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CORRELATIONS BETWEEN PHYSIOLOGICAL PARAMETERS AND PATHOLOGICAL PROCESS

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By employing a method of correlation adaptometry to great amount of medical experimental data two new effects are observed. 1 - the increase of correlations between physiological parameters for groups of people with slight diseases or on the stage of remission when compared with healthy ones. 2 - the effect of decrease of physiological parameters correlations when disease becomes heavier or people have exacerbation. These effects are simulated by ecologo-evolutional model. Besides that the system of equations simulating the dynamics of adaptation is written in Appendix.

Development of new areas, in particular regions of Extreme North, caused great migration of population to these regions. Changes in mode of life and environment increase adaptational strain [1, 2, 3]. Therefore, it is very important to estimate the degree of this strain. One of the methods of such estimation was proposed by A. N. Gorban and Ye. V. Smirnova and was called as a method of correlation adaptometry [4, 5].

This method is based on the effect of elevating of the correlation level between physiological parameters of healthy people with the increasing of adaptation load. The effect was qualitative explained by means of ecology-evolutional model (in the following we shall refer to this model as "factors- resource- selection ") [4, 5, see also previous paper in this issue]. This model is grounded on the basis of optimum principles in biology [7, 8, 9, 10, 11, 12].

It was also noticed in [6, 13] that there is a certain relation between the degree of correlations between physiological parameters and the level of sick rate. The [14] and the present paper are devoted to elaboration of this relation.

This paper consists of three sections. The first section contains the descriptions of indices of correlatedness of physiological parameters. The second section goes over experimental results. The third section of our paper is dealing with. theoretical explanation and discussion of these results.

1. Indices of Correlatedness

For the sake of completeness we give summary of indices of correlations between the physiological parameters [15, 5]. Experimental data are represented by data matrix **X**$(n \times m)$, so that x_{ij} equals to the value of j-th parameters of i-th man. The matrix **Z**$(n \times m)$, so that $z_{ij} = (x_{ij} - \bar{x}_j)/s_j$ is called as standard form of data matrix **X**. Here, $\bar{x}_j = \frac{1}{n} \sum_{i=1}^{n} x_{ij}$ and $s_j^2 = \frac{1}{n} \sum_{i=1}^{n} (x_{ij} - \bar{x}_j)^2$. Matrix of pair correlations **R**$(n \times m)$ (or simply correlation matrix) is given as $R = \frac{1}{n} Z^t Z$.

All indices of correlatedness we obtain from the correlation matrix **R**.

1. Weight of correlation graph **G**.

$$G = \sum_{\substack{i \neq j \\ |r_{ij}| \geqslant \alpha}} |r_{ij}|$$ i. e. **G** is a sum of absolute values of correlations of "strongly connected" parameters (in our investigations α is about 0. 5).

2. Functional parameters of the spectrum of correlation matrix: $f_2(\Lambda)$, $f_3(\Lambda)$ and $f_6(\Lambda)$.

$$f_2(\Lambda) = \sum_{j=1}^{n} \lambda_j^2$$

$$f_3(\Lambda) = \lambda_1 / \lambda_k$$

$$f_6(\Lambda) = \sum_{j=2}^{n} (\lambda_{j-1} / \lambda_j),$$ where $\Lambda = \{\lambda_1, \lambda_2, \ldots, \lambda_m\}$ - eigen - values. of $R(m \times m)$ and $\lambda_1 \geqslant \lambda_2 \geqslant \quad \geqslant \lambda_k > \lambda_{k+1} = \lambda_{k+2} = \quad = \lambda_m = 0$.

3. Number of main components **l**.

l is defined by $\frac{1}{m} \sum_{j=1}^{l} \lambda_j \geqslant 0.95$, $\frac{1}{m} \sum_{j=1}^{l-1} < 0.95$.

2. Experimental Data

This section considers change of correlations between physiological parameters in presence of different diseases: a) ARD (acute respiratory disease), b) bronchitis and pneumonia, c) different forms of chronic bronchitis.

A) Comparative analysis of correlations between the lymphocyte metabolism indices of healthy and frequently heaving ARD inhabitants of Extreme North and middle latitudes of Siberia [6, 13].

There were investigated 183 men at the age 18-45 years, inhabiting in Krasnoyarsk and Norilsk. All people were divided into four groups in accordance with following qualitative signs: 1) residence - regions of middle latitudes of Siberia (Krasnoyarsk) and Extreme North (Norilsk); 2) frequency of cold diseases - frequently or long being ill and practically healthy people. Twenty indices of metabolism were analyzed. There were fulfilled bioluminiscence definition of activities glucose- 6 phosphatdehydrogenase, glyserol- 3 -phosphatdehydrogenase, lactatdehydrogenase, malatdehydrogenase, malatdehydrogenase NAD(P) and concentration of ATP. Besides, the containing of catecholamines and serotonines in leukocytes of pericardial blood were established by fluorescent method. For all the data we carried out all calculations used in the method of correlation adaptometry (see section 1).

Comparative analyses of correlatedness extent between lymphocyte metabolism parameters allows us to make following conclusions:

1) The weight of correlation graph of newly come inhabitants of Extreme North is greater than one of inhabitants of mid-latitude of Siberia (Fig. 1).

2) The weight of correlation graph of frequently and long being ill people is greater in comparison with the one of practically healthy people from the same region.

3) The difference between correlation graph weight, that caused by difference in ecological conditions is greater than the one caused by diseases influence.

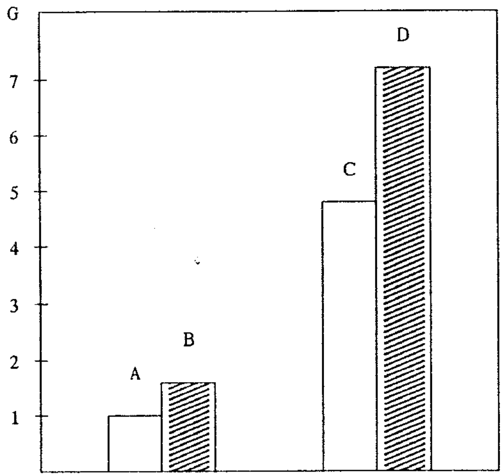

FIG. 1 The correlation graph weight for the lymphocyte metabolism intra cell indices:

A - Krasnoyarsk, healthy people;

B - Krasnoyarsk inhabitants with frequent ARD illness;

C - Norilsk, healthy people;

D - Norilsk inhabitants with frequent ARD illness.

