VISUALIZATION OF AMPLITUDE-PHASE RELATIONSHIPS IN ENTRAINMENT PROCESSES

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In the present research the visualization of amplitude-phase relationships in entrainment processes is based on the expression serial time sections [3] allow tracing the behavior of different parameters of any rhythmical component of spectrum during a time which includes spans before, during and after any synchronizing (desynchronizing) event. There is a simple and noninvasive method for acquiring information on the visualization of amplitude-phase relationships. The method used the mathematical and graphic analysis simultaneously visualization the dynamics of amplitude, its statistical significance and acrophase in entrainment processes, the three modifications of serial sections was elaborated: procedure of adding logarithms of P-values-matrices, plotting 2D image and 3D image.

As examples for illustration serial section method, automatic measurements of blood pressure (BP), both systolic (S) and diastolic (D), and heart rate (HR) were used. Five flights from Minneapolis (USA) to Saint-Petersburg (Russia) crossing 9 time zones and 4 flights in the opposite direction were performed during that time (during the second return flight, no measurements were taken).

The simultaneous drop in amplitude and the rapid shift in acrophase associated with West-to-East flights, and more gradual changes for East-to-the-West flights led to the hypothesis that the rapid entrainment is performed by collapse of the rhythm at a singularity time point.

Application of the present method has allowed the authors to carry out visualised dynamic chronobiological the control parameters of cardiovascular system.

The method has higher diagnostic value in comparison with well-known procedures of an estimation of chronomedicine.

Key words: entrainment processes, chronome, changing environmental conditions, 2D & 3D graphs arranged, computing gliding spectra, spectral domain, Program DYP (Dynamic Periodogram, adaptation of different cardiovascular variables, adaptation of different cardiovascular variables, West-to-East flights (W-E), East-to-West flights (E-W), shifting direction of the circadian and circasemidian spectral components.

Introduction (background). Biological rhythm, periodic biological fluctuation in an organism that corresponds to, and is in response to, periodic environmental change. In biometrically processing temporal series of biodata, time (T) may be regarded as a systematic parameter which is independent on the biological variable under scrutiny. Time illustrates how the biovariable changes, but it is not the causal determinant of that change, which, in turn, depends on the dynamic properties of living matter.

Statistically speaking, phenomenon Y and time T are associated, but time is not a random variable, its progression being numerically predictable.

In general, the level of Y (Yt) at a given time (t) is related to the precedent value. For this reason, any temporal series may be said to be autoregressive and historical. If the relationship between Y and T maintains itself unchanged, we will have a linear temporal phenomenon. If the relationship changes spontaneously we will have a non-linear temporal event. If the relationship resumes the same value at t time we will have a cyclic phenomenon.

In descriptive terms, temporal data of a cyclic phenomenon, based on a given unit of time can be divided into various components: 1. a fundamental harmonic component that expresses the true periodic structure of the rhythmic phenomenon; 2. one or more subharmonic components whose period is a submultiple of the principal wave; 3. a random component that corresponds to the noise eliminated by the oscillatory curve.

Thus, biological noise is typical in a discrete series, and it influences the biometrical estimates of numerical statistics. However, biological noise is not accounted for in the continuous series, and it has very little influence on analytical statistics. In biometrically analyzing time data series, chronobiology applies both methodologies, i.e., 1. Numerical or non-inferential or macroscopic chronobiometry; 2. Analytical or inferential or microscopic chronobiometry.

Understanding the message of chronobiology requires renunciation of the concept of homeostasis or adaptation, as well as a reformulation of the biological principles dictated by C. Bernard. Chronobiology holds that the physiology of vital functions does not answer to the laws of steady state, invariance, or the unconditional return to the initial equilibrium following a perturbation.

At the present time there is a limited number of scientific researches on an estimation chronome's method for the analysis of velocity of adaptive reactions during changing environmental conditions.

Objective (aim). Prove scientifically that the methods visualization of amplitude-phase relationships at entrainment processes give rise to descriptive, integrative and evolutive chronobiometry during adaptive processes in chronome in the changed environmental conditions.

