Cybernetics and Systems Analysis, Vol. 31, No. 6, 1995

SOFTWARE–HARDWARE SYSTEMS

MATHEMATICAL METHODS OF DETECTION OF BIOLOGICAL AND HELIOGEOPHYSICAL RHYTHMS IN THE LIGHT OF DEVELOPMENTS IN MODERN HELIOBIOLOGY: A PLATFORM FOR DISCUSSION

É. N. Chirkova

UDC 551.50+577.31

A. L. Chizhevskii, the founder of heliobiology, proved [44] that all biological processes on Earth depend on the 11-year solar activity cycle. However, the level of theoretical biology and computer science in the 1940s-1950s was insufficient for this outstanding Russian scientist to identify biological and solar rhythms with periods shorter and longer than 11 years, nor was he able to establish the mechanism by which heliorhythms affect the course and intensity of life processes.

We have continued the heliobiological studies begun by Chizhevskii, invoking the modern tools of the theory of self-tuning control systems, cybernetics, and molecular biology. On the whole, our research has moved in four directions.

1. Development of a general algorithm for identification of hidden rhythms with unspecified periods given a limited sample of biological and heliophysical data.

2. Identification of the parameters (periods, phases, amplitudes) of solar and biological rhythms of various dimensions. Improvement of the classification of biorhythms and heliorhythms with periods shorter and longer than 11 years.

3. Establishment of main regularities characterizing the relationship of biological and heliophysical rhythms. Development of a methodology for long-term scientific forecasting of variations in the characteristics of life processes given the rhythms of solar activity variation.

4. Creation of a theoretical platform supporting the heliobiological phenomena discovered by Chizhevskii. Substantiation of the electromagnetic (wave) nature of the biological clock on molecular, cellular, systemic, organism, and population levels.

Some concrete results have been obtained in all four directions during the last 25 years of scientific work. These results have been described in various articles: a complete list of the studies for 1970-1992 is given in [51], and the operation of the biological clock mechanism on the molecular and cellular levels is discussed in [52].

The present article develops a universal mathematical method for detection of biological and heliophysical rhythms (the first of the four directions listed above), and provides a critique of the results obtained when rhythms are identified by other methods.

MATHEMATICAL IDENTIFICATION OF BIORHYTHMS AND HELIORHYTHMS OF VARIOUS FREQUENCIES. PHYSICAL THEORY OF COMPOUND OSCILLATIONS

The theory of self-tuning control systems developed in considerable detail in engineering assumes the existence of positive feedback, which is responsible for discreteness, cyclicity, and internal consistency in the operation of all system components. Since living organisms, the biosphere, and the solar system are clear examples of self-tuning control systems, the laws governing the operation of control systems [13] should be incorporated in the development of mathematical methods for the identification of rhythms hidden in the dynamics of biological and heliophysical variables.

Translated from Kibernetika i Sistemnyi Analiz, No. 6, pp. 139-157, November-December, 1995. Original article submitted May 5, 1995.

1060-0396/95/3106-0903$12.50

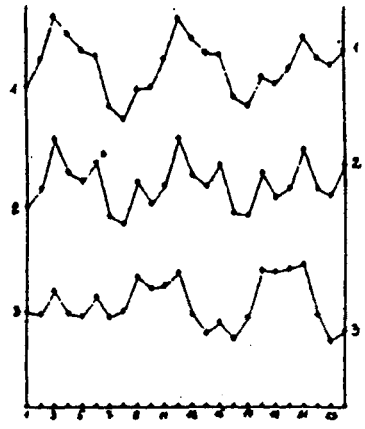

Fig. 1

The modern biorhythmology acknowledges the existence of a number of simultaneous rhythms of various frequencies for each life-activity variable [9]. For instance, the same blood component can display diurnal, seasonal, and even multiannual rhythms, which coexist and form a complex hierarchy of rhythms of a single variable.

> *The autonomous existence of different-frequency rhythms of the same variable and, at the same time, the interdependence of biorhythms of different variables determined by the operating laws of different parts of the single control system of the organism is called rhythmostasis of the particular organism.*

It follows from this definition that the observed dynamics of any biological variable is a mixture of different-frequency biorhythms and noises (irregular fluctuations produced by a variety of factors).

If the mixture of rhythms comprising the dynamics of the observed variable contains a rhythm whose amplitude is much greater than the amplitude of all other rhythms, then this high-amplitude rhythm will be visible in the recorded graph. It is in this way that the 11-year cycles were originally observed in the solar activity and in the behavior of biological variables, leading Chizhevskii to discover the interrelationship between solar rhythms and the rhythms of terrestrial life processes. However, even in those rare cases when rhythms can be visually observed on graphs, the researcher is unable to estimate with confidence the phase or the amplitude of the observed rhythms, because they are "contaminated" by other oscillatory processes occurring in the dynamics of the relevant variable.

Since the dynamics of the observed variables may contain rhythms and noises of different frequencies, the identification of biorhythms and heliorhythms includes the following tasks: 1) identification of the entire system of significant rhythms present in the dynamics of the variable; 2) separation of a particular rhythm from the mixture of other rhythms (rhythms with other frequencies) and noise; 3) determination of the probability p that the identified rhythm is noise (a rhythm is viewed as identified with sufficient confidence if $p \leq 0.05$); 4) determination of the parameters of the identified rhythm: the mean level G, the period T or the frequency $1/T$, the amplitude of oscillation about the mean level A, and the initial phase of oscillation φ at the time when observations begin.

The procedure of estimating the probability that the observed rhythm is in fact noise has been adequately developed only for harmonic (sinusoidal and cosinusoidal) oscillations [10]. We will therefore use cosinusoidal oscillations as a model of rhythms. On the whole, each sinusoidal oscillation modeling a particular biorhythm or heliorhythm is described by the formula

$$X_t = G + A \cdot \cos\left(\frac{2\pi \cdot t}{T} - \varphi\right), \tag{1}$$

where X_t is the value of the variable at the current time instant, G is the mean value of the variable, A is the oscillation amplitude about the mean value, φ is the phase (the shift angle of the cosinusoidal curve pinpointing the location of the first peak on the time scale), T is the oscillation period, and t is the elapsed time since the beginning of observations.

It is obviously necessary to analyze the parameters of each rhythm included in the total dynamics of the relevant variable. Yet in the popular mathematical methods currently used for the identification of biorhythms and heliorhythms (see [25, 35, 43], and elsewhere) the components of interest to the researcher are "identified" with total disregard of other rhythms present in the overall dynamics. The existing methods thus ignore the functional interrelationship between the rhythms of interest and all other rhythms, which in reality are part of a single hierarchy.

As a result, many modern chronobiologists and heliophysicists who attempt to determine the presence or absence of a particular rhythm make the serious mistake of ignoring the phases and amplitudes of other rhythms that contribute to the overall dynamics of the observed variable. It is clear from the examples considered below that changes in phases and amplitudes of component rhythms, keeping the period and the number of rhythms in the observed dynamics fixed, alter the graphical pattern of the process, and in the final analysis lead to incorrect decisions about the presence or absence of particular rhythms in the process.

For example, add up three cosinusoidal curves with the following parameters: 1) $T_1 = 10$, $A_1 = 10$, $\varphi_1 = 120°$; 2) $T_2 = 8$, $A_2 = 8$, $\varphi_2 = 90°$; 3) $T_3 = 3$, $A_3 = 6$, $\varphi_3 = 360°$. The result is one curve. Figure 1 demonstrates the overall dynamics obtained by summing the three cosinusoidal curves (curve 1), by changing the amplitudes of the component cosinusoidal curves (curve 2), and by changing the phase of one of the cosinusoidal curves (curve 3). The abscissa axis measures time (in conventional units), and the ordinate axis measures the observed variable (also in conventional units).