4) The behavior of all other indices of correlatedness (functional parameters $f_2(\Lambda)$, $f_3(\Lambda)$ and $f_6(\Lambda)$) and the number of main components 1 is similar to the one of correlation graph weight (see fig 2).

Therefore, ARD can be considered as additional extreme factor elevating adaptational load visible even in extreme climatogeographical conditions of Norilsk. Thus, the analysis results confirm that in the conditions of strong adaptational loads the level of correlatedness between the physiological parameters reflects adaptational strain extent.

B) Comparative analysis of correlations between the indices of the lipid metabolism in the presence of bronchitis and pneumonia [16, 13].

There were observed 63 healthy children and 353 ones with acute bronchitis at the age between 1-3 years inhabiting in the regions of Extreme North. The lipids were split into fractions by thin layer chromatography, with prior determination of total lipids by bichromatic method to be follow by densitometry of the chromatography obtained, to estimate the isolated fractions of lipids and phospholipids. There were 14 clinically-laboratory parameters examined: total lipids, phospholipids (PL), free cholesterol (FC), free fatty acids (FFA), triglycerids (TG), cholesterol ethers (CE), lysophospholipids (LP), serine - sphingolicyne (SSL), phosphatidylcholine (PC), phosphatidyl-ethanolamine (PEA) and their rations.

All the children were divided into groups according with following qualitative signs:

1. The stage of basic disease:

1. 1 - healthy children;

1. 2 - children, having bronchitis at the highest stage;

1. 3 - children, having bronchitis (convalescence);

1. 4 - children, having pneumonia at the highest stage;

1. 5 - children, having pneumonia (convalescence).

2. The availability of accompanying diseases:

2. 1 - residual signs of rachitis, exudative diathesis, hypotrophy;

2. 2 - accompanying diseases are absent.

The correlation graph weight **G** and functional parameters f_2, f_3, f_6 were calculated.

Considering the correlatedness between lipid metabolism indices on the different stages of basic disease, we can make some conclusions (Fig. 3):

1) The disease results in appreciable decrease of correlation graph weight both during the arctic day and in the arctic night.

2) The correlatedness is less as disease is heavier (1. 2 → 1. 4; bronchitis → pneumonia).

3) When the state of sick children become better, the correlatedness will increase (convalescence stage).

Besides that we analyzed correlatedness between physiological parameters in the groups of children , having different stages of basic disease both in the presence and absence of accompanying diseases (Fig. 4, 5). For children with health bronchopulmonary system, accompanying diseases lower the level of correlatedness between physiological parameters. For children with pathology of bronchopulmonary system, accompanying diseases usually lower level of correlatedness too. It is true for all indices of correlatedness.

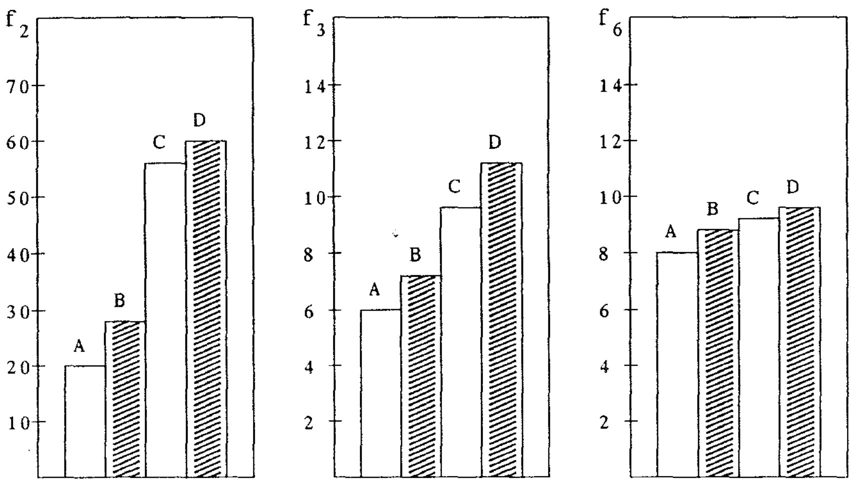

FIG 2. The functional parameters of correlation matrix spectrum $f_2(\Lambda)$, $f_3(\Lambda)$, $f_6(\Lambda)$:

A - Krasnoyarsk, healthy people,
B - Krasnoyarsk inhabitants with frequent ARD illness ;
C - Norilsk, healthy people;
D - Norilsk inhabitants with frequent ARD illness.

Thus, we obtain a new qualitative picture: the correlatedness between physiological parameters decreases when disease is in the highest stage and increases in recovery. The accompanying diseases reduce correlatedness.

C) Comparative analysis of correlations between physiological parameters on the different stages of chronic nonspecific bronchitis [17, 13].

Examination of 136 men, inhabitants of Extreme North having chronic obstructive bronchitis was carried out. The tested groups consists of 117 men, inhabitant in Krasnoyarsk.

People with chronic obstructive bronchitis (COB) divided into two groups according to clinical course of exacerbation. The first group contained patients having COB with bronchospastic syndrome in the acute stage (BRON), the second group contained patients having COB with signs of inflammation (INTOC). Besides, there was the third group of people with COB in the remission stage (POL).