Material and Methods. The method used the mathematical and graphic analysis simultaneously visualization the dynamics of amplitude, its statistical significance and acrophase in entrainment processes, the three modifications of serial sections was elaborated: procedure of adding logarithms of P-values-matrices, plotting 2D image and 3D image.

Computing gliding spectra in any spectral domain was elaborated as the second step of the development of the serial section approach. In 1978 V.M. Sysuev [4] proposed it for R-R intervals analysis of electrocardiograms. The method was developed later for both equidistant time series on the basis of Fourier transformation [5, 6] and for non-equidistant data on the least squares approximation [7, 8].

As examples for illustration serial section method, automatic measurements of blood pressure (BP), both systolic (S) and diastolic (D), and heart rate (HR) were used. They had been carried out by GSK, a man of 72 at the start of observations on March 31 1998, using the ABPM-630 monitor from Colin Medical (Komaki, Japan) and the TM-2421 monitor from A&D (Tokyo, Japan) during more than 11 years, with measurements every 30 minutes with several occasional gaps (total of about 200,000 records of every variable). Five flights from Minneapolis (USA) to Saint-Petersburg (Russia) crossing 9 time zones and 4 flights in the opposite direction were performed during that time (during the second return flight, no measurements were taken).

Results. Entrainment processes arise in chronome at changing environmental conditions, especially at shifting synchronizer's timing [1, 2]. Serial time sections [3] allow tracing the behavior of different parameters of any rhythmical component of spectrum during a time which includes spans before, during and after any synchronizing (desynchronizing) event. MESOR, amplitude, acrophase and their confidence intervals, as well as P-value itself are taken into account. Their dynamics usually is presented as several 2D graphs arranged on the paper sheet in consecutive rows (Fig. 1, Fig. 1A).

