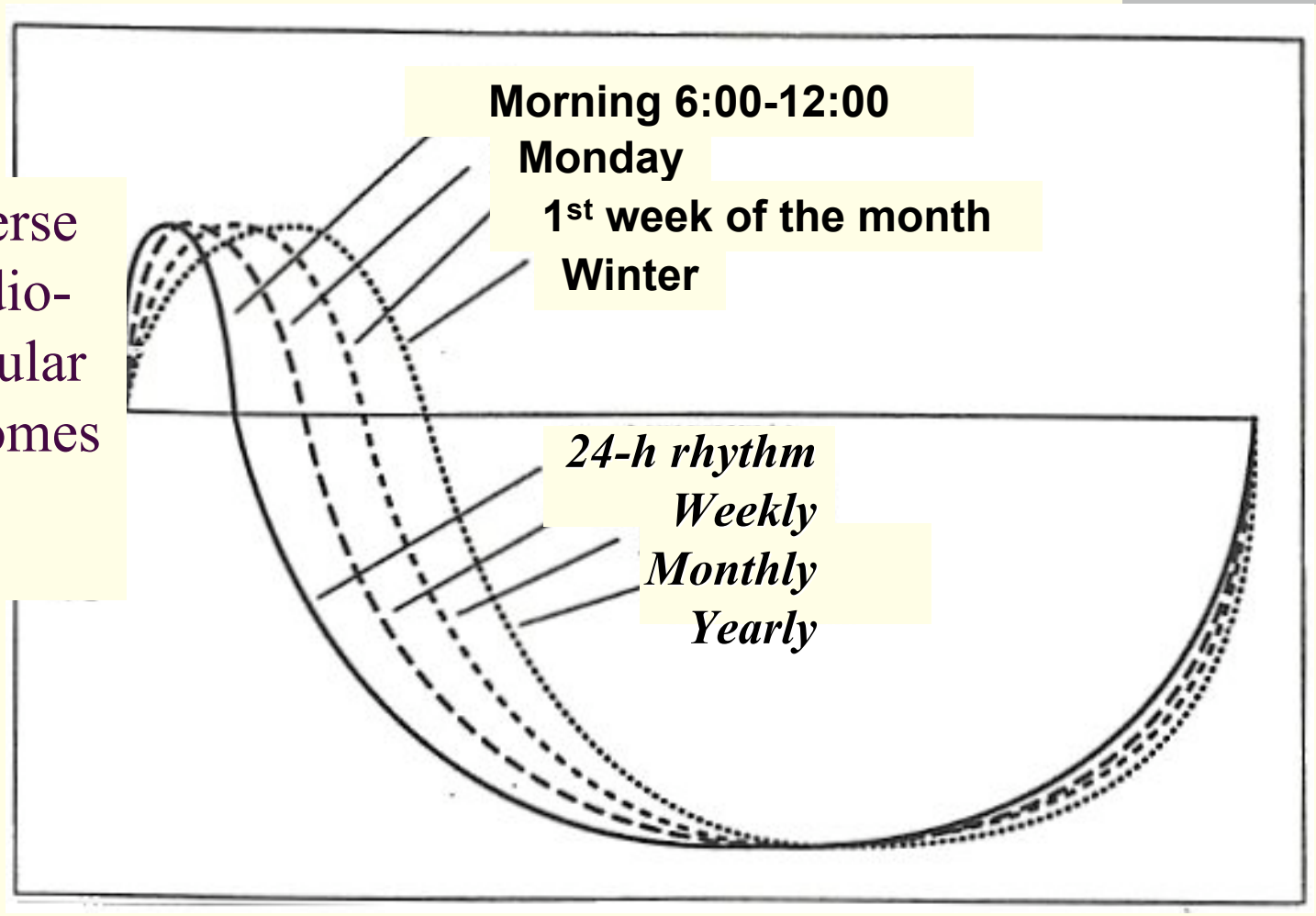
Life has biological rhythm, not only photic, but also non-photic rhythms

- **Visible photic effect** （太陽光）
  - Circadian rhythm（24-hr、地球の自転）
  - Circasemidian rhythm（12-hr、月の魔力）
  - Seasonal rhythm（12-month地球の公転）
- **Invisible non-photic effect** （地磁気・宇宙線など）
  - Weekly rhythm
  - Trans-year rhythm, Cis-year rhythm

Halberg F, Neuroendocrinol Letters, 2004

Time structures of adverse cardiovascular outcomes



Zipes DP, Circulation, 1999

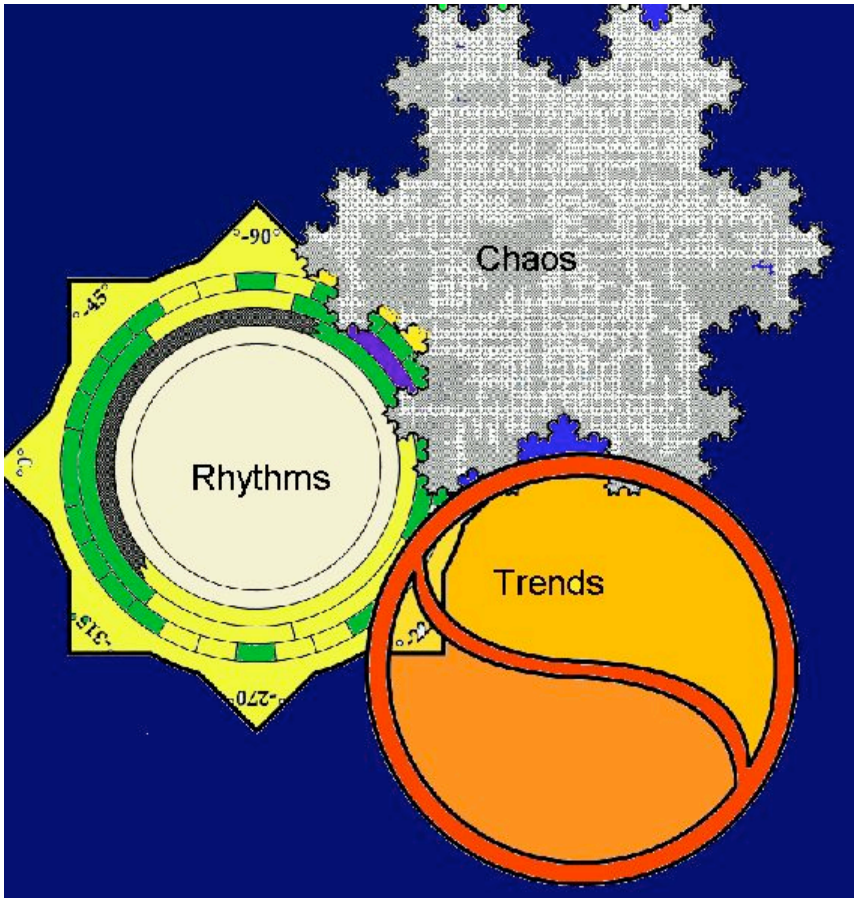
What is Chronomes ?