We see from Fig. 1 that, although all three curves are produced by the same rhythms, it is impossible to decide the existence and the occurrence time of the acrophases of these rhythms, because all three resultant dynamics are perceived as totally different and virtually uncorrelated rhythmic processes. This is an obvious result in terms of the physics of compound oscillations [10]: each component rhythm provides more information about the process than the overall resultant dynamics (like the information about the state of the heart provided by an ECG).

Studies that do not identify the phases and the exact amplitudes of all rhythms in the dynamics of the observed variable cannot be regarded as scientifically valid biorhythmological or heliophysical studies.

LIMITS ON POSSIBILITY OF IDENTIFICATION OF VARIOUS RHYTHMS IN THE OBSERVED DYNAMICS OF VARIABLES

Mathematics imposes rigorous demands on every experiment, and the following mathematical considerations must be noted:

the shortest rhythm that can be identified in the observed dynamics of a variable is the rhythm whose period is equal to double the time between successive observations;
the longest rhythm that can be identified in the observed dynamics of a variable is the rhythm whose period is equal to the total observation time minus the time between successive observations.

For instance, if we make daily tests on our subjects or observe the solar activity every day, two days is the shortest period that can be identified on the basis of these data. If the total observation time is 30 days with measurements made every day, the longest identifiable period is 29 days.

Although this is an obvious rule, it is constantly ignored by many researchers. For instance, diurnal rhythms are discussed on the basis of variable dynamics observed over 21 or even 15 hours (numerous examples from monographs [21, 39]), often with a very limited number of observations and variable time intervals between observations (see [16, 20], and elsewhere).

DEVELOPMENT OF A MATHEMATICAL METHOD FOR IDENTIFICATION OF RHYTHMS OF VARIOUS FREQUENCIES

The existing popular mathematical methods include "cosinor analysis" [42], the method of "cosinor bodies and cosinor caves" [15], various modifications of correlation analysis, including solution of correlation equations by the Chebyshev tech-

TABLE 1. Comparison of the Parameters of Matching Rhythms in the Variation of Wolf Numbers Identified from Samples of Different Length (dispersion $\pm 2m$)

Rhythm	Sample length, days	Period, T	Amplitude, A	Phase shift for March 12, 1984, $\varphi°$
Monthly	32	29,5 ± 1,8	30,6	221
	121	28,6 ± 0,5	18,4	237
Semi-monthly	32	15,5 ± 0,7	36,6	261
	121	16,3 ± 0,6	20,0	307
Semi-weekly	32	10,1 ± 0,9	15,9	242
	121	11,0 ± 0,1	13,9	238
Weekly	32	7,3 ± 0,5	14,8	152
	121	7,0 ± 0,01	13,8	150

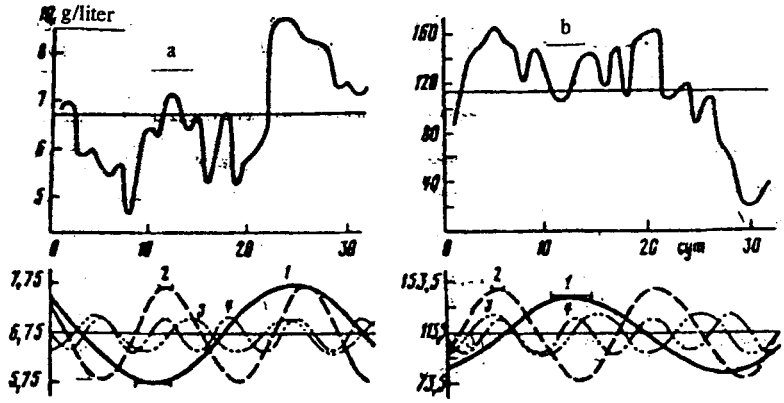

Fig. 2

nique [33], the least squares method combined with successive approximations [5], and an integrated mathematical approach to the analysis of quasi-periodic processes in chronobiology and geophysics [35]. These methods, however, do not meet the above formulated requirements of rhythm identification, and each in its own way fails to provide confidence estimates for the decision concerning presence or absence of hidden rhythms and their parameters in the observed variable dynamics.

A more appropriate approach could be provided by modifying the mathematical method of spectral analysis [4, 41], but the use of spectral methods in biorhythmology runs into three limitations: 1) spectral methods require large volumes of data, whereas in real-life biological studies the number of observations of each variable is limited by objective possibilities; 2) spectral methods do not readily estimate the true period and phase of the observed variables, which is inadmissible in biorhythmology, where frequency and phase carry information about the individual features of the living organism and temporal consistency of the life-sustaining metabolic processes; 3) because of the incessant self-adjustment of the rhythms of various variables in the organism to changes in external and internal factors affecting the organism functions, we need a method that determines the drift of the identified period about the mean and allows for the possibility of temporal coexistence of relatively prime periods in the observed hierarchy of rhythms of a particular variable.

To overcome these difficulties, which restrain the development of biorhythmology and heliobiology, we have developed a mathematical method for reliable identification of rhythms with unknown periods from small samples of biological and heliophysical data [37, 45, 46]. The proposed method is universally applicable for solution of problems in heliobiology, meteorology, chronobiology, and chronomedicine. The algorithm for this method has been constructed using the following mathematical techniques.

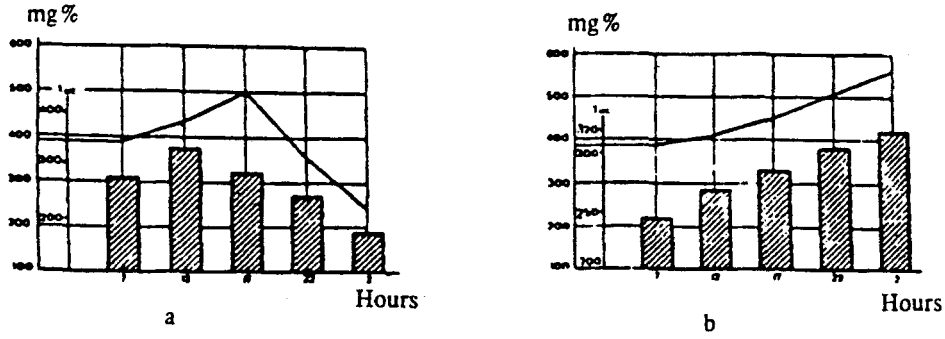

Fig. 3

1. Simultaneous identification of a hierarchy of different-frequency biorhythms from a small sample of observations made at constant time intervals is performed by periodogram analysis [4] supplemented with estimates of probability that the identified harmonic is "white noise". The relevant model is stated in the form $X_t = m_t + \varepsilon_t$, where X_t is the observed time series, m_t is a periodic function of the form

$$m_t = \alpha_0 + \sum_{i=1}^{m} (\alpha_i \cdot \cos \omega_i t + \beta_i \cdot \sin \omega_i t), \tag{2}$$

ε_t is "white noise" with the parameters $N(0, \sigma)$; α_0, α_i, β_i, $\omega_i = 2\pi/T_i$ are unknown parameters.

The estimators a_0, b_i, a_i of the true parameters α_0, β_i, α_i are calculated from the formulas

$$a_0 = \frac{2}{N} \sum_{t=1}^{N} X_t, \qquad a_i = \frac{2}{N} \sum_{t=1}^{N} X_t \cdot \cos \omega_i t,$$

$$b_i = \frac{2}{N} \sum_{t=1}^{N} X_t \sin \omega_i t, \qquad a_k = \frac{1}{N} \sum_{t=1}^{N} X_t \cdot (-1)^t, \tag{3}$$

if N is even.