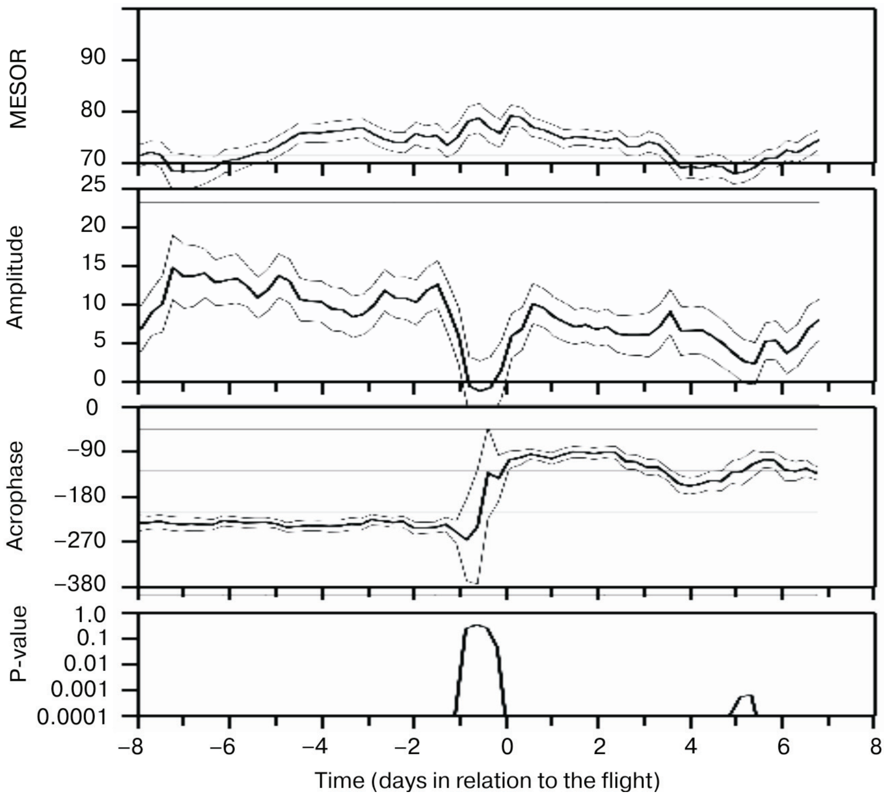
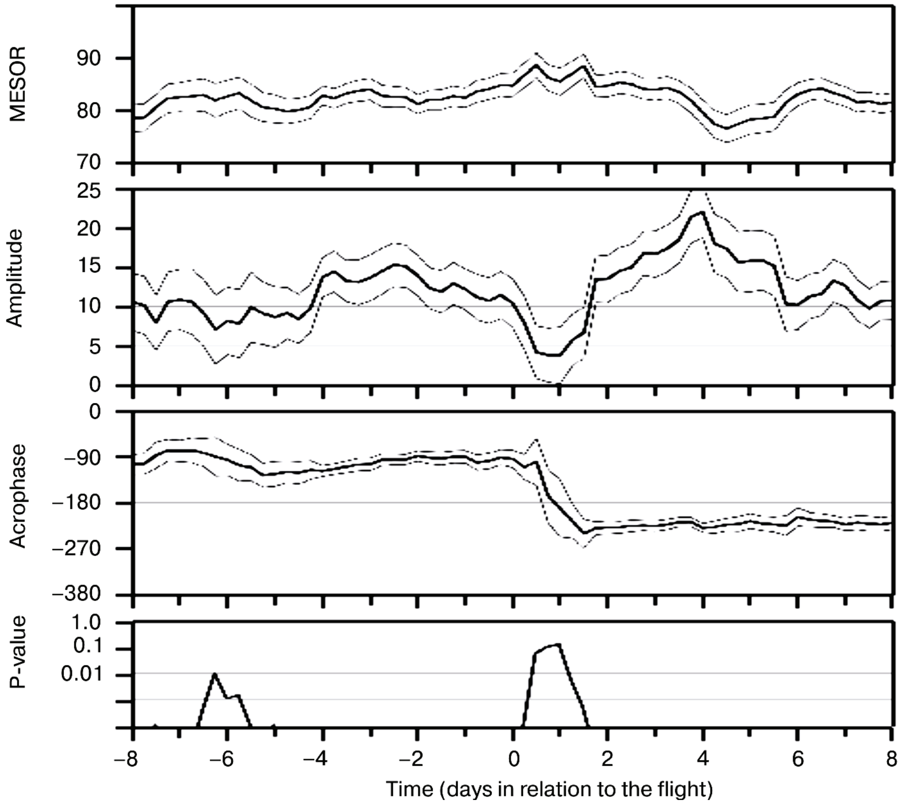


Fig. 1. Dynamics of different parameters (serial sections) of 24-hour spectral component*: west-to-the-east flight crossing 9 time zones

*Results of automatic measurements of diastolic blood pressure every 30 minutes using TM2421 monitor (A&D Company, Japan) in 2005 by GSK, a man of 79. Flight from Minneapolis (USA) to Saint-Petersburg (Russia) 28 Sept 2005. Intervals = 48 h, increments = 6 h. Thin congruent lines — 95% confidence limits



(Fig. 1A). Dynamics of different parameters (serial sections) of 24-hour spectral component*: east-to-the-west flight crossing 9 time zones.

*Results of automatic measurements of diastolic blood pressure every 30 minutes using TM2421 monitor (A&D Company, Japan) in 2005 by GSK, a man of 79. Flight from Minneapolis (USA) to Saint-Petersburg (Russia) 29 Nov 2005. Intervals = 48 h, increments = 6 h. Thin congruent lines — 95% confidence limits

The next modification was realized as the Program DYP (Dynamic Periodogram [9]), which allows presenting the output results for dynamics of MESOR, amplitudes, acrophases and their standard errors as well as P-values, determination coefficients (percentage rhythm) and residual sums of squares for every trial period (in the limits of the chosen spectral domain) and for every time point in the series of data (depending on chosen interval and increment). The output files are matrices, and it makes it possible to use them for the next computing according to the rules of linear algebra, e.g. averaging rhythm parameters of the different individual time series (equivalent of the C. Chree's method of superposed epochs [10]).