and

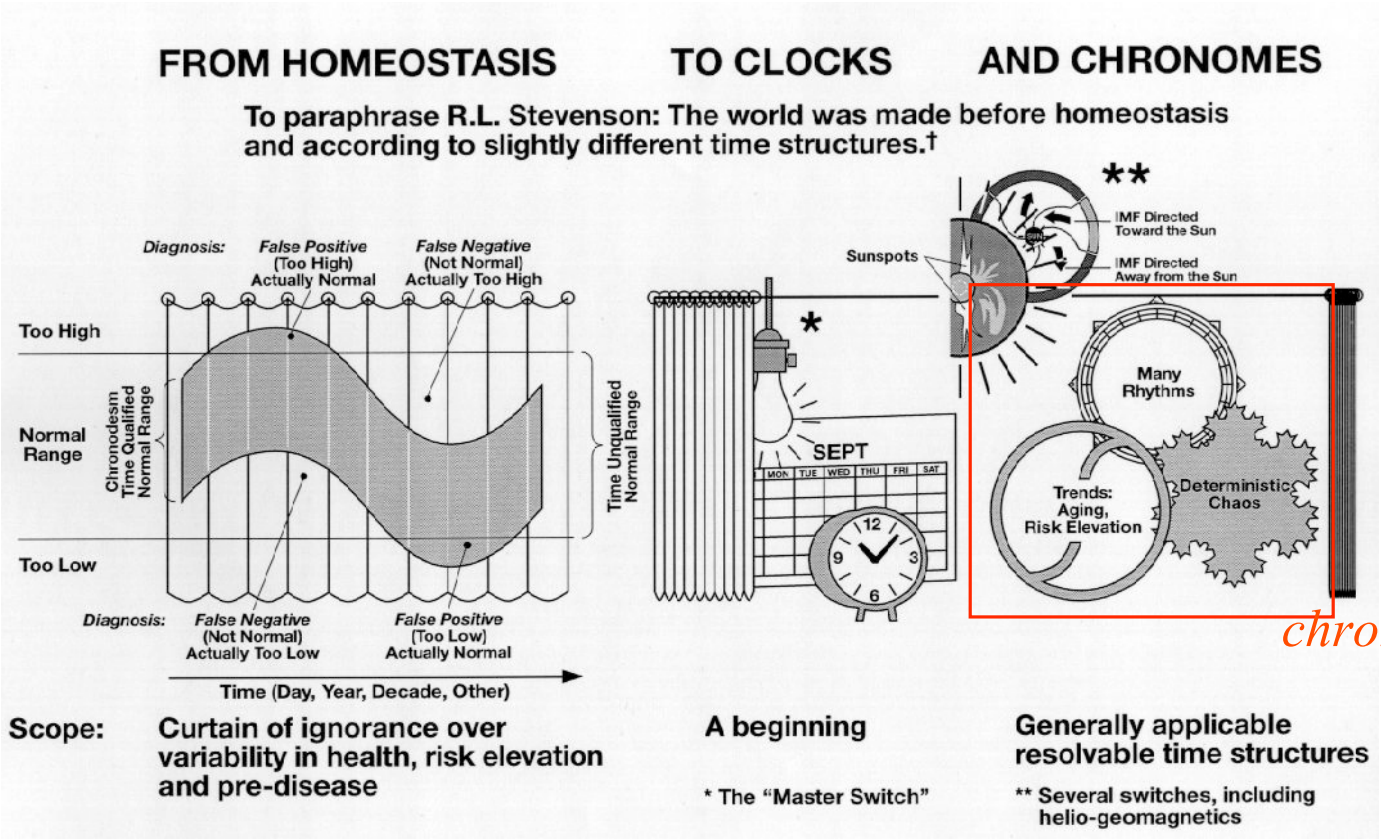
What is Chronomics ?

What is chronomes ?

Chronomes are ***time structures*** consisting of (1) multifrequency rhythms covering frequencies over 10 orders of magnitude, (2) elements of chaos, (3) trends in chaotic and rhythmic endpoints, and (4) other, as yet unresolved variability.



Chroinomics is the term against genomics, or proteomics, and it *can disclose* covered signals on the original time series data, which is not visible without resolving by Chronomics.



Chronomics maps

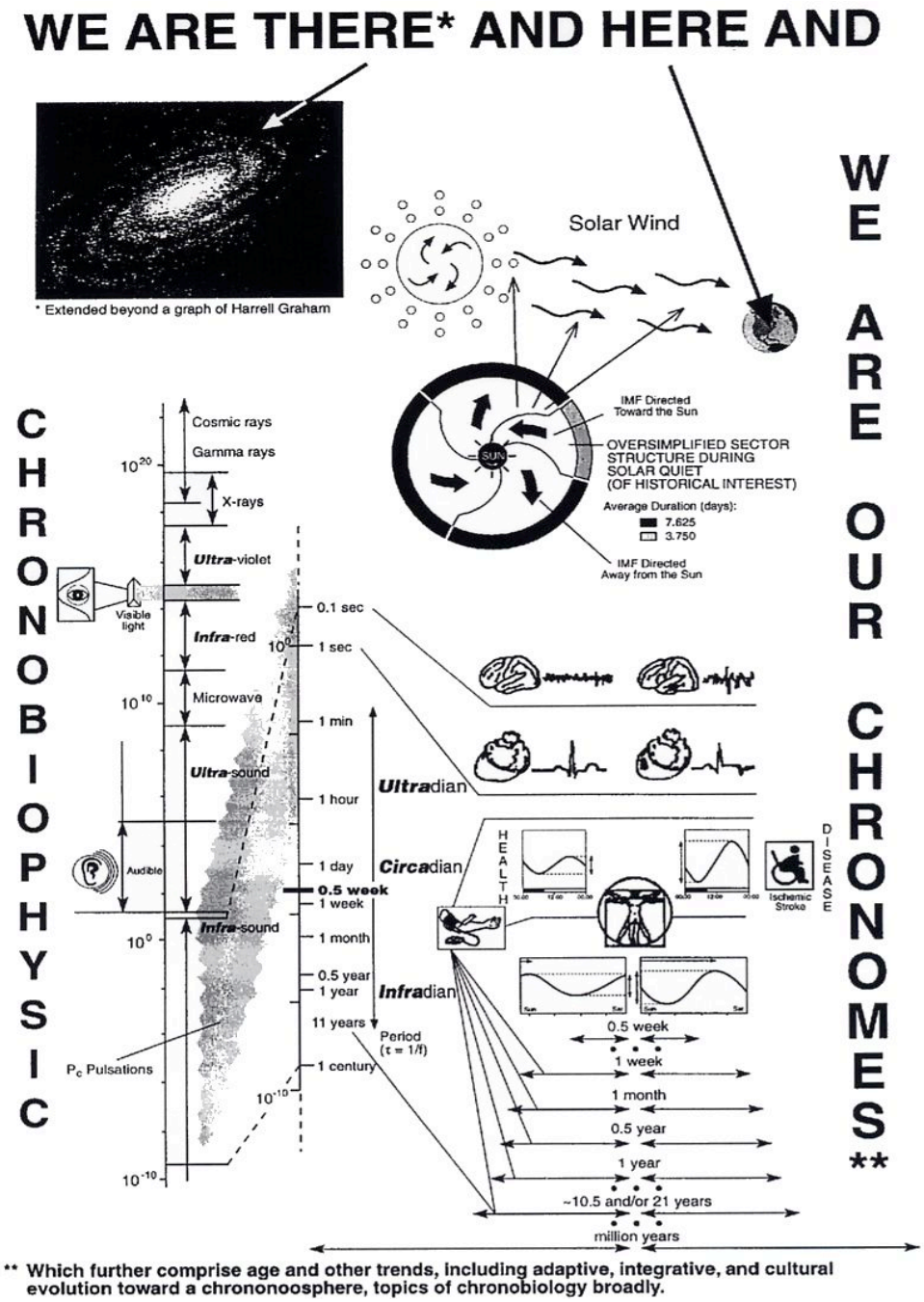
rather than merely standardizing lighting, the availability of food and daily routines (in studies on behavior in time in the proximal habitant niche)

(Halberg 1969)

Chronomics can map

the dynamics of organisms' interactions with the environment near and far broadly.

(Halberg F, 2003)