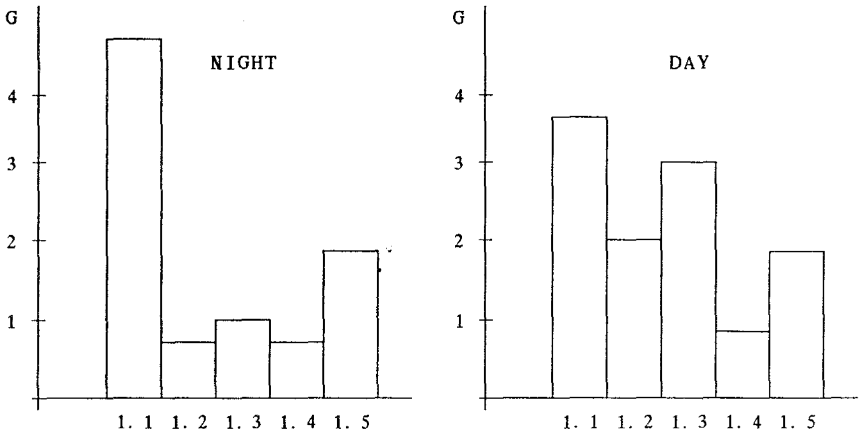

FIG. 3. The correlation graph weight in the groups with the different stages of the basic disease.

1. 1 - healthy children;
1. 2 - children with the highest stage bronchitis;
1. 3- children with bronchitis (convalescence);
1. 4 - children with the highest stage pneumonia;
1. 5 - children with pneumonia (convalescence).

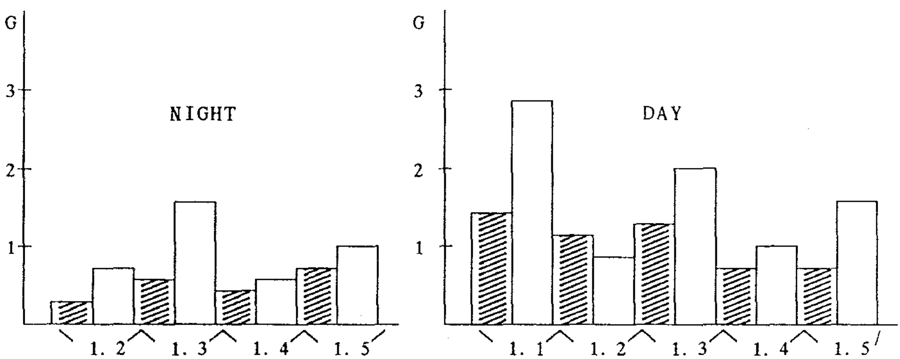

FIG. 4 The correlation graph weight in the groups with the different kinds of basic disease in case:

1 - in the presence of accompanying diseases;
2 - the accompanying diseases are absent.

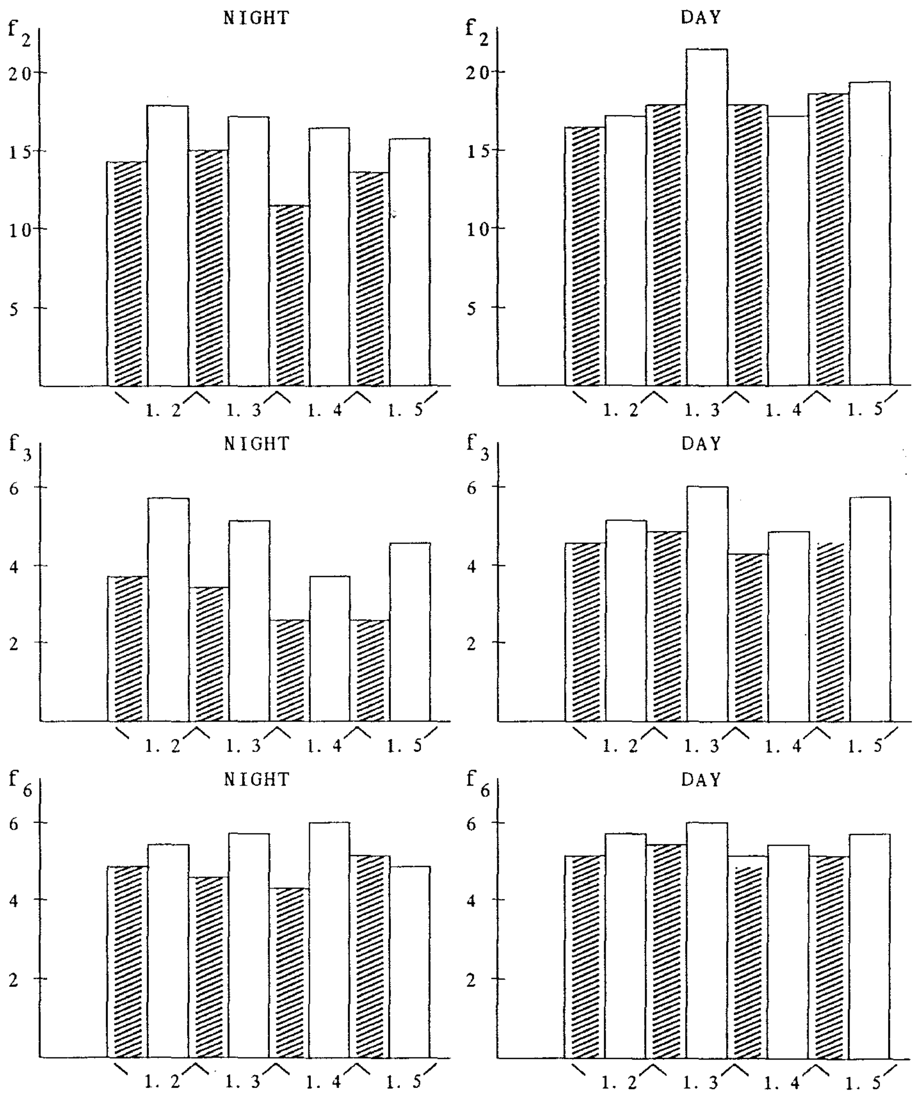

FIG. 5 The functional parameters of correlation matrix spectrum - $f_2(\Lambda)$, II - $f_3(\Lambda)$, III - $f_6(\Lambda)$ at difference stage of basic disease.

1 - in the presence of accompanying diseases;
2 - the accompanying diseases are absent.

In all these groups the functional activity of peripheral blood cells and metabolic activity of alveolar macrophages were determined. We analyzed 24 physiological parameters as: activity of different lymphocyte enzyme, some indices of peripheral blood state, activity of macrophage enzymes and functional state of granulecytes. Comparative analyses of clinical courses of these obstruction mechanisms permit to make a conclusion, that the COB with bronchospastic compound is more serious form of chronic bronchitis than the COB with signs of inflammation. In this case frequent exacerbation, reducing of remission time, durable dyspnea, cough and e. t. c. were observed.