Especially important in these terms is the procedure of adding logarithms of P-values-matrices, which makes it possible not only to reveal but at the same time to amplify (or to neglect) statistical significance of mutually coinciding spectral components in groups of comparable objects. As en example, Fig. 2 demonstrates regularities of adaptation of different cardiovascular variables across all transmeridian flights mentioned above. Rapid crossing of 9 time zones during the West-to-East flights (W-E) in all variables results in singularity in behavior of 24-hour cardiovascular oscillator. Gradual adaptation during East-to-West flights (E-W) accompanied by their interruptions for the night span lasting about 12 hours (see Table 1) produces correspondingly gradual entrainment. 12-hour oscillator demonstrates no singularities (note that after the rapid dislocation crossing 7 time zones, phase adjustment occurred in shorter time span at E-W but not at W-E flights).

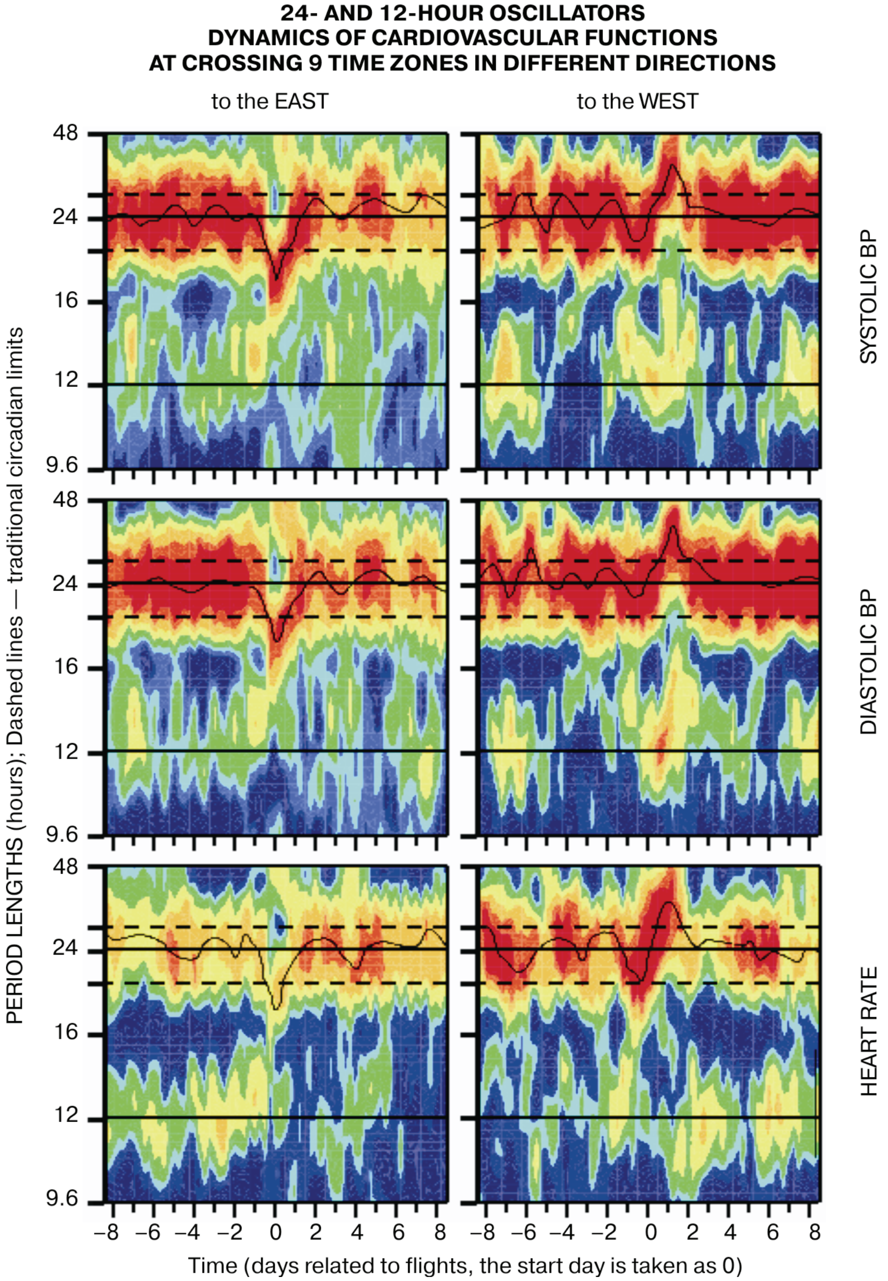


Fig. 2. 12-hour spectral component could not been revealed statistically significant during all time of observation when an interval of 48 hours was used for analysis (48 observations in every interval was insufficient)

Table 1

Schedule of the flights in 2005* Central Standard Time of USA

Events	CST Time	Trip duration
Departure from Minneapolis	Sep 28 15:25	15 h 05 min
Interruption the flight in Amsterdam for 3 hours		
Arrival lo St-Petersburg	Sep 29 6:40	
Departure from St-Petersburg	Nov 28 7:50	26 h 55 min
Interruption die flight in Amsterdam for ~ 12 hours (night rest in the hotel)		
Arrival to Minneapolis	Nov 29 10:45	