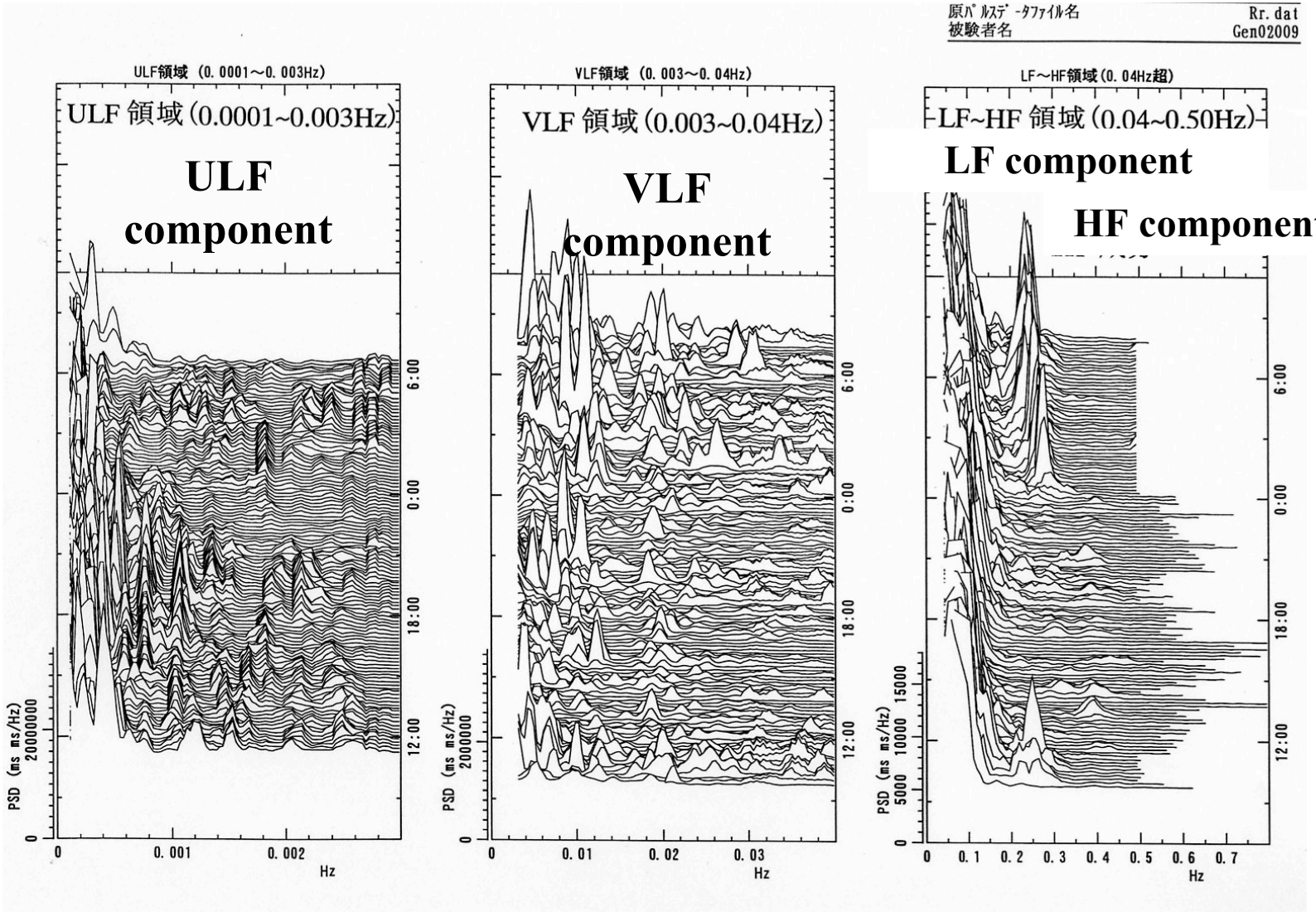
As an example,

Chronomics for HR variability

Chronomics (time structures) of HR variability include,

***3-s** (HF-Component of HRV), **10-s** (LF-component of HRV), **5-min** (VLF-component of HRV), **3-h** (VLF-component of HRV), and **circadian**, **weekly**, and **trend** of age*

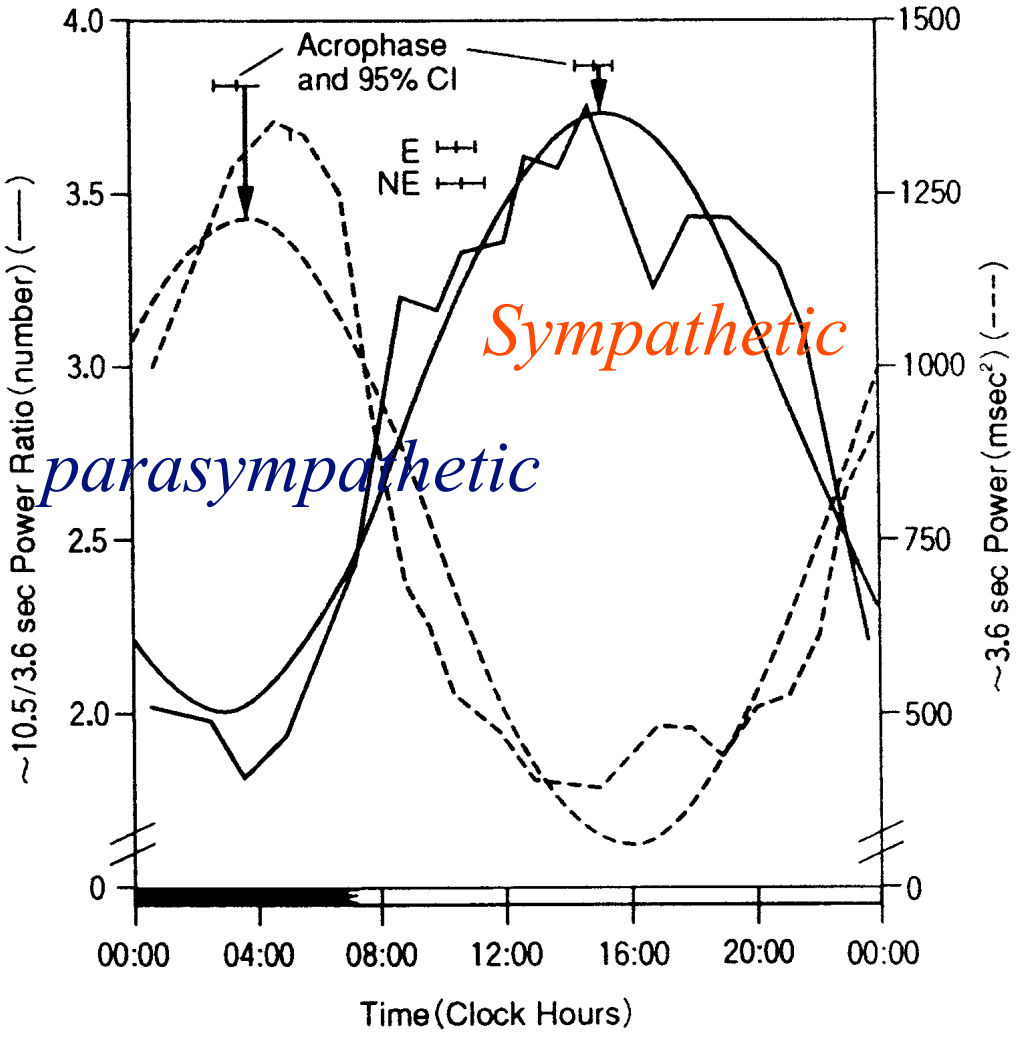
An example of Heart Rate Variability of a healthy young



Circadian Profile of Parasympathetic (HF-comp) and Sympathetic (LF/HF) activity, estimated by the 24-hr HR Variability analysis

Average of 218 healthy men (3-92 yrs of age)

Otsuka K,. Computers in Cardiology 26:587-590, 1999

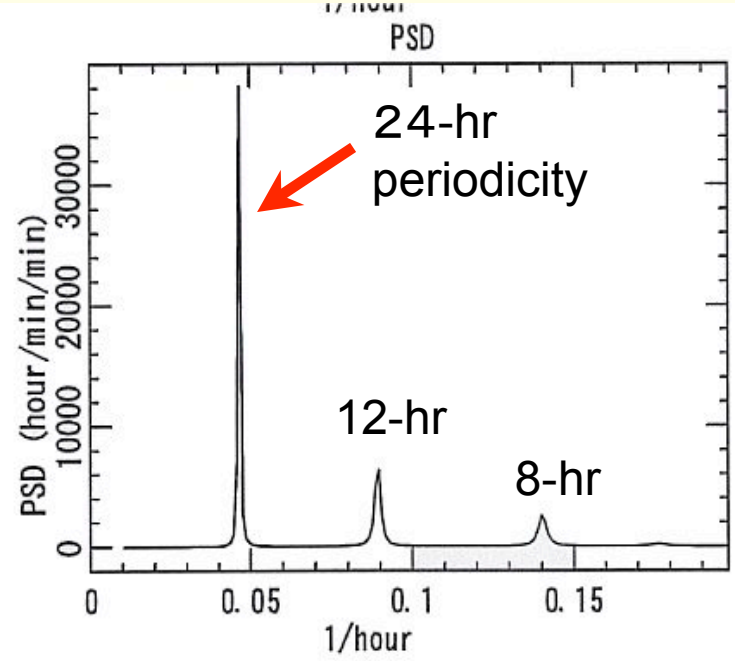


	"Tone"	
	"Sympathetic"	"Parasympathetic"
P:	<0.001	<0.001
MESOR±SE:	2.88±0.04	769±24
Double Amplitude (95% CI):	1.70 (1.46, 1.96)	904 (763, 1045)
Acrophase (95% CI):	14:51 (14:26; 15:24)	03:36 (03:00; 04:12)