Therefore, we dispose values of correlatedness indices correspondently with disease extant (Fig. 6, 7). We obtain pictures which are similar to previous ones: more heavy form of disease degree of correlatedness. In addition, extreme ecological conditions of Norilsk lower correlations graph weight and functional parameters f_2, f_3, f_6 for any kind of exacerbation course of chronic bronchitis.

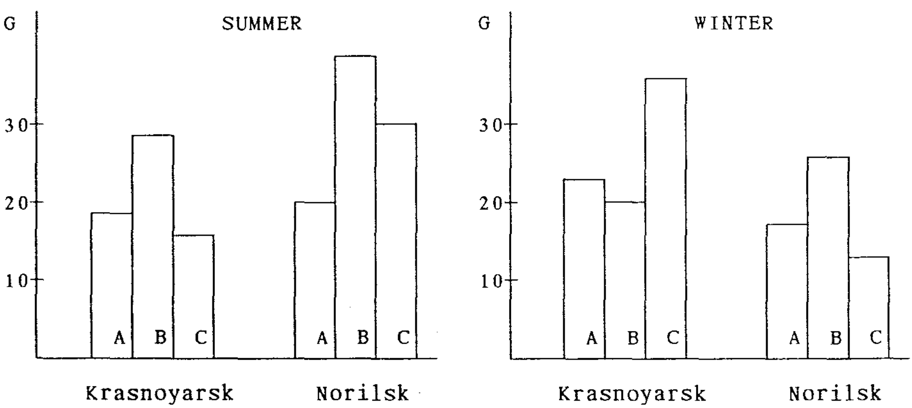

FIG. 6 The correlation graph weight G for the people with different mechanisms of exacerbation COB:

A - COB with bronchospastic syndrome;
B - COB with signs of inflammation;
C - COB without exacerbation.

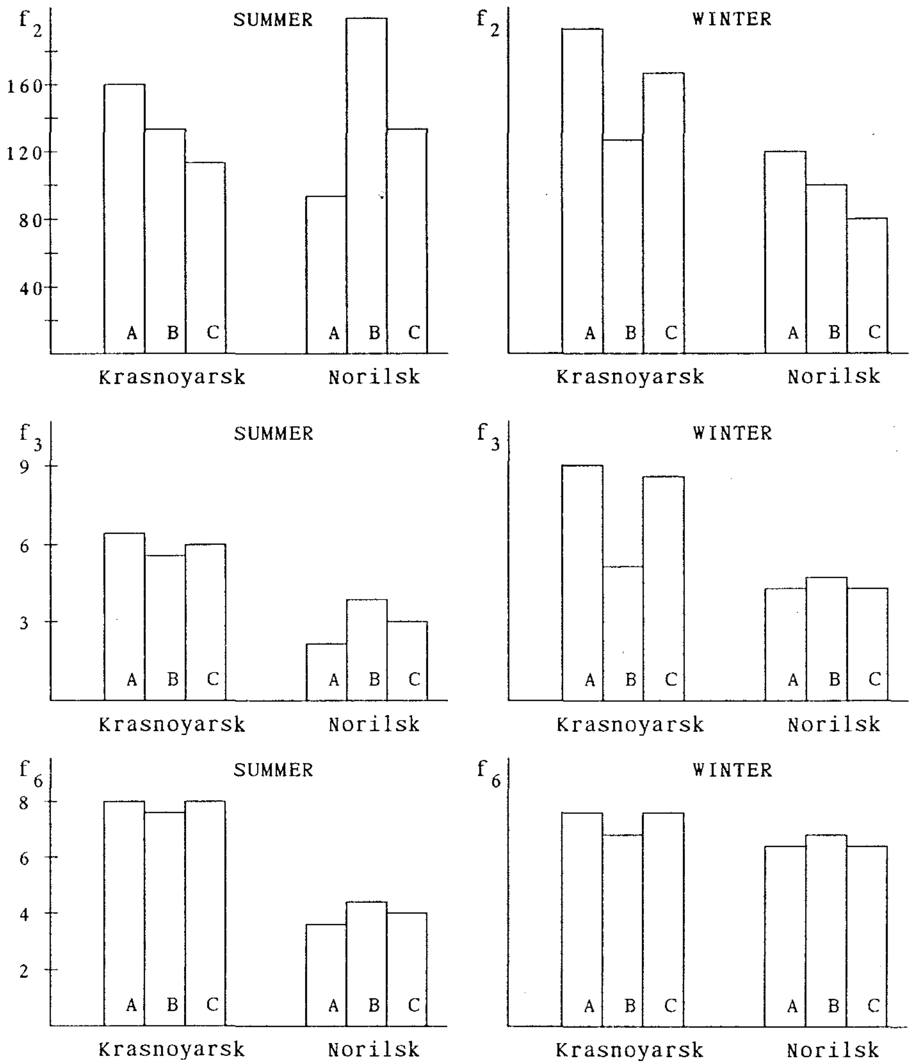

FIG. 7 The functional parameters of correlation matrix spectrum I – $f_2(\Lambda)$, II – $f_3(\Lambda)$, III – $f_6(\Lambda)$ for the people with different mechanisms of exacerbation COB:

A – COB with bronchospastic syndrome;
B – COB with signs of inflammation;
C – COB without exacerbation.

Thus, considering the different kinds of exacerbation of the same disease and different stages of the pathological process, we obtain new interest effects. One of them consists in reducing of correlations between the physiological parameters during disease intensification. In this case accompanying disease and strained ecological conditions give additional reducing of correlatedness indices. The other effect is that for healthy people or people with slight diseases (remission stage, stage of convalescence e. t. c.) the influence of additional factors increases the level of correlations between the physiological parameters.