The sample periodogram is constructed by the formula

$$S_i = a_i^2 + b_i^2, \tag{4}$$

and then we calculate the statistics

$$u_i = \frac{S_i}{S_1 + S_2 + \ldots + S_k}, \quad i = 1, 2, \ldots, k. \tag{5}$$

The statistics are ordered in a descending sequence. For the maximum statistic, the probability that the square of the amplitude of the zeroth component exceeds the level $S_{\max}$ is given by the formula [4]

$$P(u > u_{\max}) = \sum_{p=0}^{r} (-1)^p \binom{k}{p+1} [1 - (p+1)u_{\max}]^{k-1};$$

$$\binom{h}{g} = \frac{h!}{g!\,(h-g)!}, \tag{6}$$

where r is the greatest integer not exceeding $k - 1$ for which $1 - (r + 1)u_{\max} \geq 0$.

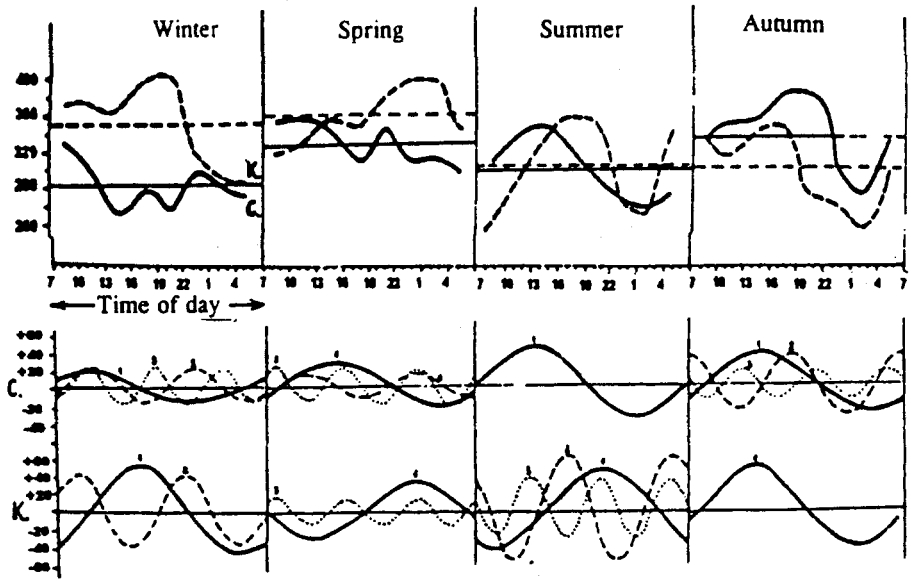

Fig. 4. Natural dynamics (top) and identified hierarchies of rhythms (bottom) in the variation of the number of thrombocytes during the day in the blood of healthy males C. and K. in different times of the year: winter, Jan. 21-22, 1984; spring, April 21-22, 1984; summer, July 21-22, 1984; autumn, Oct. 28-29, 1984. The horizontal axis gives the time of day; the vertical axis gives the concentration of thrombocytes in 1 μl.

The probability that the noise exceeds the level S_i, $i = 2, 3, \ldots$, is estimated from the formula

$$P(u > u_i) = \frac{k!}{(i-1)!} \sum_{p=1}^{r} \frac{(-1)^{p-i}(1-pu_i)^{k-1}}{p(k-p)!(p-i)!}, \tag{7}$$

where the index i corresponds to the place of the estimated amplitude among the ordered statistics $\{u_i\}$, and r is the greatest integer for which $1 - ru_i > 0$.

This analysis makes it possible to identify the presence of significant harmonics with a period which is a multiple of $k\Delta t$, where Δt is the quantization increment.

2. By reducing the original sample length (omitting the last values, and then the first values) we alter the sample period and the periods of the harmonics that are multiples of the sample period. This procedure provides an opportunity to compare the confidence of the significant harmonics in each computation cycle, because rhythms with close frequencies have different point confidence estimates. In this way, we can search for significant amplitudes by minimizing the probability of their inclusion in "white noise", and also establish the statistical dispersion of the parameters of individual rhythms. Rhythms selected by this test are characterized by their amplitude and phase shift relative to the starting point, and in multidimensional cases involving comparison of different hierarchical systems the proposed method makes it possible to compare the relative shifts of the parameters of different rhythms, and thus obtain a fairly full characterization of the state of a living system as a whole. The selectivity of this technique is estimated by the following expression [41]:

$$\hat{a}_i = \sum_{j=1}^{m} a_j \left\{ \frac{\sin[(\omega_i - \omega_j)k\Delta t]}{(\omega_i - \omega_j)k\Delta t} + \frac{\sin[(\omega_i + \omega_j)k\Delta t]}{(\omega_i + \omega_j)k\Delta t} \right\} = \sum_{j=1}^{m} a_j \left\{ R[(\omega_i - \omega_j)k\Delta t] + R[(\omega_i + \omega_j)k\Delta t] \right\}, \tag{8}$$

where m is the number of harmonics in the time series, j is the index of all other harmonics, $R = \frac{\sin\lambda}{\lambda}$, $\lambda = (\omega_i - \omega_j)k\Delta t$.

It follows from this formula that the estimate error of a cosinusoidal component will be less than 0.09 if $|\omega_{j+1} - \omega_j|k\Delta t > 8$.

TABLE 2. Period of Diurnal Biorhythm of Potassium Excretion in Urine for Healthy People and for Patients with Neurocirculatory Dystonia, as Determined by Different Methods

Heathy			Sick		
Subject	Period (hrs)		Subject	Period (hrs)	
	Method [5]	Our method		Method [5]	Our method
3	24,0	24,9	CAB-44	28,0	24,0
5	24,0	22,1	LAB-30	28,0	24,2
6	24,0	26,5	CAB-45	36,0	26,0
9	24,0	27,0	LAA-11	36,0	26,7
12	24,0	22,6	LAA-51	28,0	26,6
13	24,0	23,4	LAA-29	28,0	24,0
14	24,0	not detected	LAA-64	32,0	27,0
16	24,0	22,9	LAA-65	28,0	not detected
18	24,0	27,3	CAB-10	24,0	22,7
22	24,0	25,2	CAB-31	24,0	21,3
33	24,0	24,0	CAB-46	36,0	26,8
35	24,0	24,7	CAB-52	32,0	not detected
Group average ($\bar{M} \pm 2m$)	24,0 ± 0,0	24,6 ± 1,0	Group average ($\bar{M} \pm 2m$)	30,0 ± 2,4	24,8 ± 1,2

TABLE 3. Biorhythm of Frequency of Cardiac Contractions in Patient B Before and After Chronotherapy

Observation	Average level ($\bar{M} \pm 2m$)	Period (h)	Amplitude	Phase (deg.)	Error pobability (p)
Before chrono-therapy	75,17 ±3,18	24,0	8,232	285,68	0,008
After chrono-therapy	72,11 ±1,78	60,0	3,067	293,93	0,010
		34,0	2,683	191,15	0,041
		14,67	1,170	273,27	0,028

3. By Kotel'nikov's theorem, errors are unavoidable at low frequencies with small samples. Maximum freedom from errors when identifying the true phase and amplitude relationship in a complex hierarchical system of biorhythms and heliorhythms is achieved by successive "filtering" of the carrier components (a procedure similar to analog filtering in radio engineering). This procedure identifies with confidence low-amplitude biorhythms in the presence of high-amplitude components in the observed hierarchy of rhythms.