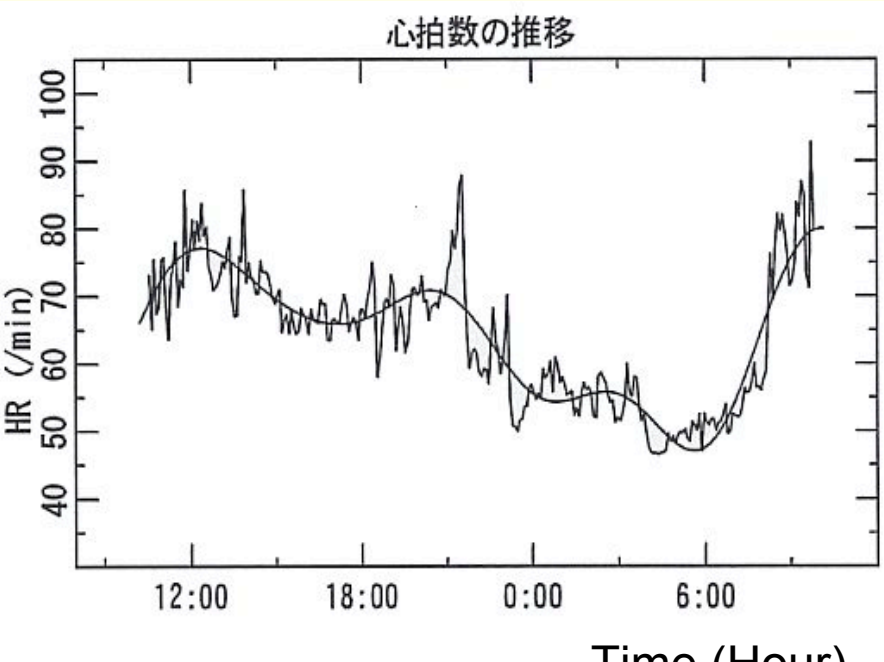
Circadian periodicity of Heart Rate
MEM spectral analysis