3. Model "Factors-Resource-Selection" and it's Generalization

It was shown in [5, 18] that effect of elevating of the level of correlatedness between physiological parameters can be qualitatively understood in the framework of the model "factors-resource-selection" (FRS). We remind that the essence of the effect is that the degree of correlatedness between physiological parameters of some group of people appeared in new environment decreases in the course of adaptation to these new conditions (about the choice of measurable parameters see [13] and below). Model FRS in its simplest form can be expressed as follows: extreme conditions (conditions of environment) are represented by the set of nonnegative numbers (factors) $f_1, \ldots, f_n$ so, that the values $f_1=f_2=\ldots=f_n=0$ correspond to the optimum (see below). For example as a factors concentrations of poisons in atmosphere, absolute value of difference between average-year temperature and some favorable (see below) one e. t. c. can be taken. The ability of organism to adaptation is set by number $\mathbf{R}>0$ (resource of adaptation). The process of adaptation is considered as optimization (maximization) of some functional

$$\mathbf{K} = \Phi(\tilde{f}_1-\alpha_1 r_1, \ldots, \tilde{f}_n-\alpha_n r_n) \tag{3. 1}$$

by means of changing of arguments $r_i \geqslant 0 \quad \forall\ i$.

The argument r_i obey the condition $\sum_{i=1}^{n} r_i \leqslant R$ i. e. the model describes the redistribution of the resource of adaptation $\mathbf{R}$ between factors with the aim of compensation of negative influence of the factors on **the** organism. In (1) $\alpha_i>0$ **are** factor compensation effectiveness and $\tilde{f}_i$ is factor f_i after normalization (all $\tilde{f}_i$ i are expressed in some common scale). Thereafter, we omit wave over f_i. About Φ, it is supposed that Φ is monotonically decreasing function in every direction:

$$\frac{\partial\Phi}{\partial f_i} \leqslant 0 \quad i \tag{3.2}$$

(arguments of Φ are nonnegative, therefore Φ has a maximum in $f_i=0$ - optimal conditions).

Biological sense of functional was discussed carefully in [19]. It differs when populations are considered during periods of different durations. When the time of observation is shorter than average lifetime of individual organism, it can be considered as mortality (with sign minus i.e. as **R** s higher, the mortality is smaller). The effect of elevating of the level of correlations between physiological parameters can be obtained in the assumption of simplest form of Φ:

$$\Phi(x_i) = -\max\ (f_i - \alpha_i r_i)\ ,\quad x_i = f_i - \alpha_i r_i \quad i=1,\dots,n, \tag{3.3}$$

$$\text{that is } \mathbf{K} = -\max\ (f_i - \alpha_i r_i)\kappa\kappa \tag{3.4}$$

So, the form of Φ supposes, that factor system under consideration can be regarded as Libig's system. The fact that factor system is Libig's means that the functional (whose maximum is the aim of adaptation in FRS) depends only on such factors, that has a maximum deviation from optimum. Under this assumption it is evident that adaptation leads to smoothing of values $f_i - \alpha_i r_i$ that is to κ depending on the greater number of factors. In turn the dependence on the greater number of factors causes the decreasing of correlatedness between physiological parameters (more details see in [5] and in Appendix).

Let us consider the group of people frequently having ARD. It is evident that it is necessary to regard the fact of having disease in the model FRS by means of introducing some parameter characterizing the duration and extend of disease to the model.

It can be made by two different ways :

1-st way consider parameter characterizing the extent of disease as an additional factor that equals to zero for healthy people.

2-nd way reduces disease to decreasing of adaptational resource proportionally to the extent of disease.

In essence, both in 1 and 2 ways disease reduces the amount of adaptational resource consuming for compensation factors that are not concerned with disease. The difference between 1 and 2 ways is that in 2 way the amount of resource consuming by disease depends only on the disease extent (the value of certain parameter) but in 1 way this amount depends on all other factors in addition to the disease extent. Let's at first discuss the common features of 1 and 2 ways.

Both ways of regarding of disease leads to increasing of physiological parameters correlations under some additional reasonable assumptions.

Let's consider diagrams in Fig. 8.

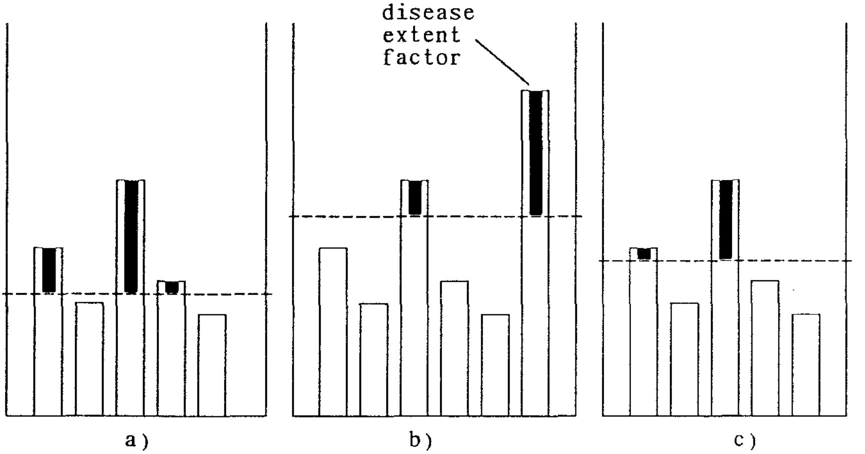

FIG. 8 Relations between the factors and adaptational recourse for
a) healthy people;
b) 1 - st way of the disease regarding;
c) 2 - nd way of the disease regarding.

Columns in this Figure imply the values of factors and besides the compensated part of factors is shared (here for simplicity $\alpha_i=1 \ \forall \ i$). The dashed line is drawn at the height $-\mathbf{k}$ (the model functional $\mathbf{k}=-\max(f_i-r_i) \quad i=1,\ldots,N$).

The level $-\mathbf{k}$ intersects columns that corresponds to factors, which functional $\mathbf{k}$ really depends on. The greater number of such factors the lower level of correlatedness of physiological parameters. Figure 8a) contains the diagram for group of healthy people. The group of frequently having diseases is represented in

Figure 8b) and 8c). The 1 way (additional factor) of regarding the disease is represented in Fig 8b) and 2 way (resource decreasing) is in Fig 8c). We can see from Figures 8a)b)c) that the level of correlatedness lower for healthy people than for people having disease at the same conditions (factors in 8a)b)c) are equal). We have to note that at drawing fig 8b) there was made an additional assumption that factor representing the extent of disease is sufficiently great and comparable with the maximum among other factors.