Resolving power of the method depends on two options: the length of the interval (a window taken as quasi-stationary) and the value of the increment of gliding procedure: the more rapid changes should be caught, the shorter should be both options, however such approach might mask some general regularities because the gliding (averaging) effect and statistical significance of results become weaker. This is the reason why in examining some time series, it is necessary to make several analyses using different intervals and increments.

Fig. 2 shows that the 12-hour spectral component could not been revealed statistically significant during all time of observation when an interval of 48 hours was used for analysis (48 observations in every interval was insufficient). To better reveal the behavior of this component, the interval was increased up to 14 days (336 observations per interval).

Effect is demonstrated in Fig. 3: shift of acrophases is shown contemporarily for both 12- and 24-hour components (only they were picked out from the whole matrix obtained by the DYP-procedure). The results of different flights in turn were averaged and 95% confidence intervals computed. Statistical significance became enough to declare that entrainment of those components was reached by shifting phases in different directions.

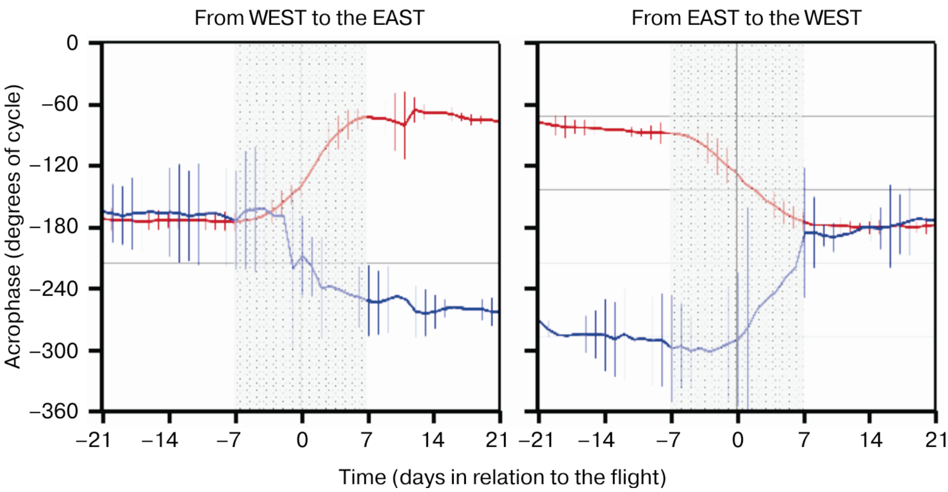


Fig. 3. Phase shift of 24- (red) and 12-hour (blue) spectral components during flights crossing 9 time zones*

*Results of automatic measurements of diastolic blood pressure every 30 minutes using TM2421 monitor (A&D company, Japan) in 1999—2007 by GSK, a man of 73 at the first flight. 5 flights from Minneapolis (USA) to Saint-Petersburg (Russia) and 3 ones in opposite direction. Data averaged by flights. Vertical bars — 95% confidence limits. Intervals = 14 d, increments = 1 d. Dimmed areas correspond to the interval widths