4. If the mean level of the variable displays persistent growth or decline (for instance, the growth of a child, the decrease of air temperature from summer to winter, etc.), the mean-level variation is approximated by a polynomial of not higher than second degree.

The entire system of procedures has been coded and implemented on an IBM PC. The following steps are successively executed: 1) data entry and input of analysis control parameters; 2) elimination of the linear trend described by a polynomial of first or second degree from the original time series; 3) expansion of the data in a Fourier series; 4) construction of a periodogram of the observed series, computation of statistics, and estimation of the significance of the identified harmonics; 5) forward and backward reduction of sample length followed by repetition of steps 3 and 4; 6) forward and backward reduction of sample length after successive subtraction of significant harmonics from the original time series, followed by repetition of steps 3 and 4; 7) printing out the results; 8) graphic display of the identified hierarchy of rhythms; 9) estimation of the correlation of the original time series with the theoretical dynamics (the latter is the sum of the identified rhythms).

In addition to the described procedures, the significant rhythms identified by computer are combined after step 7 into statistical groups, the trend of the parameters ($\bar{M} \pm 2m$) is computed within each group, and a decision is made concerning the number and the parameters of the rhythms in the observed dynamics of the variables. This "manual" procedure remains

the most time consuming "bottleneck" in the proposed method, and it requires further improvement of the algorithm with the purpose of eliminating the subjective factor from final decision.

The selectivity of the algorithm was tested in a series of computer experiments solving 13 test problems proposed by the expert Council of Chronobiology in 1990. The test problems were constructed by summing harmonics with known parameters and mixing the sum with "noise". For instance, given a small number of sample values from the time series, the numerical sequence was simulated by formula (2). The first simulation generated 32 values of a time series with period T = 28, amplitude A = 10, and phase shift φ_1 = 320°; the standard deviation was σ = 1. Analysis of the time series in the presence of noise produced amplitude and phase estimates of A = 9.8 and φ_1 = 328°, respectively. In the second example, mixtures of two periodic components were filtered in the presence of the same noise level: the first component remained as before, while the second component was taken with amplitude 7.6, phase shift 180°, and periods 9, 13, and 17, which are relatively prime with the first period. The analysis revealed a sharp peak in the confidence estimates of the second harmonics, producing period estimates of 9, 13, and 16.5 respectively with corresponding amplitudes of 7.12, 7.48, 7.10 and phase shifts of 192°, 194°, 174°. On the other hand, the confidence estimate of the first harmonic with T = 28 "spread out" over a relatively broad frequency band. Subtracting the second harmonic estimates from the original time series, we obtained substantially improved estimates of the first harmonic parameters in a sequence of three runs: A = 10.7, φ_1 = 339° with period estimate T = 28.8; A = 11.4, φ_1 = 328° with period estimate T = 30; and A = 10.4, φ_1 = 320° with period estimate T = 28.6.

Figure 2 is an example of identification of monthly and weekly biorhythms in the variation of the number of leukocytes in the blood of a healthy subject conducted by the proposed procedure (32 daily blood samples from March 12 through April 12, 1984). Here 1 is the monthly rhythm, 2 is the semi-monthly rhythm, 3 is the sesqui-weekly rhythm, and 4 is the weekly rhythm. The rhythms with T_1 = 28.0 ± 1.6 days and T_2 = 13.6 ± 0.8 days (the dispersion is everywhere $\pm 2m$) had the highest amplitudes and were identified with confidence $p = 0.9 \cdot 10^{-6}$ and $0.7 \cdot 10^{-5}$ respectively without preliminary "filtering." Three other biorhythms with periods T_3 = 9.3 ± 0.0 days, T_4 = 6.4 ± 0.8 days, and T_5 = 2.6 ± 0.3 days were identified with confidence p = 0.047, 0.001, and 0.020 respectively, but only after preliminary "filtering" of the monthly and semi-monthly rhythms. All in all, the identification of these five biorhythms in a month of observations required analyzing 446 different frequencies in the leukocyte dynamics in the blood of the patient. Only 26 of these rhythms proved to be significant ($p \leq 0.05$), and these significant rhythms were reduced to only five biorhythms by averaging rhythms with very close parameters. Four of these are shown in Fig. 2a.

Figure 2 also shows an example in which the same procedure is applied to analyze hidden periodicities in the 32-day dynamics of Wolf numbers (derivatives of the number of sun spots, their areas, and luminous intensity from March 12 to April 12, 1984). We see that analysis of the probable presence of 446 frequencies in the dynamics of this heliophysical variable also revealed 5 significant rhythms: a monthly rhythm with a period of 29.5 ± 1.8 days ($p = 0.3 \cdot 10^{-3}$), a semi-monthly rhythm with a period of 15.5 ± 0.7 days ($p = 0.5 \cdot 10^{-7}$), a sesqui-weekly rhythm with a period of 10.1 ± 0.9 days (p = 0.010), a weekly rhythm with 7.3 ± 0.5 days (p = 0.004), and a semi-weekly rhythm with 3.6 ± 0.4 days (p = 0.048).

Analysis of the rhythmograms in Figs. 2a and 2b shows that the monthly and semi-monthly rhythms in the variation of leukocyte concentration in human blood and of the Wolf numbers occur in antiphase with one another. Specifically, these are the rhythms that determine the dynamics of the observed processes in the given time interval. Comparison of the dynamics of the two processes and determination of the association between them by any methods of correlation analysis could not possibly detect the antiphase behavior with such statistical confidence. We thus conclude that

the correlation methods often used by researchers for estimating the interrelationship of biological and heliophysical data are not valid without preliminary determination of the significant rhythmic components in the dynamics of the variables of the self-tuning control systems under comparison.

As the sample of Wolf numbers is increased to 121 days (from January 1 to April 30, 1984), the proposed procedure detects 9 significant component rhythms. The matching rhythms — 4-weekly, 2-weekly, 1.5-weekly, and weekly — from the 32-day and 121-day samples had the same phase and period, allowing for the "drift" around the mean (Table 1). However, the amplitudes of the monthly and semi-monthly heliorhythms in the short sample were almost double the corresponding amplitudes from the long sample, which points to instability of this parameter and is consistent with the actually observed changes in Wolf numbers [11]. A similar regularity was noted also in a comparison of the parameters of the hierarchy of rhythms of the A_k-index determined from 32-day and 400-day samples.

The proposed procedure has been applied to detect a large number of biorhythms in the blood of man and animals, ranging from 8 h to 2.5 years (experiments covering 1969-1987), and we have also confidently detected the existence of 30 different rhythms of solar and geomagnetic activity, lunar gravitation, and meteorological variables in the same time range (see [2, 27-29, 47, 49-51], and elsewhere).

The proposed mathematical method for detection of rhythms was first developed and discussed at a conference on mathematical methods in biology in 1976 [45]. An improved algorithm and the results produced by the algorithm were discussed and subsequently approved for publication at special seminars at the Keldysh Institute of Applied Economics of the Russian Academy of Sciences [37] and at the Institute of Cybernetics of the National Academy of Sciences of Ukraine [46]. A review and a critique of the conventional methods for detection of bio- and heliorhythms in comparison with our methods were undertaken at the Faculty of Mathematics of Moscow State University [48].

ANALYSIS OF THE RESOLVING POWER OF MATHEMATICAL METHODS USED FOR DETECTION OF BIOLOGICAL RHYTHMS IN SCIENTIFIC AND CLINICAL PRACTICE

The interest in the problem of biorhythms has markedly increased in recent years in connection with its application to prevention and treatment of various diseases.