This assumption (frequent diseases strongly influence to adaptation process) seems to us quite reasonable. Thus, both suggested ways of disease regard in the framework of FRS result in elevating of correlations between physiological parameters of groups of frequently having diseases people as compared with groups of practically healthy people. So this effect (first observed in [6]), has satisfactory explanation in the framework the of FRS model without changes in assumption underlining FRS.

The cause for such differences consists in that in 1 way the disease extent (expressed in some common for all factors units) is considered as factor and is compared with other factors. Let us consider following model situation. Let we have some strong stress factor (strongest among all other factors including the disease extent factor in 1 way) acting on the group of people with slight diseases. Due to this stress factor the level -**k** increases in both ways 1 and 2 (see Fig 9). But, in 1 way the share of resource consuming by disease decreases (compare Fig 9a) and 9b)) when in way 2 it remains constant.

Thus if the 1 way is relevant, the presence of the stress factor results in disappearing of external traces of disease (in the sense of aninfluence on the recourse distribution). Such phenomenon is absent when 2 way is relevant and appearing of stress factor only even greater displays the lack of the resource because of the disease. By means of described difference it is possible to define which way is more adequate in some concrete situation under consideration.

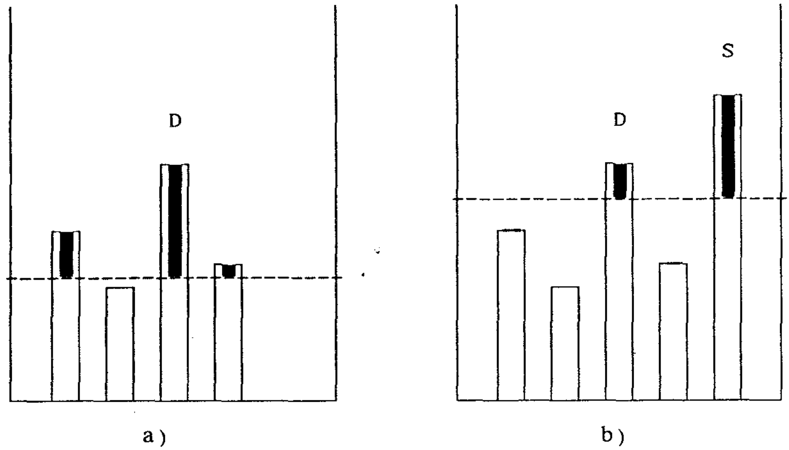

FIG. 9 The difference between 1-st and 2-nd ways of the disease regarding:

a) 1 - st way of the disease regarding;
b) 2 - nd way of the disease regarding.
D - disease extent factor;
S - stress factor.

We should notice here that we don't think one of the ways (1 and 2) of regarding disease in FRS to be correct in all situations. Rather than there are two (may be not quite distinct) groups of disease. One of these groups is described more adequate by 1 way while another - by 2way. We think that this question requires more detailed investigation.

There was observed in [14] and confirmed in present paper (see experimental results) on the base of additional experimental material new effect. This effect consist in decreasing of correlatedness level between physiological parameters when groups of people with heavy diseases are under consideration (the discussion what is the "heavy" disease see below) in comparison with groups of people with "sligth" diseases. This effect can not be explained without essential changes in FRS model.

Let us discuss the limits of employment of the FRS model. There are few assumptions on the ground of FRS. We discuss them successively.

1) The assumption that environment can be described by the set of numbers (factors). This assumption seems to us to be quite general and we shall remain in it's framework in this paper.

2) The assumption that the process of adaptation reduces to distribution of the resource between different factors. We notice here that, introducing several different types of resource as it seems don't change the qualitative conclusions from the model [5].

From the other side, all conclusions can be essentially changed if we assume that the way of resource distribution is changed in the presence of heavy disease.

For example, systems of resource distribution simply stop working or works haphazardly or may be have some inertia (compensation of greatest factor continues even when it is not already maximal one). The description of the inertial systems of resource distribution requires attracting dynamic (depending on time) equations on r_i.

3) The assumption about the existence of the functional **k**.

In the paper of D. Haldane [10] for the process of evolution certain functional was introduced having sense of coefficient of reproduction averaged by several generations. As theof characteristic period of adaptation is much less than the time of generation it would be not quite correct to transfer this concept to adaptation in it's original sense. The empiric fact is, however, that the assumption about the existence of such functional (for adaptation it's sense is something like increasing of the mortality under the influence of environment) is very useful for formalization of the theory and conclusions resulted from it's existence don't contradict to common sense. Therefore in this paper we shall not waive this assumption, although the question about it's foundations needs without any doubts in more serious investigations.

4) The assumption about Libig's system of factors. This assumption is apparently strongest of all and transcending beyond it's framework is unavoidable. In [17] the systems of factors with synergetic groups of factors are discussed . There was shown that the adaptation results in decreasing of the number of actually acting factors in these groups. Thus, when the group of factors is synergetic the correlatedness between physiological parameters at the end of adaptation is higher (in contradiction with Libig's case) than at the beginning. So, if heavily sick people were described by model with synergetic system of factors it would explain the decreasing of correlatedness between their

physiological parameters in comparison with healthy people.

5) The assumption that decreasing of the number of really acting factors causes the increasing of the correlatedness between the physiological parameters.

In this paper we remain in the framework of this assumption. More details about connection between the number of really acting factors and extent of correlatedness between physiological parameters reader can find in Appendix. There is the simplest model of the resource distribution dynamics of that proves the increasing of the number of really acting factors (in Libig's system) results in decreasing correlatedness between the physiological parameters is presented.

Thus, the above discussion of FRS model foundations shows that the rejection from assumption 2, 4 permits to explain the effect of decreasing of correlatedness between physiological parameters of heavily sick people groups when compared with healthy people. There are two ways of such explanation:

1 way - rejection from Libigness of factor system. Great increasing of one of the factors for example the extent of disease factor (the extent of disease is factor here in according with 1 way of regarding disease in FRS) can transcend adaptational system beyond the limits of area when factor system is Libig's one (function Φ beyond the limits of Libig's strongly depends on all it's arguments).