Circadian Rhythm

MEM Power Spectrum

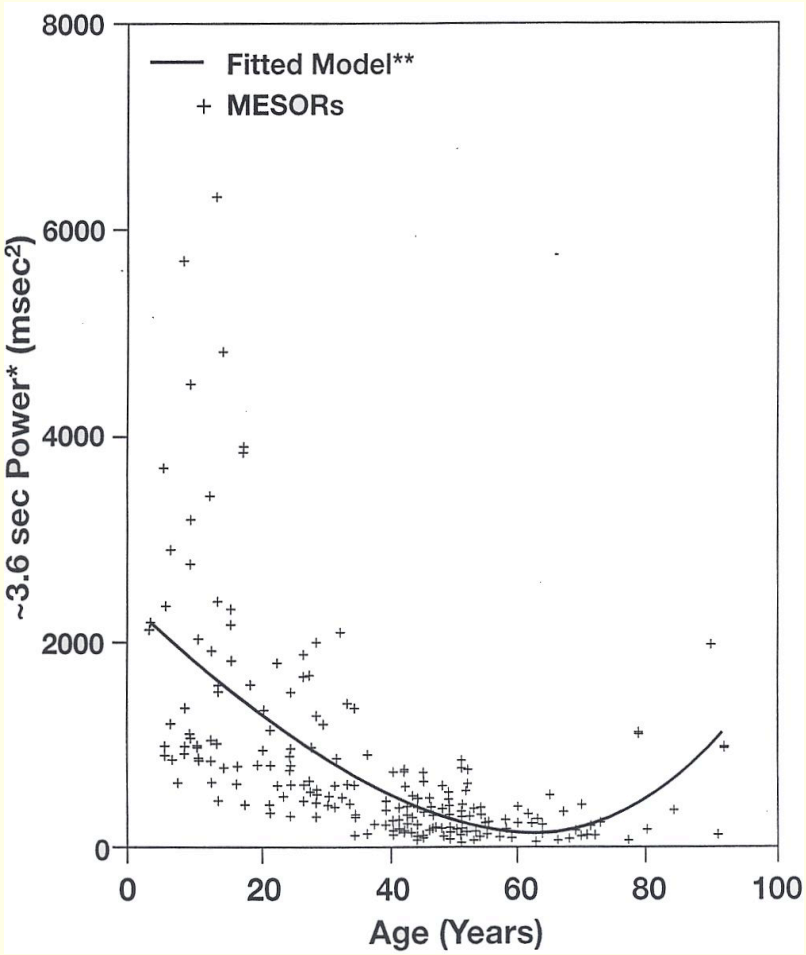


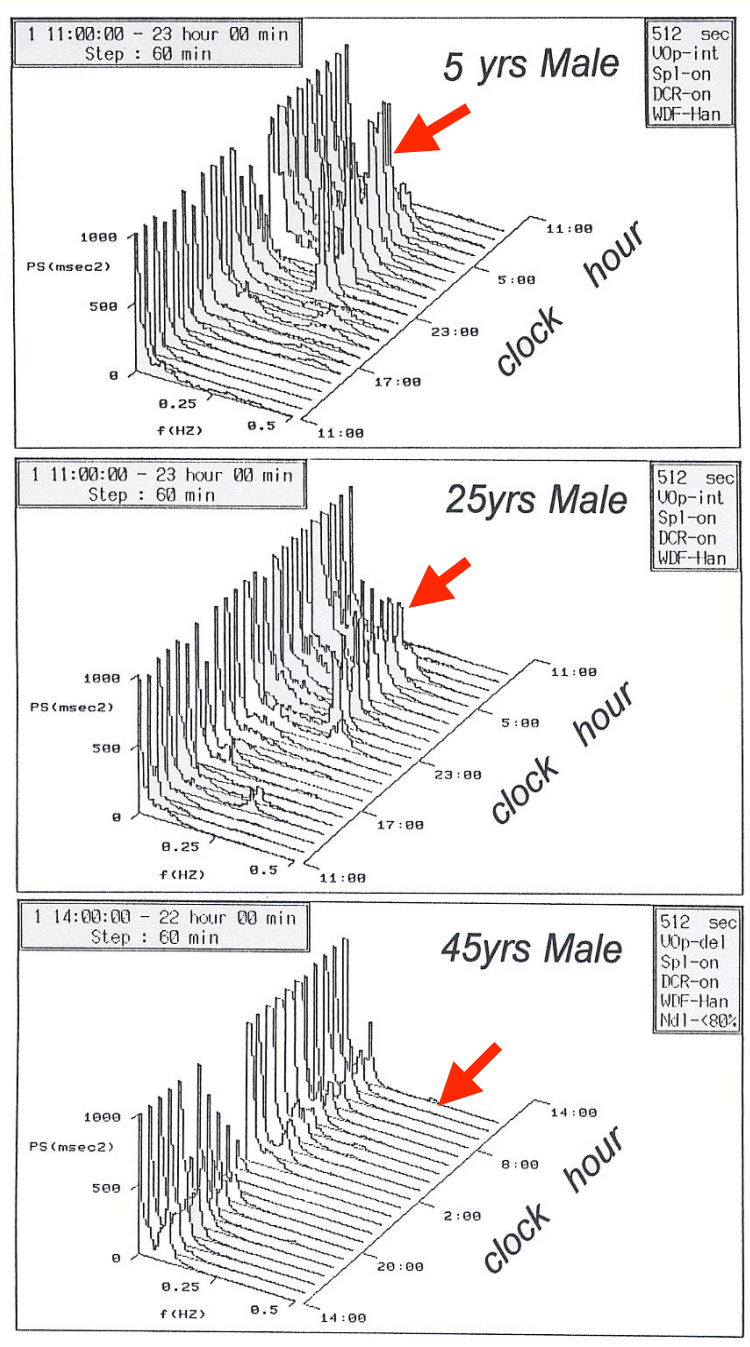
Circadian variation of HR



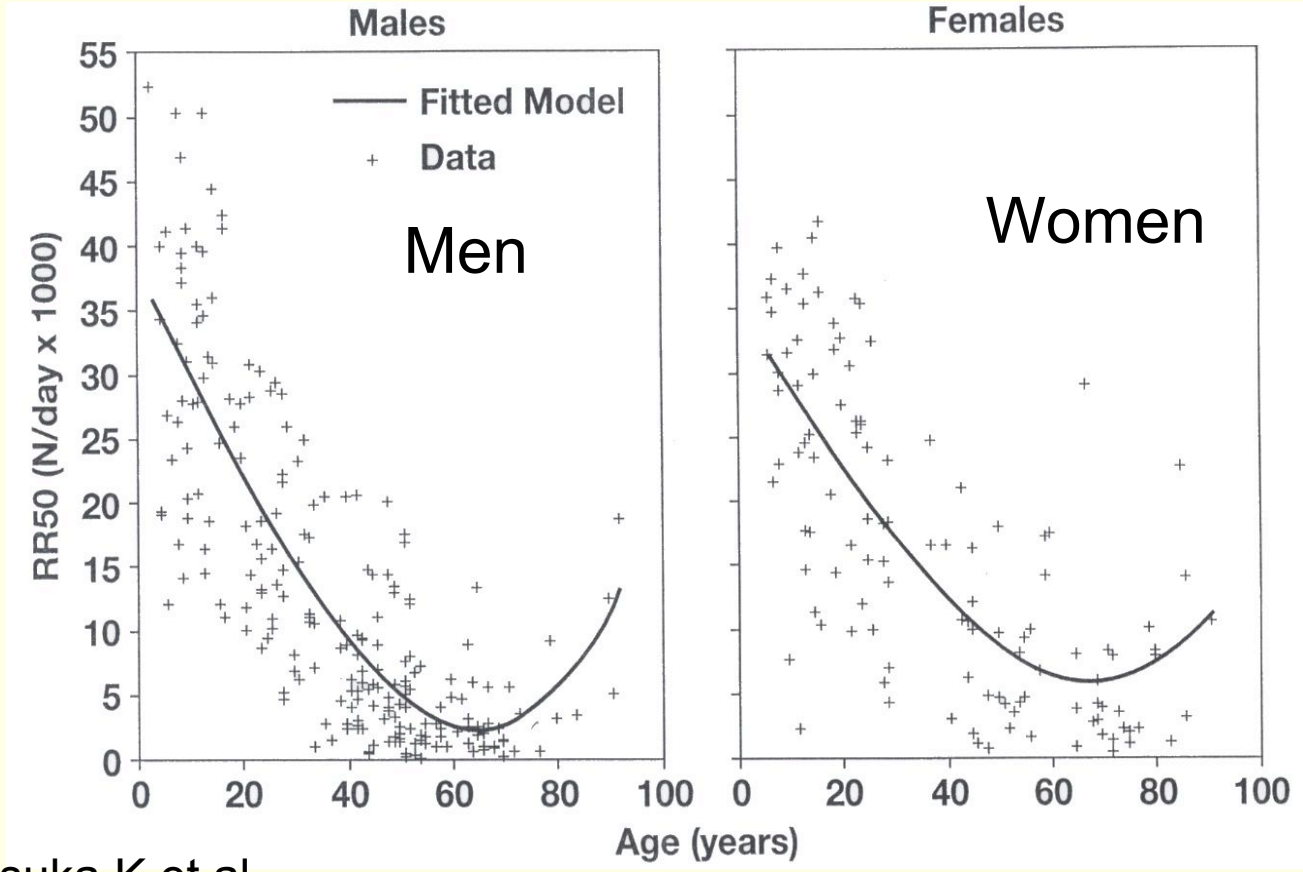
Time (Hour)

Decrease in Parasympathetic activity (HF-component) with Aging





Decrease in Parasympathetic activity (HF-component) with Aging



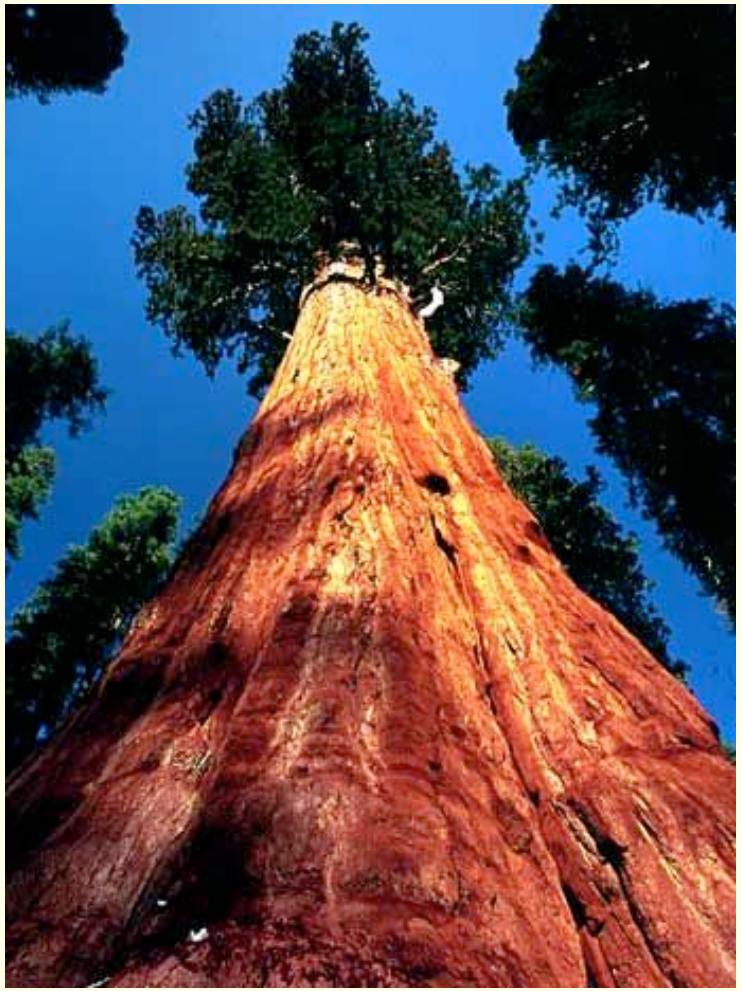
Slope of the fitted line is larger in men

Otsuka K et al.,
Computers in Cardiol,
1997

An example of tree rings chronomics

As an aspect of chronomics, assessing broad time structures (of chaos, trends and cycles) in physiological and physical environmental variables and their interactions,

the fractal nature of tree rings is here determined.

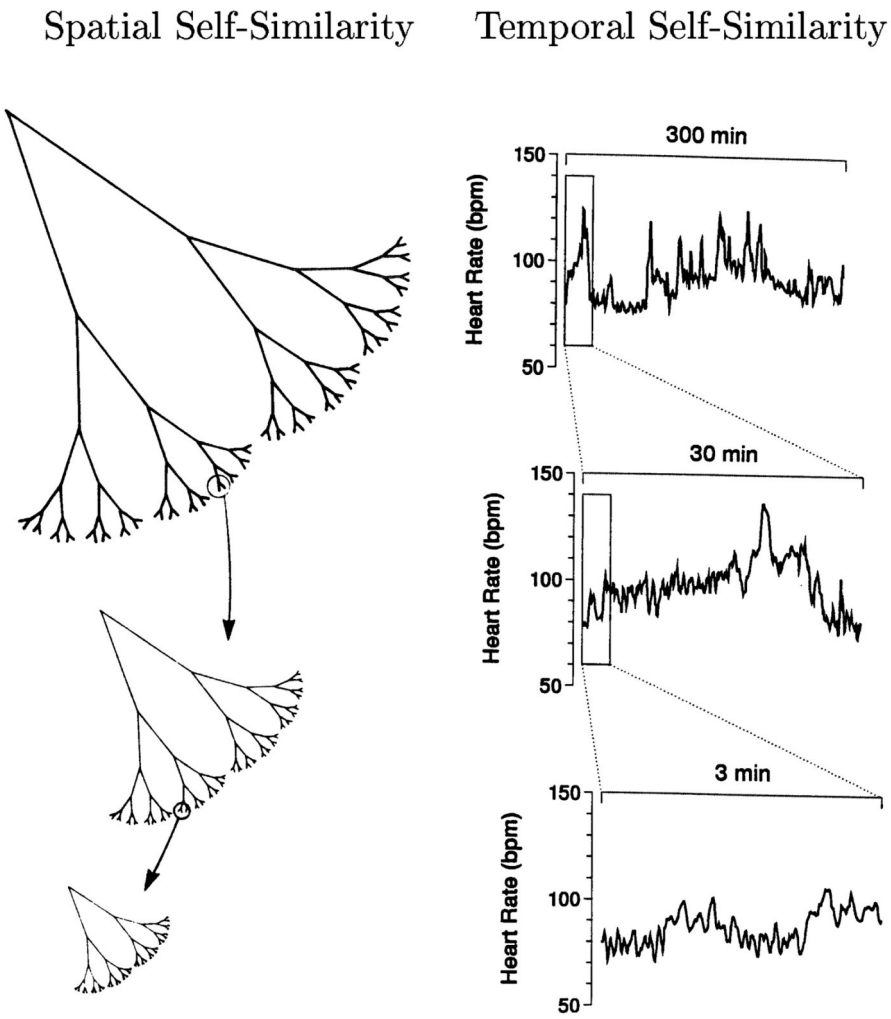


Fractal analysis as one of the method of "***chronomics***"

- Fractal is one of the characteristic of chaos or complexity. In this investigation we examined the chrono-geocomplexity by analyzing the fractality of tree rings grows.
- The concept of a fractal is most often associated with irregular geometric objects that display self-similarity. ***Fractal forms are composed of subunits (and sub-sub-units, etc.) that resemble the structure of the overall object.***
- In an ideal model, this property holds on all scales. The real world, however, necessarily imposes upper and lower bounds over which such scale-invariant behavior applies.

Fractals

- Many non-Euclidean structures in nature, *such as branching trees, wrinkly coastlines, and the rough surfaces of mountains,* are fractal.
- A number of complex anatomic structures also display fractal-like geometry.