The simultaneous drop in amplitude and the rapid shift in acrophase associated with West-to-East flights, and more gradual changes for East-to-the-West flights led to the hypothesis that the rapid entrainment is performed by collapse of the rhythm at a singularity time point. The interval and increment shortenings should be the way to support (or to reject) this hypothesis, and DBP was analyzed using 30-hour intervals and 1.5-hour increments. The observations related to the flights in 2005 were taken as an example (Table 1). Again, gliding spectrum was computed by the program DYP, and results dealing only with the 24-hour component were picked out and used for the next plotting.

To show simultaneously the dynamics of amplitude, its statistical significance and acrophase, the third modification of serial sections was elaborated: plotting 3D image, which can be presented instead of a set of consecutive 2D graphs.

Shift of acrophases is shown contemporarily for both 12- and 24-hour components (only they were picked out from the whole matrix obtained by the DYP-procedure).

On the 3D Fig. 4A, time in relation to the flight is scaled as X-axis, acrophases of rhythm as Y-axis, and relative amplitudes (A/M*100%) as Z-axis. Shading the amplitudes corresponds to different levels of statistical significance. Such graph (being plotted in MS Excel) can be turned during its creation around each of the axes, to make it visible and mostly distinguishable those details which deserve the most attention. At the elevation 90° and rotation 0°, the phase shift may be observed in 2D mode, at the elevation 0° and rotation 90°, dynamics of amplitude, and at the elevation 0° and rotation 180°, the variability of acrophase before and after flight as well as its time shift might be shown (Fig. 4B).

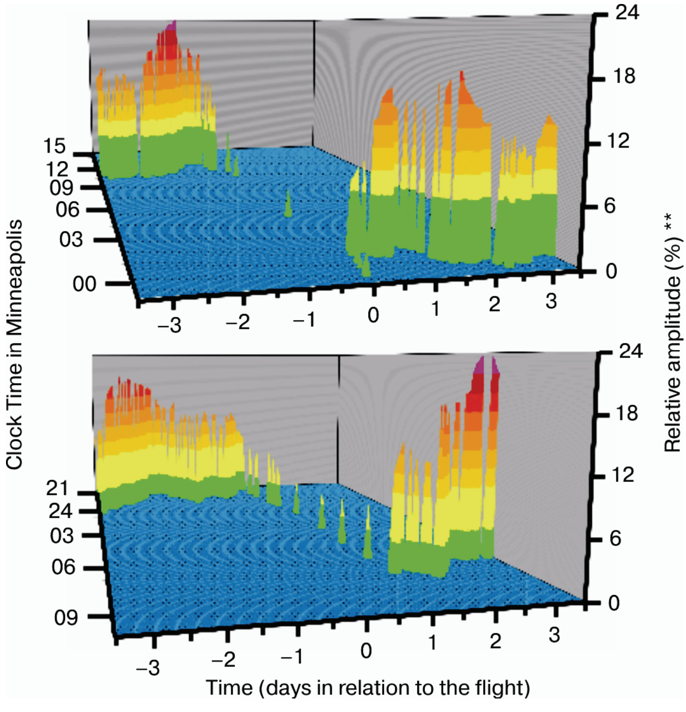


Fig. 4A. Visualisation of amplitude-phase relationships during west-to-east (top) and east-to-west (bottom) flights crossing 9 time zones*

* Results of automatic measurements of diastolic blood pressure every 30 minutes using TM2421 monitor (A&D company, Japan) in 2005 by GSK, a man of 79. Flights from Minneapolis (USA) to Saint-Petersburg (Russia) and back.