So the factor system becomes synergetic one, **k** depends on all factors and correlatedness between physiological parameters decreases.

To be more detailed let us conspire following "phase diagram" (for the sake of simplicity we confine ourself by two factors system - see Fig. 10). Here the set of meanings of factors f_1, f_2 is divided into three parts. In part 1 the assumption about Libigness of factor system works. This assumption probably works in some adjacency of optimum (f_1, f_2 are very small see [13]).

Where f_1 and f_2 are greater the area of synergeticness (part 2 of Fig. 10) is situated. And it is evident that the part 3 must exist where organism dies (the area of catastrophic death).

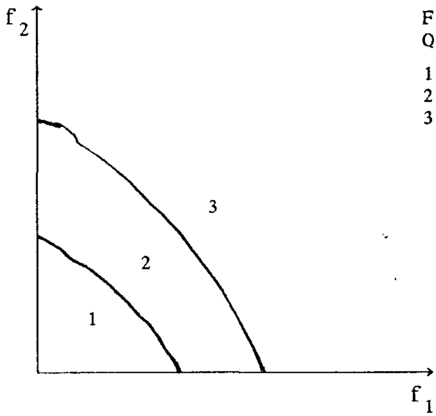

FIG. 10.
Qualitative "f_1-f_2" phase diagram:
1 - the area of Libigness;
2 - the area of synergeticness;
3 - the area of catastrophic death.

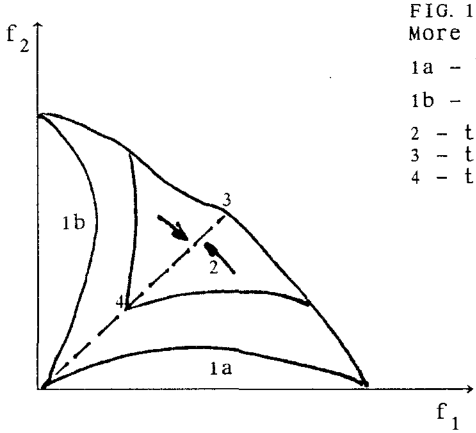

FIG. 11.
More detailed "f_1-f_2" phase diagram:
1a - **k** depends only on f_1
1b - **k** depends only on f_2
2 - the area of synergeticness;
3 - the area of catastrophic death;
4 - the area of transition.

Fig. 10 is very schematic one. We present also our version of more detailed "phase diagram" (see Fig. 11). Here 1a(b) is area where **k** depends only on factor $f_1(f_2)$ (both 1a) and 1b) are the areas of Libig's principle realization). Part 2 - is the area of synergeticness of factor system f_1 and f_2 (arrows point the directions of decreasing **k**). Part 3 - is the area of catastrophic death and part 4 is the area of transition between Libigness and synergeticness that is when **k** depends on both f_1 and f_2 but the influence of f_1 and f_2 is not mutually amplifying.

2 way - the decay of adaptational system. Heavy disease result in that the resource distribution don't go as it should be.

This process of distribution stop corresponding to the aim of maximization of **k**. Because of it **k** becomes dependent on all factors and correlations between the physiological parameters increase(see Appendix).

It is evident that the above two ways have some correspondence with two ways of regarding diseases of light extent in FRS, although this connection haven't to be very strict. As it already was in the case of slight diseases in practice we most probably have both mechanism of correlations decay.

So we have considered the two new effects: effect of elevating of the correlatedness level between physiological parameters of groups of frequently being ill people in comparison with healthy ones (the case of slight disease) and the effect of decreasing of correlatedness between physiological parameters of groups of heavily sick people when compared with healthy people. Both these effects can be represented by following conditional scheme (see Fig. 12).

Here the notion of disease heaviness should be explained. Without any doubts we strongly simplify the reality by characterizing disease by one parameter (disease extent). Actually any disease is characterized by a great number of parameters and reducing them to the single parameter (disease extent) is possible

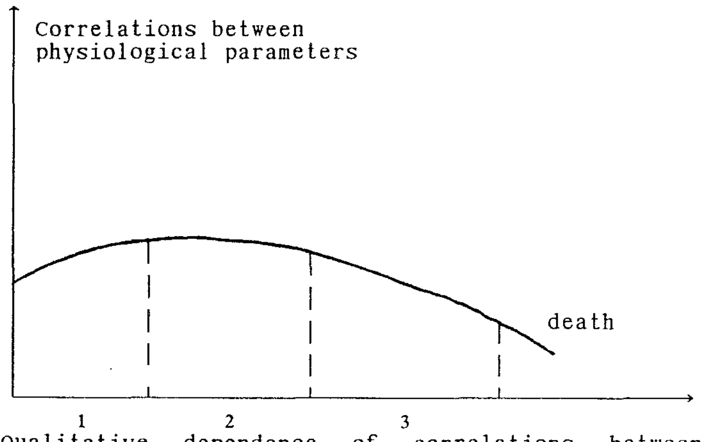

FIG. 12 Qualitative dependence of correlations between the physiological parameters from the disease extent.

1 - region of "slight desease;
2 - transient region;
3 - region of "heavy" desease.

may be only from the point of view organism's adaptational system. There exist methods defining the disease extent but in this paper we don't consider the problem of formalization disease heaviness criterion [13]. We need in the only assumption that such criteria really existand in appraisal of medical experts saying us "sligh" or "heavy" disease we have for this group of people. It isn't senseless because we don't shift all job to medical experts shoulders but only ask them to give appraisal of the disease extent (two-grade-scale: "slight" or "heavy") and than the correlatedness between the physiological parameters itself can serve as a measure of disease extent for the group of people.

In conclusion we notice that constantly used index of correlatedness between physiological parameters is not defined unambiguously (see section 1). The question about correct (adequate and sensitive) choice of this index is considered in [5, 15].

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APPENDIX

THE CONNECTION BETWEEN THE NUMBER OF RELEVANT FACTORS AND THE CORRELATEDNESS BETWEEN THE PHYSIOLOGICAL PARAMETERS

This appendix contains the example of the simplest model of resource distribution dynamics. We show on this model how the increasing of the number of relevant (from which functional **k** strongly depends on) factors results in decreasing of correlatedness between physiological parameters.