Fractals

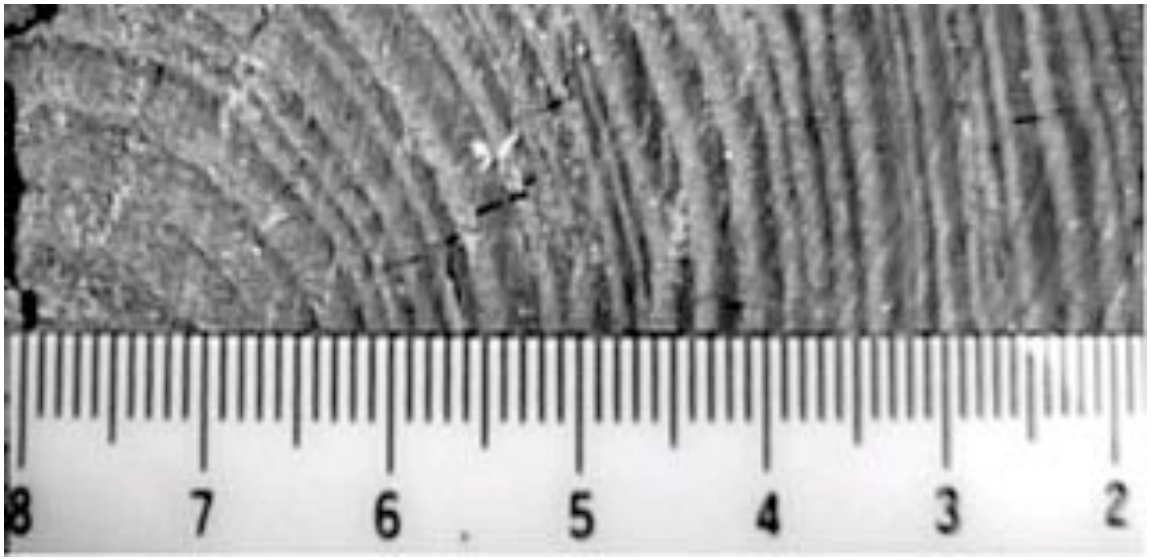
- Application of fractal analysis may provide new approaches to *assessing risk of the living* and *forecasting sudden death in animals including the human*.
- Elucidating the fractal nature *involved in physiologic control and complex signaling networks* is emerging as a major challenge in the postgenomic era.

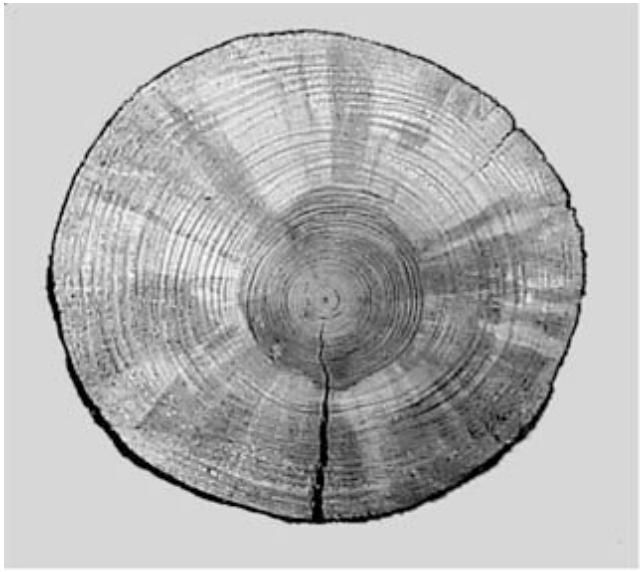
Tree rings chronomics

- For the analysis, the average measurements of studies on 11 sequoia trees were taken from reference*, *pp.119-123*, covering 2189 years.
- In this investigation we analyzed fractal nature of the time series of tree ring width. Power spectrum of the time series of 2175 years of them was analyzed by the Maximum Entropy method (MEM).

** Douglass AE. Climatic cycles and tree-growth. Vol. 1. Washington: Carnegie Institution; 1919 p. 128 Vol. 2, Washington: Carnegie Institution; 1936, p. 172.*

Tree Ring of Sequoia





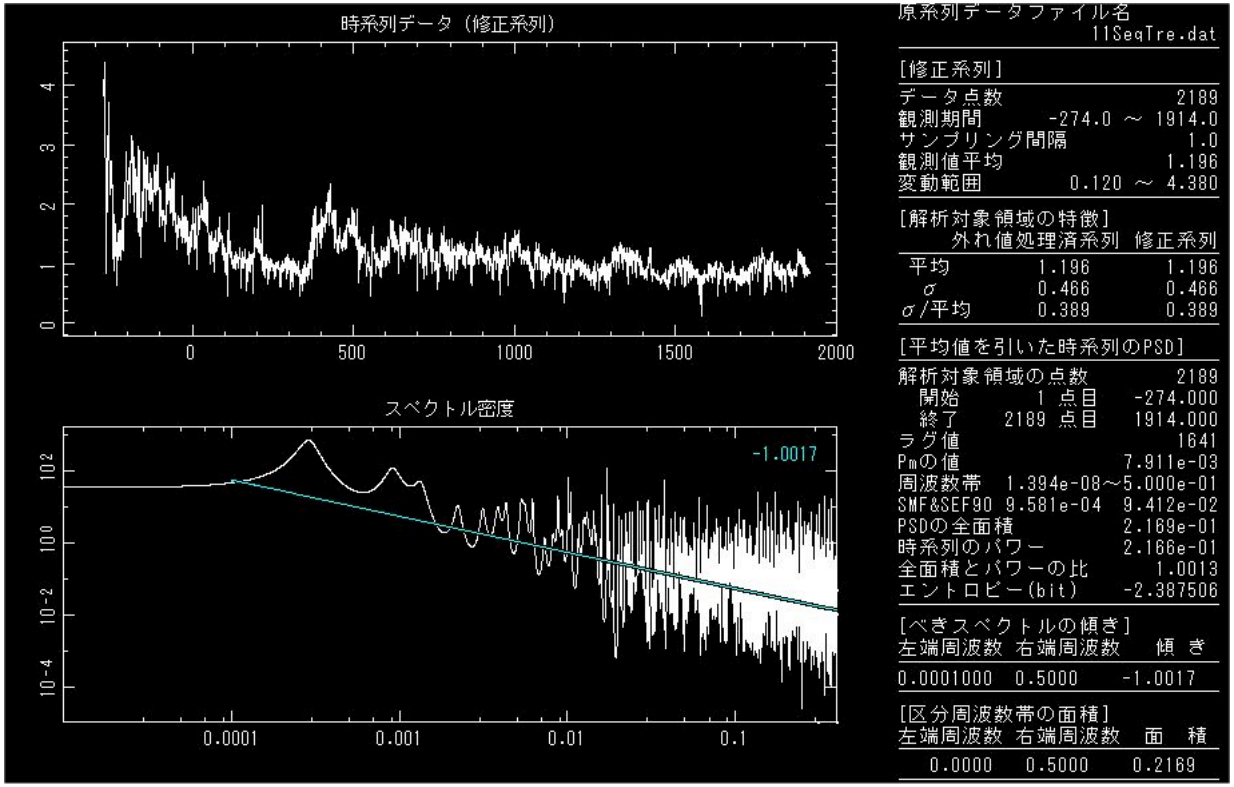
It seems of interest to look for a proxy marker of solar activity in tree ring widths that cover the past 2000 years or more.

1/f analysis of tree rings , as one of the chronomics

- A robust line fitting algorithm of log (power) on log (frequency) was then applied to the power spectrum between 10^{-4} and 0.50 cycles/year, and the slope (β) of this line was calculated.
- This frequency band was chosen on the basis of the observation regarding the linear relationship between log (power) and log (frequency) in this frequency band.