Despite the clearly positive impact of the ideas of biorhythmology on the development of practical and theoretical medicine, chronobiologists still display a highly superficial attitude to the requirements that must be observed for mathematical detection of biorhythms in limited-length time series characterizing the physiological state of patients and healthy subjects. This creates a danger that methods of pseudo-diagnosis and pseudo-therapy will find their way into clinical practice, and possibly cause more damage than good to the health of the patients.

Before examining the conventional methods, we should note that chronotherapy may proceed in two ways [34]: 1) by choosing the time to administer the drug based on the notion of a normal rhythm of functions in every human being and the change of this rhythm in pathological cases (group chronotherapy); 2) by choosing the time to administer the drug based on an analysis of rhythms of the particular patient (individual chronotherapy). We will apply our mathematical method, and also the basic premises of heliobiology developed by Chizhevskii, to assess the effectiveness and also the theoretical and practical validity of the methods of chronodiagnosis and chronotherapy of cardiovascular diseases, which are applied in various hospitals throughout the CIS.

PREDICTION OF EXACERBATIONS AND FATALITIES BY CALCULATING "CRITICAL DAYS" FROM PHASE RELATIONSHIPS OF SOME HUMAN BIORHYTHMS

The universal practice of predicting the critical states of the human organism from phase relationships of physical, emotional, and intellectual biorhythms that became fashionable in the 1970s has affected many people in the CIS and other countries. It has also influenced the clinical research of predicting the acuteness of cardiovascular pathology [40]. The wide popularity of the method was made possible by the commercial sale of personal biorhythm detectors and the promise of business organizations to provide prediction of "critical days" by computer.

This technique can be classified as a method of individual chronodiagnosis and chronotherapy. It assumes the existence in every person of a 23-day physical biorhythm, a 28-day emotional biorhythm, and a 33-day intellectual biorhythm. The phase relationships of these rhythms are calculated by simply dividing the number of days since the person's birth by the period of each biorhythm.

Despite the considerable popularity and persistent promotion, this method of calculating critical days places the entire human ontogenesis in the realm of the fates, and does not withstand scientific critique for two reasons.

1. Even if we accept that only these three aggregate variables determine the physical state of the human organism, we have to ask why is it that critical days are calculated using only the phase relationships of the near-monthly rhythms, ignoring the existence of other (annual, seasonal, etc.) rhythms, possibly with higher amplitudes, in the overall dynamics of each variable? For instance, the 28-day emotional rhythm is only one of a large hierarchy of emotional rhythms, which may include

annual, seasonal, multidiurnal, and diurnal rhythms of this aggregate variable (similarly to the intra-monthly leukocyte rhythms in Fig. 2). The summation of numerous biorhythms of the physical state of the organism during the life of an individual will produce a highly ambiguous result when the age in days is divided by 23. The same applies to the dynamics of the emotional and intellectual state of the human subject.

It is impossible to decide on the occurrence of "critical" state of a human organism because we ignore the laws of phase-amplitude interaction for the entire set of biorhythms of each variable and lack information about the interaction of the hierarchies of rhythms of various variables. To justify such chronodiagnosis, we have to conduct an enormous number of continuous multiannual individual studies of the physical, emotional, and intellectual state of a large number of people, depending on their sex, age, place of residence, and physiological state (the presence of various diseases), identify all the rhythms entering the dynamics of these variables, find aggregate statistical regularities describing the fluctuations of these variables, and only then attempt to apply these regularities to determine the "critical days." This will require the application of an appropriate mathematical apparatus of biorhythm identification.

2. The "critical days" method raises even greater theoretical objections, because it totally ignores the fundamental law of nature (life in the solar rhythm) discovered by A. L. Chizhevskii, who for the first time predicted the intensity of terrestrial biological processes from the phase of the 11-year solar activity cycle.

The study of the interaction of the own rhythms of living organisms and the heliogeophysical rhythms provides researchers (see [27, 28, 46, 51], and elsewhere) with the necessary key for the development of methods of long-range prediction of the state of the human organism from the sum of the current phases of solar activity rhythms.

Still, we would like to note in conclusion that the scientifically unfounded "critical days" method is not the most harmful of near-scientific inventions, because it typically encourages people to be more circumspect and attentive to their health in certain days. This is hardly damaging for the human condition.

CHRONODIAGNOSIS AND CHRONOTHERAPY BASED ON STANDARD PATTERNS OF PEAKS IN THE DIURNAL DYNAMICS OF PHYSIOLOGICAL VARIABLES OF NORMAL AND PATHOLOGICAL CASES

Diurnal rhythms (in contrast to multimonthly, monthly, and even weekly rhythms) are judged by many chronobiologists to be more accessible for study for the following reasons: 1) the 24-h rhythm is implicitly defined by the Earth's rotation about its axis, and there is no need to invoke a mathematical apparatus for its identification; 2) it is relatively easy to determine the dynamics of the variables over a short time interval.

Numerous studies indicate that the individual diurnal dynamics of variables is unstable even in healthy people and animals (the instability is less pronounced only for variables that are connected with the change from day to night, and also with the "sleep–wakefulness" cycle). These observations have suggested the hypothesis of "a drifting diurnal-rhythm acrophase" (see [36] and elsewhere).

Despite the instability in the time of occurrence of peaks and valleys in the diurnal dynamics of biological variables, most researchers ignore this fact (see [16, 20, 21, 23, 33, 39], and elsewhere) and restrict the procedure to visual examination of the diurnal-average dynamics of the relevant variables. In this way, the researchers ignore the existence of a whole set of other rhythmical components (shorter and longer than 24 h) in the diurnal dynamics, whose phases and amplitudes depend not only on the physiological state of the subjects, but also on the spontaneous environmental rhythms that constitute the background for biological research.

Most researchers dealing with chronopathology and chronotherapy of cardiovascular diseases cite as the basis the monographs of the leading Russian chronotherapist R. M. Zaslavskaya [16, 21]. Let us examine the method for detection of standard patterns of diurnal biorhythms in normal and pathological cases using the examples from these monographs, which have been incorporated in the textbook of chronomedicine [20].

Figure 3 borrowed from [16, 20, 21] shows an example of detection of standard diurnal-rhythm patterns for the level of fibrinogen and the number of thrombocytes in healthy subjects and in stenocardia patients. Even without special mathematical education, we see that the curves in Fig. 3 are purely accidental and do not represent a standard pattern of diurnal variation of the corresponding variables. The reasons for this are the following: 1) the graphs do not reflect the influence of sex and age characteristics of the rhythms on the diurnal dynamics of fibrinogen and thrombocytes; in particular, the information for the group of healthy subjects includes observations of both adolescents and seniors, whereas a large body of current literature indi-

cates that the diurnal-rhythm acrophase has an age-dependent drift (see [38] and elsewhere); 2) the rhythm patterns are inferred from the shape of the total averaged curve ignoring the dispersion of the observations ($\pm 2m$), i.e., the statistical significance of the extrema on the plotted curves is not proved; 3) the effect of seasonal factors on the dynamics of the two variables is ignored (Fig. 4 shows that seasonal effects may be considerable); 4) the number of observed categories (five) is clearly insufficient for drawing reliable conclusions on the regularities of the diurnal dynamics of the variables; and most important of all, 5) the analysis does not extract the diurnal biorhythms of the variables from the total dynamics, which is a mixture of different components and noise.