** Green corresponds to the amplitude values at $P > 0.05$. Intervals = 30 h, Increments = 1.5 h

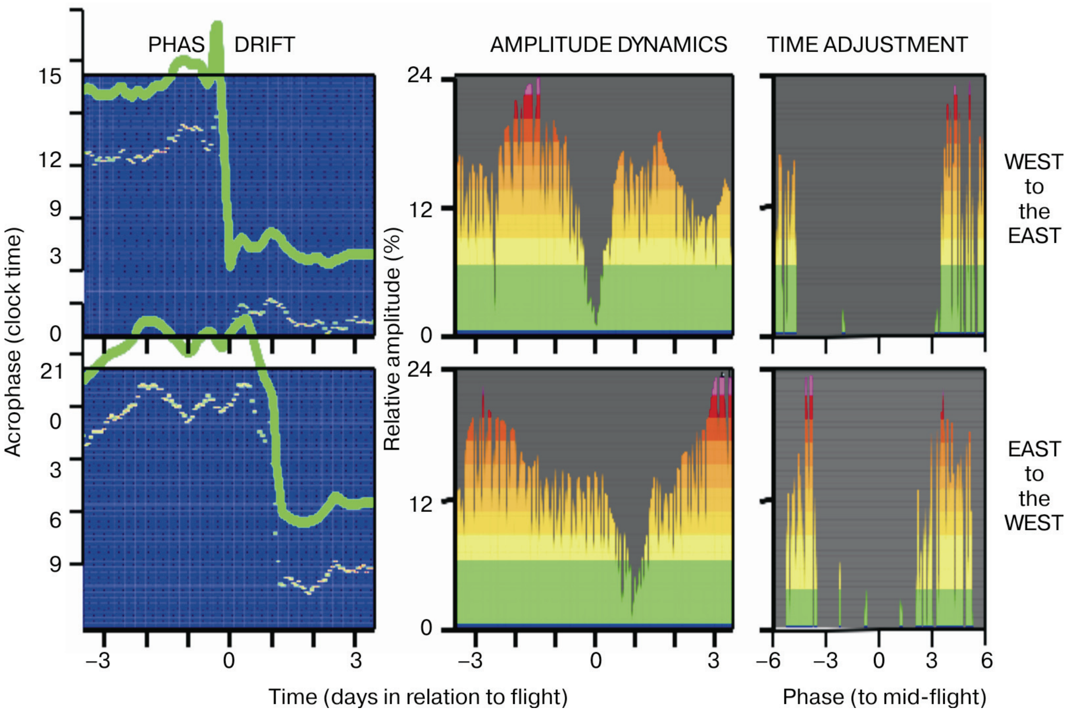


Fig. 4 B. Different projections of the 3D image demonstrate various aspects of entrainment

Discussion. This article is a concise attempt to outline the principles and methods of chronobiology. Thereby in biometrically processing temporal series of biodata, time (T) may be regarded as a systematic parameter which is independent on the biological variable under scrutiny. Time illustrates how the biovariable changes, but it is not the causal determinant of that change, which, in turn, depends on the dynamic properties of living matter. We hope that these guidelines will be useful to the clinical practice, aerospace medicine, environmental health etc. More research is necessary, particularly in the identification of useful circadian phase and amplitude relationships markers that might help to define chronom type of patients.

Conclusions. The method has higher diagnostic value in comparison with well-known procedures of an estimation of biorhythms. It has been shown simultaneously the dynamics of amplitude, its statistical significance and acrophase. The three modification of serial sections was elaborated: procedure of adding logarithms of P-values-matrices, plotting 2D image and 3D image. The visualization of amplitude-phase relationships in entrainment processes allows to carry out the dynamic control at any stage chronoadaptation of organism.

REFERENCES

[1] *Halberg F, Halberg E, Barnum CP, Bittner JJ.* Physiologic 24-hour periodicity in human beings and mice, the lighting regimen and daily routine. In: Withrow RB, editor. Photoperiodism and Related Phenomena in Plants and Animals. Ed. Publ. No. 55. Washington DC: AAAS; 1959. p. 803—878.