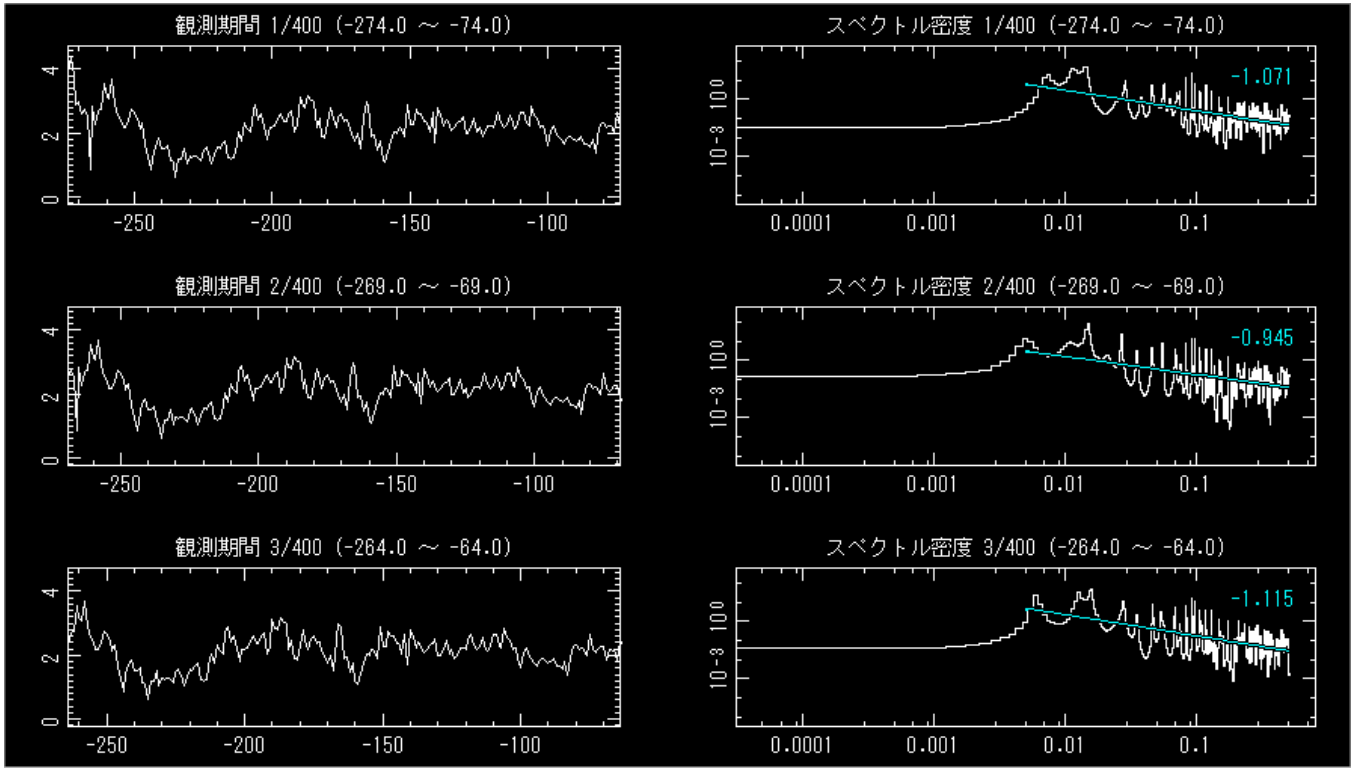
Result 1:

- As shown in the bottom of this Fig., the slope (β) of this line was -1.002. *It has been known that the slope (β) around -1.00 means fractal nature,* which reflects such system is under physiologic control.



Result 2:

- ✓ Next, we observed variability of the fractal nature of tree ring width **along with growing and aging** **for over 2000 years**,
- ✓ by using **every 200-year** time series **overlapping 5 years**.
- ✓ Left side of this Fig shows three examples of time series data of 200 years, and

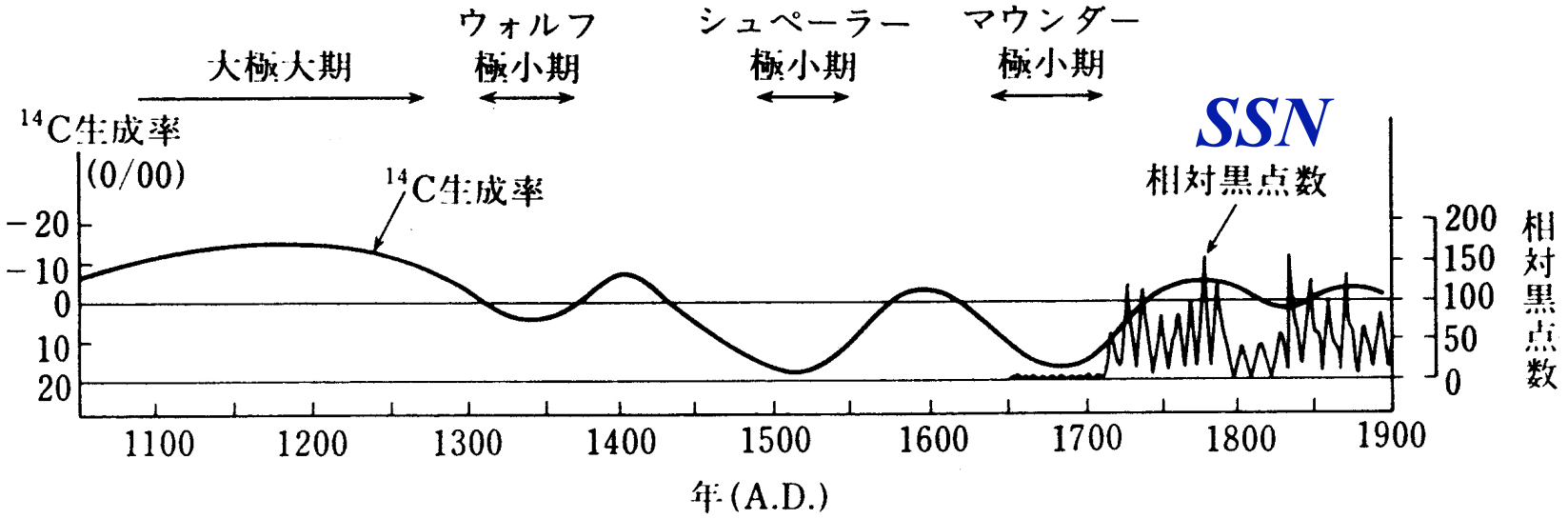


✓ The right side shows each MEM spectrum of the three power-law behaviors shown as log (power) on log (frequency) scales.

Solar activity and Tree rings' width

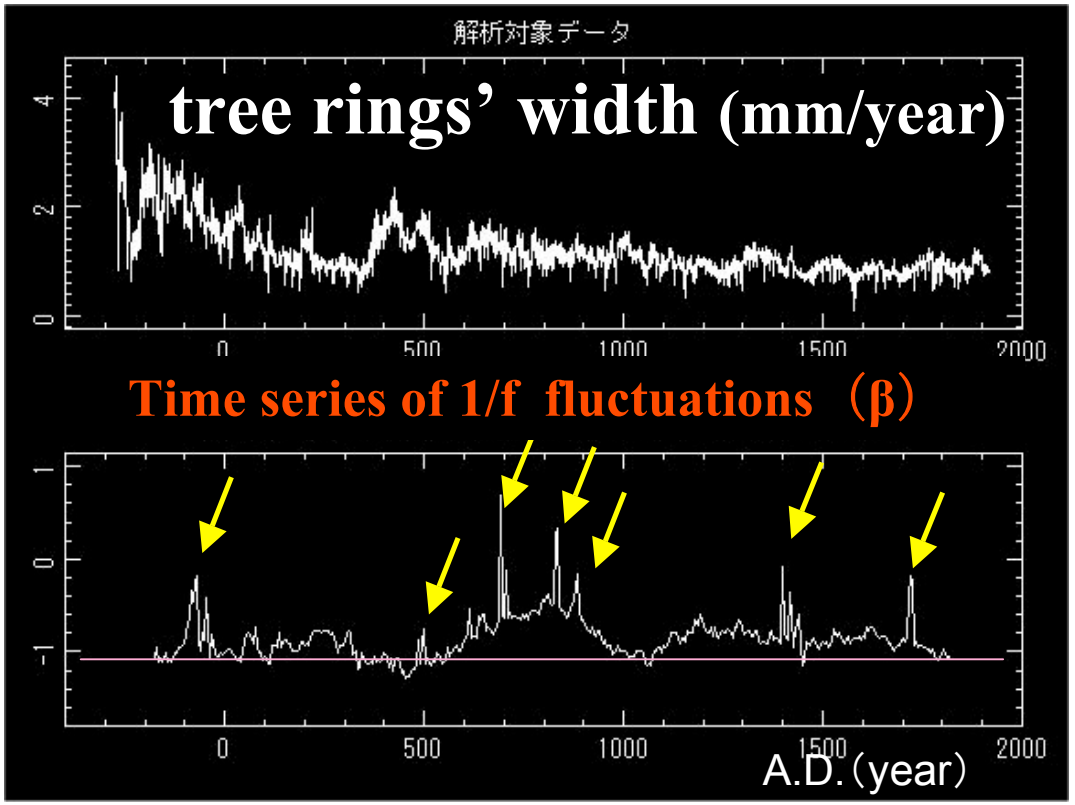
Physicists' records of **sunspots** are not long enough to look for cycles half a millennium in length.