To demonstrate the futility of discussing diurnal biorhythms from the shape of the total diurnal dynamics of a particular variable, Fig. 4 shows the diurnal dynamics and the identified biorhythms ($p \leq 0.5$) for the concentration of thrombocytes in the blood of two healthy males in different times of year. Although the observations were made on two young males living under identical conditions (in a military base), we see from Fig. 4 that the initial diurnal dynamics of the number of thrombocytes in the blood of these two subjects has both seasonal and individual characteristics, which must be taken into consideration when developing recommendations for chronodiagnosis and diurnal chronotherapy.

The lack of a theory explaining the phenomenon of "drifting diurnal-rhythm acrophase" is entirely attributable to the neglect of the physical theory of compound oscillations by mathematicians working on the development of mathematical methods for identification of biorhythms [24, 35, 36]. Indeed, if in Fig. 1 we continue in the horizontal direction the curves obtained by the summation of three rhythms in any of the alternatives, the shape of the curves after the 24th interval will be totally unlike the dynamics in intervals 1-24, because the periods of the rhythms forming the total dynamics are not integer multiples of one another. But this relative primality of the rhythms is only one of the possible reasons for the phenomenon of "drifting diurnal-rhythm acrophase." Another, more essential and permanently present reason for "acrophase drift" is the superposition of weekly and semi-weekly rhythms (36-, 48-, 60, and 72-h biorhythms; 3.5-, 4-, 5-, and 6-day biorhythms) on the diurnal dynamics.

IDENTIFICATION OF DIURNAL-BIORHYTHM ACROPHASES BY "COSINOR ANALYSIS" AND THEIR USE FOR CHRONOTHERAPY

The "cosinor analysis" method proposed by Halberg in 1965 [42] remains the most popular mathematical technique for identification of diurnal biorhythms (see [3, 8, 18, 19, 26, 39], and elsewhere). Historically, "cosinor analysis" is a positive step forward compared with the previous methods, because it attempts to estimate the confidence of the location of the acrophase on the time scale of the diurnal biorhythms of the observed variables. However, large-scale studies of biorhythms by this method have established its practical inconsistency: the authors who critique this method [12, 31] claim that it does not detect the 24-h biorhythm in the presence of high-amplitude oscillations of other components from the hierarchy of diurnal biorhythms (in the graphs the result is a two-peak, three-peak, etc., curve).

The cosinor method applied to the natural dynamics of the number of thrombocytes shown in Fig. 4 failed to detect the 24-h biorhythm for subject C. in the winter and for subject K. in the summer. Our method, on the other hand, established the presence of 24-h biorhythms in all the eight thrombocyte curves. In the time series where the cosinor method failed to detect the diurnal rhythm, the amplitude of the diurnal biorhythms was equal to or less than the amplitude of the 12- and 8-h biorhythms.

Application of various mathematical techniques to improve the group location of diurnal-biorhythm acrophases determined by the cosinor method (see [17, 20, 35, 36], and elsewhere) does not guarantee correct inference regarding the presence or absence of diurnal biorhythms in the observed variables.

Paradoxically, the justified criticism of cosinor analysis as a method for detection of diurnal biorhythms has not stopped experimental researchers and experts from widely applying this method to human patients for chronodiagnosis and chronotherapy.

The lack of theoretical and practical justification for clofelin and anaprilin chronotherapy of hypertonia is clearly evident in the work of Zaslavskaya and co-authors [18, 19]. With the objective of reducing the number of drugs administered to patients, the authors recommend administering the medication based on the time of appearance of the diurnal maximum in the arterial pressure (AP). However, Zaslavskaya and co-authors themselves stress in the body of their papers and even present tabular data [18] which indicate that, before the commencement of chronotherapy, the cosinor method failed to detect diurnal AP biorhythms in any of the patients (!). If diurnal biorhythms were not detected, how was it possible to determine the time

of appearance of the diurnal AP maxima, which were supposed to guide us in administering the medication? To compensate for the limitations of the cosinor method the authors introduce standard diurnal-biorhythm patterns for normal and pathological cases (the construction of these standard patterns has been discussed in the previous section). It is here that these standard patterns find their use! They provide guidelines for administering the medication to the patients. With this approach we can hardly speak of biorhythm-based therapy (chronotherapy). We can only speak of studying the effect of reduction of clofelin and anaprilin dosage and frequency on AP dynamics in hypertonic patients. Zaslavskaya's patients, who did not reveal any diurnal rhythm before the commencement of "chronotherapy," naturally acquired this rhythm under the influence of repeated forced reduction of AP at certain times of the day (according to the standard "pattern"). After a sufficiently long application of this regime, all the patients acquired after "chronotherapy" an imposed diurnal AP rhythm, whose amplitude was sufficient to record a 24-h rhythm by cosinor analysis. This is interpreted by the authors as an indication rhythmostasis normalization and success of chronotherapy.

In conclusion of our discussion of the inconsistency of chronotherapy regimes based on preliminary detection of biorhythms by cosinor analysis, we should note that even the improved version of this method [15], which detects 12-, 8-, and 6-h components in the diurnal dynamics of the variables, does not meet the requirements that are necessary for making inferences about the parameters of diurnal biorhythms. By Emel'yanov's method [15], each biorhythm is isolated separately from the original dynamics of the variable, ignoring the possible presence of other rhythms and abstracting from the contribution of other harmonic components and noises to the estimated parameters of the sought biorhythm. Moreover, this method of identifying "cosinor bodies" and "cosinor caves" does not detect biorhythms with unknown (unspecified) periods.

CHRONOTHERAPY BASED ON DETECTION OF BIORHYTHMS OF UNKNOWN PERIOD BY THE LEAST SQUARES METHOD COMBINED WITH SUCCESSIVE APPROXIMATIONS

The previously described methods cannot find the true periods and phases of intra-diurnal rhythms and ignore the "acrophase drift" of these rhythms in individual patients. These shortcomings have motivated some researchers to revise their methodology and to try to develop alternative mathematical approaches to biorhythm detection. A method has been developed for determining the individual near-diurnal period on the basis of a statistical estimate of the distances between peaks in the 2-day dynamics of the observed variables [5, 6, 30]. A similar method was used earlier in various modifications to estimate biorhythms in experiments with animals [1], but it was quickly rejected by its authors [45] as unsuitable for reliable extraction of biorhythms from a complex noisy dynamic mixture of the observed variables. Since this method of biorhythm detection is insistently used and widely promoted for adoption in clinical practice (see [5, 20], and elsewhere), we will consider it in more detail.

According to the data of Aslanyan and co-authors [5], healthy people display diurnal rhythms with periods ranging from 20 to 28 h in their pulse, systolic, and diastolic AP, height of R and T teeth in the ECG, body temperature, and excretion of macro- and microelements in urine. In sick patients, the acrophase of these variables shifts, according to the authors' data, and leads to a more significant variability in the length of the near-diurnal periods than in healthy subjects (less than 20 h or more than 28 h).

Patients with rhythmostasis disorders are subjected to individual chronotherapy by prescribing a forced diurnal regime of life and medication. Medication is administered at special times, whose frequency is chosen in accordance with the length of the near-diurnal biorhythm period established for the individual patient in advance.

Subjecting the data of Aslanyan and co-authors to a more rigorous mathematical analysis by our method, we clearly reveal the practical and theoretical inconsistency of biorhythm detection by the method of [5]. Table 2 shows that the average length of the near-diurnal period of potassium excretion in urine is not significantly different for groups of healthy and sick subjects if the hidden biorhythms are identified (according to our method) with allowance for the presence of noise and other biorhythms in the observed dynamics (in this particular case, rhythms in the range of from 8 to 68 h, because Aslanyan's study spanned 72 h with urine samples taken every 4 h). In the range from 8 to 68 h, we detected individual systems of biorhythms of potassium in urine for each healthy and sick subject, which sometimes did not contain statistically significant near-diurnal components (we see from Table 2 that the near-diurnal biorhythm was not detected in three cases). For instance, for the patient CAB-46 our method detected only three biorhythms with almost identical amplitudes (60, 26, and 12.7 h); for the patient CAB-44 our method detected seven different biorhythms (the error probability in all cases was $p < 0.05$).