[2] *Pittendrigh CS.* Circadian systems: Entrainment. In Handbook Behavioral Neurobiology, v. 4, New-York, University of California Press, 1981, p. 239—268.
[3] *Halberg F.* Chronobiology // Annual Rev Physiol, 1969, v. 31, p. 675—725.
[4] *Sysuev VM.* Methods for analysis of adaptive reactions in multi-oscillatory systems. In: Adaptive reactions of brain and their prognosing. Leningrad, Sci Council in Complex Problems "Physiology of humans and animals" of Acad Sci USSR, 1978, pp 123—130 [in Russian].
[5] *Gamburtsev AG, Alexandrov SI.* [Spectal-temporal analysis]. Monitoring of natural and nature-technical systems. In: Atlas of Natural Processes, v. 1. Moscow, Institute of Physics of Earth Russ Acad Sci, 1994, p 24—25. [in Russian]
[6] *Alpatov AM.* Program "TITAN". In: Karp VP, Katinas GS. Computative methods of analysis in chronobiology and chronomedicine. Saint-Petersburg, Vostochnaja corona, 1997, p 92—94. [in Russian]
[7] *Katinas GS, Sukhodol'skaja OV.* Program "DRIFT". In: Karp VP, Katinas GS. Computative methods of analysis in chronobiology and chronomedicine. Saint-Petersburg, Vostochnaja corona, 1997, p 96. [in Russian]
[8] *Katinas GS, Halberg F, Cornélissen G, Hawkins D, Bueva MV, Korzhevsky DE, Sapozhnikova LR, Rhodus N, Schaffer E.* About 8- and ~84-hour rhythms in endotheliocytes as in endothelin-1 and effect of trauma. Peptides, v. 22, 2001, p. 647—659.
[9] *Katinas G, Nintcheu-Fata S, Cornelissen G. et al.* Moving least squares spectra scrutinize chronomics in and around us. Abstract 14, Kongres MEFA, Brno, Czech Rep., 5—8 Nov. 2002.
[10] *Chree C., Stagg JM.* Recurrence phenomena in terrestrial magnetism // Philos Trans R Soc Lond Series, Ser A, v. 227, 1928, p. 21—62.

ВИЗУАЛИЗАЦИЯ АМПЛИТУДНО-ФАЗОВЫХ ПАРАМЕТРОВ БИОРИТМОВ В ПРОЦЕССЕ ИХ СИНХРОНИЗАЦИИ

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Настоящее исследование по визуализации амплитудно-фазовых параметров биоритмов в процессе их синхронизации основано на выделении последовательных временных интервалов [3], которые позволяют прослеживать поведение различных параметров любого ритмичного компонента спектра в течение времени, которое включает промежутки до, в течение и после любого синхронизационного (десинхронизационного) случая.

Есть простой неинвазивный метод для того, чтобы приобрести информацию относительно визуализации амплитудно-фазовых корреляций. Метод использует математический и графический анализ одновременной визуализации динамики амплитуды, ее статистического значения и величины акрофазы в процессах захвата. Так же были разработаны три модификации последовательных секций: процедура добавляющих логарифмов достоверных матриц, двух- и трехмерные изображения процессов.

В качестве иллюстрации использовались последовательные ряды, которые включали: автоматические измерения кровяного давления (BP), его систолической (S) и диастолической (D) компоненты, а также частоту сердечных сокращений (ЧСС). Были проанализированы хронобиологические показатели сердечно-сосудистой системы во время пяти полетов из Миннеаполиса (США) в Санкт-Петербург (Россия), с пересечением 9 часовых поясов и четырех полетов в противоположном направлении.

Одновременное понижение амплитуды и быстрые изменения в акрофазе, связанные с полетом «с запада на восток», и более постепенные изменения аналогичных показателей в направлении полетов «с востока на запад» привели авторов к гипотезе, что быстрые изменения могут вызывать «поломку» изучаемых биоритмологических характеристик.

Применение настоящего метода позволило авторам выполнять визуализируемый динамический контроль хронобиологических параметров сердечно-сосудистой системы.

Таким образом, данный метод характеризуется более высокой прогностической ценностью по сравнению с известными способами, применяемыми в хронобиологии.

Ключевые слова: биоритмы, методы анализа.