We can see solar activity by the observation of tree rings, via "*the effects of climate upon the growth of trees*".

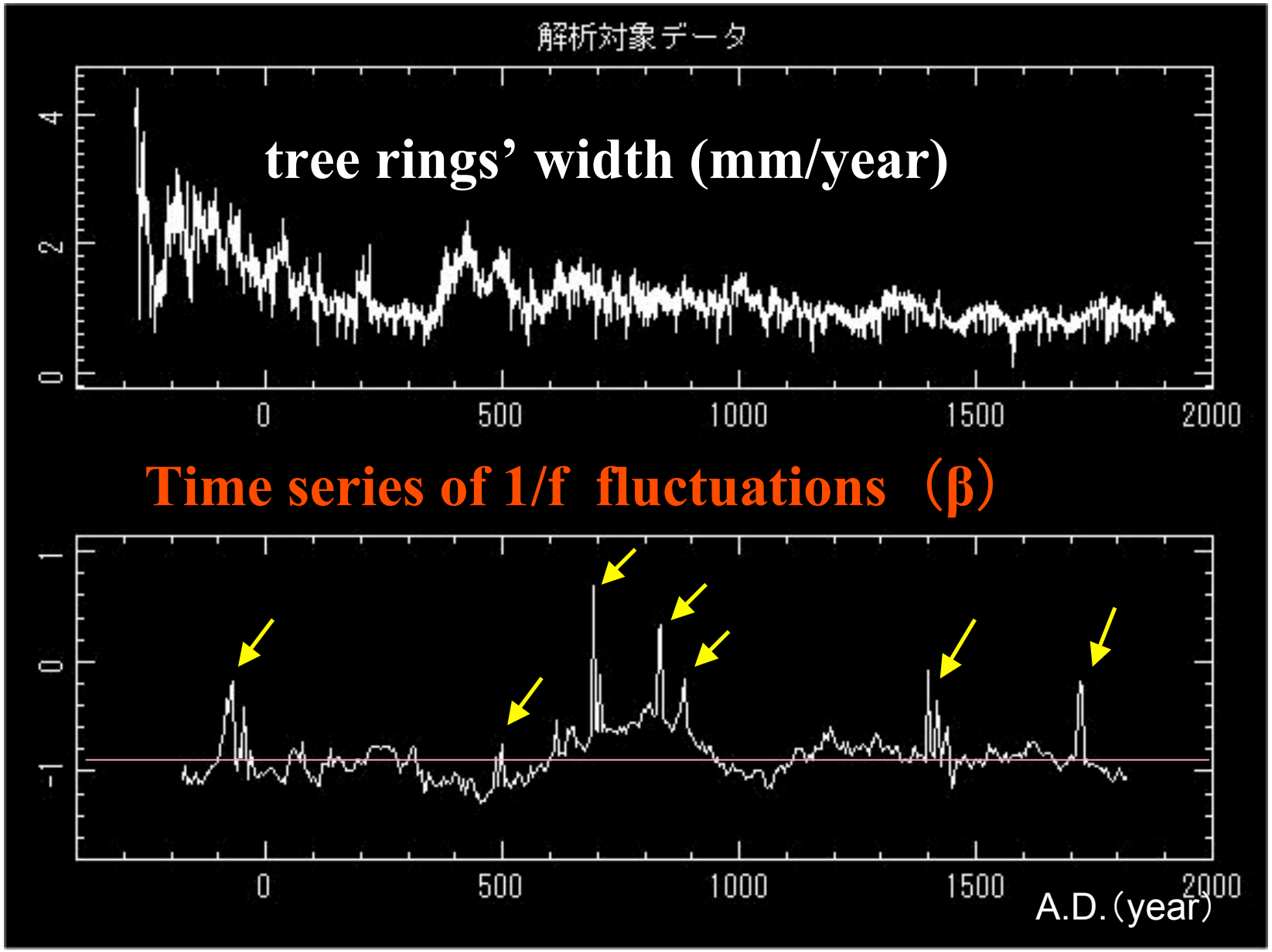


Result 3:

- ✓ **Time series of tree ring width is shown on the top of this Fig.**
- ✓ **Variability of the slope (β) of the power-law behavior is shown on the bottom of Fig, which shows episodic disruption of this fractal nature.**
- ✓ **Seven episodes (arrow) are depicted in this Fig**



Tree rings' width (mm/year) of 11 California sequoias, and variability of 1/f fluctuations (β)



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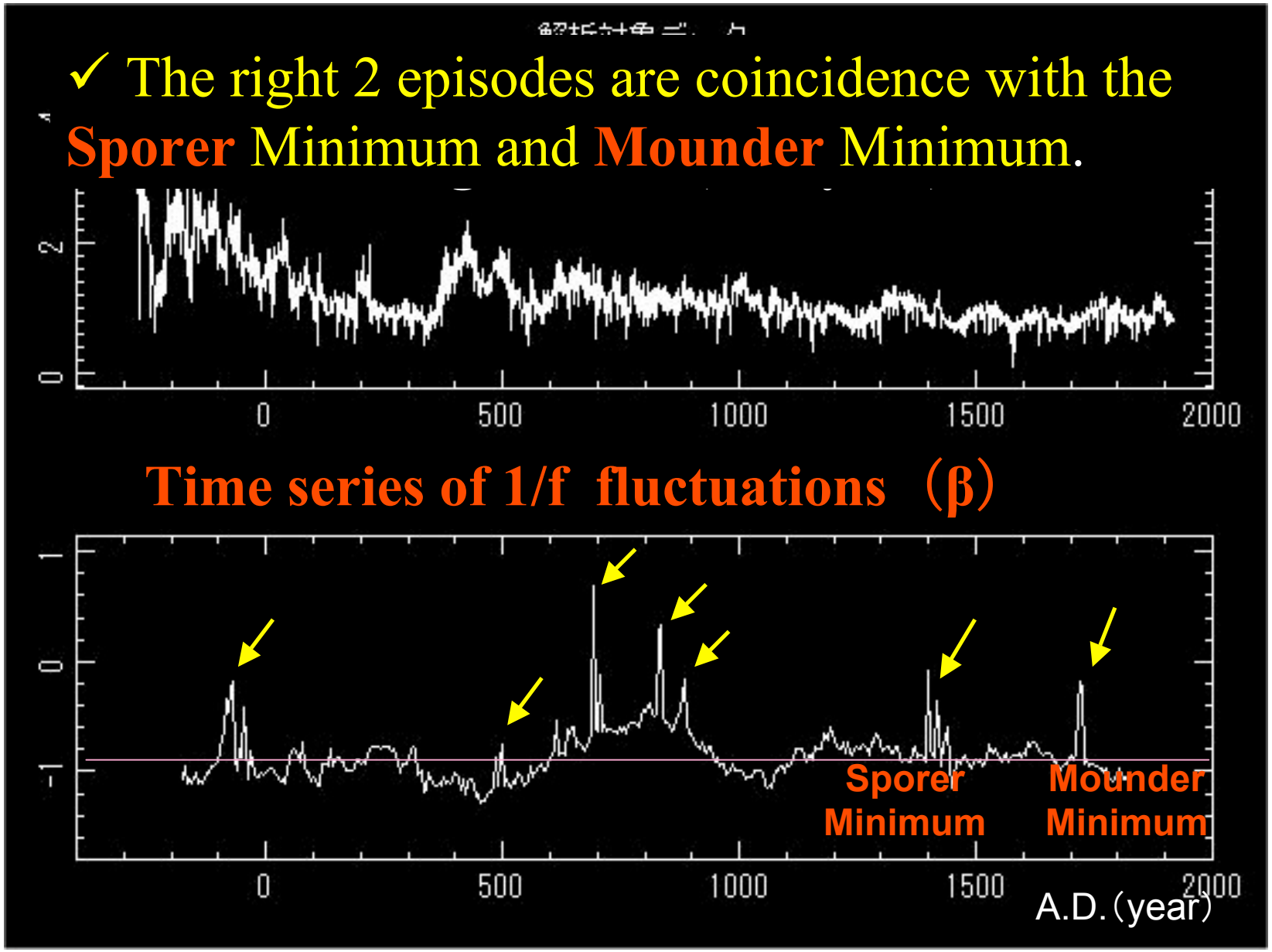

Tree rings' width (mm/year) of 11 California sequoias, and variability of 1/f fluctuations (β)

✓ The right 2 episodes are coincidence with the **Sporer** Minimum and **Mounder** Minimum.

✓ Thus, the other 5 episodic disappearance of the fractal nature may suggest climate changes happened on globally.

Time series of 1/f fluctuations （β）