Note that the errors associated with the determination of the diurnal-biorhythm period by successive approximations are highly dangerous for the patients, who are subsequently subjected to chronotherapy. Such "chronotherapy" induces desynchronization due to the artificially imposed change in the diurnal regime of sleep and medication.

As an example, we cite a case from the Erevan Institute of Cardiology of the Armenian Ministry of Health.

Patient B., age 33 years; diagnosis: hypertonia, stage IIA. Since March 4, 1983, during three days, rhythmological examination of the frequency of cardiac contraction, observations every four hours. The method of successive approximations produced an approximating sinusoid with a period of 34 h. Obsidan therapy, 40 mg dose administered with a period of 34 h, two hours before the acrophase. Therapy administered continuously during 12 days, with obsidan intake shifted daily by 10 h. The therapy was followed by another 3 days of rhythmological observation of the patient. In this stage, it was established that the period of the diurnal rhythm of the pulse had changed under the influence of the therapy from 34 h to 29 h. This was interpreted as progressive normalization of rhythmostasis in the patient.

In fact, analysis of the dynamics of the frequency of cardiac contractions of patient B. before and after chronotherapy by our method has shown (Table 3) that, before chronotherapy, only one rhythm with a period of 24 h was detected with sufficient confidence, whereas after obsidan treatment (with an interval of 34 h) the patient displayed desynchronization: the natural 24-h rhythm disappeared, and an imposed 34-h rhythm appeared, with an amplitude equal to 1/3 of the amplitude of the former diurnal rhythm.

The obvious practical inconsistency of chronotherapy pursuing the goal of normalizing the diurnal period of some variable is aggravated by the complete theoretical inconsistency of this approach. Secular observations of human patients have shown, and special studies of biorhythmologists have confirmed [9], that light is the most powerful natural regulator of the biological clock in plants, animals, and man. When traveling to a different time zone, the biological clock of both healthy and sick subjects adjusts after a certain interval to the local time of the new geographical location. This is determined by the high sensitivity of gene activation and deactivation in the process of cellular differentiation to external sources of electromagnetic radiations, and in particular to optical radiation of the Sun [7, 22, 32, 44, 52]. Therefore all living cells or complex organisms are "doomed" to track the rotation of the Earth around its axis and the alternating change of light and darkness.

CONCLUSION

Analysis of the currently available mathematical methods for the detection of biological and heliogeophysical rhythms, and also methods for comparison of independent oscillatory processes shows that the Russian and the International Societies of Chronobiologists, despite the abundance of journals and monographs that they publish, have so far been unable to fully exploit and develop the original contribution that A. L. Chizhevskii made to world science 50 years ago.

The work of the present author and her colleagues has been driven entirely by their own enthusiasm, and carried out contrary to the plans of official Councils on Chronobiology, in an atmosphere of an information blockade. Their studies have not been discussed in any survey article or textbook on chronobiology, not listed in the relevant sections of the VINITI Journals of Abstracts or in the subject catalogs of scientific libraries, not accepted for presentation at representative sessions and conferences on biorhythmology, not cited in dissertations devoted to the development of mathematical methods of detection of biorhythms. We can thus safely say that the fate of the science of heliobiology during the last 25 years remains as complex as it was in Chizhevskii's life time.

REFERENCES

1. M. M. Avramenko and É. N. Chirkova, "Spontaneous periodicity of variation of the total protein content in blood serum of healthy rabbits," Byull. Éksp. Biol. Med., No. 11, 33-35 (1972).
2. M. M. Avramenko and É. N. Chirkova, "Relationship of potassium biorhythms with heliogeophysical factors," Byull. Éksp. Biol. Med., No. 2, 208-212 (1988).
3. K. G. Adamyan, N. L. Aslanyan, and S. V. Grigoryan, "Comparative analysis of diurnal rhythms of some functional indicators of the cardiovascular system in healthy subjects and ischemic patients," Cor et Vasa, **26(3)**, 174-182 (1984).
4. T. Anderson, Time Series Analysis [Russian translation], Mir, Moscow (1976).

5. N. L. Aslanyan, "Chronobiological approach to diagnosis and therapy of some diseases of the cardiovascular system," Terapevt. Arkhiv, **58**, No. 1, 45-47 (1986).
6. N. L. Aslanyan, V. M. Shukhyan, É. M. Krishchan, and others, "Application of the analysis of variance to detect repetition of diurnal curves of sodium and potassium excretion in urine," Laboratornoe Delo, No. 1, 49-50 (1984).
7. Yu. N. Babaev and É. N. Chirkova, "Electromagnetic nature of the biological clock. Biorhythms on the molecular, cellular, and organism level," in: Problems of Chronobiology, Chronopathology, Chronopharmacology, and Chronomedicine [in Russian], Vol. 1, Ufa (1985), pp. 63-64.
8. R. A. Bagdasaryan and D. G. Asatryan, "Cosinor analysis of biological rhythms," in: Methodological Recommendations, N. L. Aslanyan (ed.), [in Russian], Inst. Kardiologii Arm. SSR, Erevan (1979).
9. Biological Rhythms [Russian translation], Vol. 1, Mir, Moscow (1984).
10. R. Bishop, Oscillations [Russian translation], Nauka, Moscow (1979).
11. Yu. I. Vitinskii, Solar Activity [in Russian], Nauka, Moscow (1983).
12. N. Ya. Goz, L. M. Malkin, and G. Krauze, "Validity of application of cosinor analysis," in: Problems of Chronobiology, Chronopathology, Chronopharmacology, and Chronomedicine [in Russian], Vol. 1, Ufa (1985), pp. 28-30.
13. F. Grodinz, Control Theory and Biological Systems [Russian translation], Mir, Moscow (1966).
14. V. A. Doskin and N. A. Lavrent'eva, Topical Issues of Preventive Medicine, A Scientific Review [in Russian], VNIIMI, Moscow (1985).
15. I. P. Emel'yanov, The Structure of Human Biological Rhythms in the Process of Adaptation [in Russian], Nauka, Novosibirsk (1986).
16. R. M. Zaslavskaya, Diurnal Rhythms in Cardiovascular Patients [in Russian], Meditsina, Moscow (1979).
17. R. M. Zaslavskaya, S. G. Duda, V. P. Karp, and M. M. Teiblyum, "Application of Watson and Williams tests for comparative statistical analysis of diurnal-rhythm acrophases of physiological parameters," in: Application of Mathematical Methods and Computers in Medical and Biological Research, abstracts of All-Union Symposium [in Russian], Leningrad (1982), pp. 44-45.
18. R. M. Zaslavskaya, M. G. Varshitskii, and M. M. Teiblyum, "Clofelin chronotherapy of hypertonic patients," Klin. Med., **64**, No. 1, 45-49 (1986).
19. R. M. Zaslavskaya, M. G. Varshitskii, and M. M. Teiblyum, "Anaprilin chronotherapy of hypertonic patients," Sov. Meditsina, No. 6, 9-11 (1986).
20. R. M. Zaslavskaya, N. L. Aslanyan, and I. E. Ganelina, "Chronobiological aspects of the pathology of the cardiovascular system," in: Chronobiology and Chronomedicine [in Russian], Meditsina, Moscow (1989), pp. 213-236.
21. R. M. Zaslavskaya, Chronodiagnosis and Chronotherapy of Cardiovascular Diseases [in Russian], Meditsina, Moscow (1991).
22. V. P. Kaznacheev and L. P. Mikhailova, Bioinformation Function of Natural Electromagnetic Fields [in Russian], Nauka, Novosibirsk (1985).
23. Yu. G. Kaminskii, Diurnal Rhythms in Metabolism [in Russian], Nauchnyi Tsentr Biologicheskikh Issledovanii AN SSSR, Pushchino (1987).
24. V. P. Karp, "Requirements from mathematical analysis of chronobiological data," in: Problems of Chronobiology, Chronopathology, Chronopharmacology, and Chronomedicine [in Russian], Vol. 1, Ufa (1985), pp. 33-34.
25. V. P. Karp and G. S. Katinas, "Mathematical methods for the study of biorhythms," Chronobiology and Chronomedicine [in Russian], Meditsina, Moscow (1989), pp. 29-45.
26. G. S. Katinas, L. V. Ermolina, and A. V. Martynikhin, "'Kosinor-Spektr KS' software: algorithms and programs," Inform. Byull., No. 4 (67) (1985).
27. F. I. Komarov, É. N. Chirkova, L. S. Suslov, and V. V. Nemov, "Relationship of annual biorhythms of the number of leukocytes in the peripheral blood of healthy people with heliogeophysical rhythms," Voenno-Meditsinskii Zh., No. 3, 27-32 (1987).
28. F. I. Komarov, É. N. Chirkova, L. S. Suslov, and others, "Biorhythmological principles of prediction of monthly fluctuations of the concentration of leukocytes in the blood of healthy people," Voenno-Meditsinskii Zh., No. 6, 29-35 (1987).

29. F. I. Komarov, É. N. Chirkova, L. S. Suslov, and others, "Relationship of annual biorhythms of the concentration of erythrocytes in the peripheral blood of healthy people with annual rhythms of solar activity variation," Kosmicheskaya Biologiya i Aviakosmicheskaya Meditsina, No. 4, 60-62 (1990).
30. É. M. Krishchan, "Application of approximation methods for detection of sinusoidal rhythms," in: Problems of Chronobiology, Chronopathology, Chronopharmacology, and Chronomedicine [in Russian], Vol. 1, Ufa (1985), pp. 36-37.
31. P. O. Mikheev, "On the analysis of experimental data by the cosinor method," in: Modern Aspects of Biorhythmology [in Russian], Inst. Druzhby Narodov, Moscow (1987), pp. 143-146.
32. F. Moses and Nam Hai Chua, "Light switches of genes in plants," V Mire Nauki, No. 6 (1988).
33. N. I. Moiseeva and R. E. Lyubitskii, The Effect of Heliogeophysical Factors on the Human Organism [in Russian], Leningrad (1986).
34. N. I. Moiseeva and L. I. Nikitina, "Chronotherapy as a method of optimizing medication," Sov. Meditsina, No. 10, 110-112 (1985).
35. M. M. Musin, I. G. Zhurbenko, and T. K. Breus, "An integrated mathematical approach to detection of biorhythms," Reprint No. 1024, Inst. Kosmicheskikh Issledovanii, Moscow (1985).
36. M. M. Musin, "The phenomenon of acrophase 'drift', variability of the biorhythm period, and methods of their investigation," in: Problems of Chronobiology, Chronopathology, Chronopharmacology, and Chronomedicine [in Russian], Vol. 1, Ufa (1985), pp. 39-40.
37. Yu. M. Nikitin, É. N. Chirkova, and V. V. Nemov, "A mathematical method for detection of biological and heliogeophysical rhythms of various frequencies," Dokl. Akad. Nauk SSSR, **290**, No. 6, 1347-1351 (1986).
38. G. N. Okuneva, Yu. A. Vlasov, and L. T. Sheveleva, Diurnal Rhythms of Gas Exchange and Blood Circulation in Man [in Russian], Nauka, Novosibirsk (1987).
39. I. E. Oranskii, Natural Therapeutic Factors and Biological Rhythms [in Russian], Meditsina, Moscow (1988).
40. A. G. Ponomareva, E. G. Shekhter, and L. A. Fomina, "Predicting exacerbation of cardiovascular diseases from the patient's biorhythm curve," Zdravookhranenie Rossiiskoi Federatsii, No. 10, 11-13 (1982).
41. M. G. Serebrennikov and A. A. Pervozvanskii, Detection of Hidden Periodicities [in Russian], Nauka, Moscow (1965).
42. F. Halberg, "Chronobiology," Kibern. Sb., Novaya Seriya, No. 9, 189-247 (1972).
43. M. K. Chernyshev, "Models and methods of mathematical biorhythmology in the study and conservation of the biosphere," in: Modern Issues in the Study and Conservation of the Biosphere, Vol. 2: Living Systems Under External Influences [in Russian], Gidrometeoizdat, St. Petersburg (1992), pp. 359-370.
44. A. L. Chizhevskii, Terrestrial Echo of Solar Storms [in Russian], Moscow (1976).
45. É. N. Chirkova, Yu. M. Nikitin, N. G. Serebryakov, and K. K. Kuznetsova, "Detection of hidden periodicities in low-frequency oscillations of some immunological and biochemical characteristics of blood in normal cases and in rabbits with chronic immunization," in: Mathematical Theory of Biological Processes, Proc. 1st All-Union Conf. On Mathematical Methods in Biology [in Russian], Kaliningrad (1976), pp. 355-357.
46. É. N. Chirkova, L. S. Suslov, and V. V. Nemov, "Mathematical model of long-range forecasting of oscillations of immunological characteristics of blood and its program implementation," Kibernetika, No. 4, 103-108 (1987).
47. É. N. Chirkova, M. M. Avramenko, O. A. Nechitailo, and V. V. Nemov, "Phase coordination of rhythms of solar activity variation and monthly biorhythms of variation of cholesterol concentration in blood serum of rabbits," Byull. Éksp. Biol. Med., No. 3, 340-345 (1988).
48. É. N. Chirkova, V. A. Egorov, and Yu. M. Nikitin, "Analysis of some mathematical methods for detection of biorhythms for chronodiagnosis and chronotherapy of cardiovascular diseases," Kardiologiya, No. 10, 72-77 (1990).
49. É. N. Chirkova, L. S. Suslov, Z. P. Klyueva, and others, "Coordination of intra-annual rhythms of the variation of hemoglobin concentration in human blood with cosmic rhythms," in: Modern Issues in the Study and Conservation of the Biosphere, Vol. 2: Living Systems Under External Influences [in Russian], Gidrometeoizdat, St. Petersburg (1992), pp. 21-27.
50. É. N. Chirkova, "Frequency and phase coordination of solar activity rhythms with biorhythms of blood in healthy patients and with wave periods of planets in the solar system," in: Cycles of Natural Processes, Hazardous Phenomena, and Ecological Forecasting [in Russian], No. 2, AEN Rossii, Moscow (1992), pp. 32-38.

51. É. N. Chirkova, L. N. Aloyants, and A. D. Deev, "Frequency and phase coordination of solar activity rhythms and wave periods of planets in the solar system with biorhythms of arterial pressure in middle-aged males," ZhRFM, No. 1-6, p. 116-139 (1993).
52. É. N. Chirkova, "Wave nature of gene activity regulation. The living cell as a photon computer," Usp. Sovrem. Biol., **114**, No. 6, 659-678 (1994).