First of all let us write the system of differential equations for r_i (the resource consuming for the compensation of i-th factor). This system must ensure that when $t \to \infty$, all r_i

$(i=1,...,n)$ tend to the values which maximize function $\mathbf{k}=\Phi(f_1-r_1,...,f_n-r_n)$

For example

$$\frac{\partial r_i}{\partial t} = \alpha\frac{\partial k}{\partial r_i} - \frac{1}{n}\sum_{j=1}^{n}\frac{\partial k}{\partial r_j}\,\theta(\sum_{k=1}^{n} r_k - R) \qquad (A.1)$$

where α - some constant , $\theta(x) = \begin{cases} 1 & x\geqslant 0 \\ 0 & x<0 \end{cases}$

It is evident from (A.1) that at the extremum $\frac{\partial r_i}{\partial t} = 0$, $i=\overline{1,n}$ and signs in the right hand of (A.1) correspond to maximization of **k** when $t\to\infty$. Besides that the equation (A.1) make sure that

$$\text{if} \qquad \sum_{k=1}^{n} r_k = R,$$

$$\text{then} \qquad \frac{\partial}{\partial t}(\sum_{i=1}^{n} r_i)=0 \qquad (A.2)$$

that is the whole amount of the resource is $r_1+r_2+...+r_n \leqslant R$.

The measured quantities in the method of correlation adaptometry are the different physiological parameters of a man. The values of these parameters are connected with the values of external factors, state of organism and so on in very complicated manner.

In our simple model we consider that the values of physiological parameters are determined by the values of the resource r_i (the set of values r_i is in our model " the state of organism"). So, the correlations between the physiological parameters are determined by the correlations between the resources and if we assume the function of resource → parameters transformation to be quite smooth we can calculate correlatedness between resources instead the one between physiological parameters.

Now we have to understand how to introduce the chance to the dynamic equations (A.1),(A.2). The real scattering of measured parameters is due to many reasons. Among them: the difference between organisms, the difference between the effectivenesses of acting factors on the men in different conditions. Indeed, the effectiveness of external factors action on the men depends on conditions of habitation, kinds of their job, their mode of life and so on.

We consider here only the second reason for parameters scattering. We replace external factors $f_1, f_2, \ldots, f_n$ in (A.1) to $f_1+\xi_1, f_2+\xi_2, \ldots, f_n+\xi_n$, where $\xi_1, \ldots, \xi_n$ - are random quantities describing oscillations of effective external factors from man to man. For simplicity we consider $\xi_1, \ldots, \xi_n$ as normalized and Gaussian:

$$<\xi_i> = 0 \qquad i=1, \ldots, n$$

$$<\xi_i \xi_j> = \delta_{ij} \qquad i, j=1, \ldots, n \qquad \text{(A.3)}$$

Here < > means average by people in the group under consideration.

We shall show now that the system (A.1) - (A.3) describes the increasing of the correlations between r_i in the course of time for the function **k** of Libig's type.

Let us consider the function

$$\mathbf{k} = \varphi\ [\max_i\ (f_i - r_i + \xi_i)] \qquad \text{(A.4)}$$

where φ is monotonically decreasing function. We confine ourselves to the case $i=1,2,3$. We rewrite equation (A.1) for that moment when already $r_1+r_2+r_3=R$ and $f_1-r_1>f_2-r_2>f_3-r_3$:

$$\frac{\partial r_1}{\partial t} = \alpha\left(\frac{\partial k}{\partial r_1} - \frac{1}{3}\frac{\partial k}{\partial r_1}\right)$$

$$\frac{\partial r_2}{\partial t} = -\alpha\frac{1}{3}\frac{\partial k}{\partial r_1} \qquad \text{(A.5)}$$

$$\frac{\partial r_3}{\partial t} = -\alpha\frac{1}{3}\frac{\partial k}{\partial r_1}.$$

From (A.5) we obtain:

$$r_2 = C - \frac{r_1}{2} \qquad \text{(A.6)}$$

$$r_3 = D - \frac{r_1}{2},$$

or with the help of (A.2):

$$r_2 = C - \frac{r_1}{2} \qquad \text{(A.7)}$$

$$r_3 = R - C - \frac{r_1}{2}.$$

It is evident from (A.7) that the number of the main components $l=1$ and we have for correlation matrix R_{ij}:

$$R_{ij} = \frac{<r_i r_j> - <r_i><r_j>}{\kappa(<r_i^2>-<r_i>^2)(<r_j^2>-<r_j>^2)} = \begin{pmatrix} 1 & -1 & -1 \\ -1 & 1 & 1 \\ -1 & 1 & 1 \end{pmatrix} \qquad \text{(A.8)}$$

and for spectrum

$$\lambda_1=3, \lambda_2=\lambda_3=0 \tag{A. 9}$$

From (A. 9) we see that the correlatedness between r_i at one relevant factor f_1 $(f_1-r_1>f_2-r_2>f_3-r_3)$ is maximal.

The evolution of (A. 5) results in $f_1-r_1= f_2-r_2> f_3-r_3$ and instead of (A. 5) we have:

$$\begin{aligned}
\frac{\partial r_1}{\partial t} &= \alpha \left[\frac{\partial k}{\partial r_1} - \frac{1}{3} \left(\frac{\partial k}{\partial r_1} + \frac{\partial k}{\partial r_2} \right) \right] \\
\frac{\partial r_2}{\partial t} &= \alpha \left[\frac{\partial k}{\partial r_2} - \frac{1}{3} \left(\frac{\partial k}{\partial r_1} + \frac{\partial k}{\partial r_2} \right) \right] \\
\frac{\partial r_3}{\partial t} &= -\alpha \frac{1}{3} \left(\frac{\partial k}{\partial r_1} + \frac{\partial k}{\partial r_2} \right)
\end{aligned} \tag{A. 10}$$

Function (A. 4) needs some regularization in the case $f_1-r_1= f_2-r_2$. We suppose that real function hasn't cusps and $\frac{\partial k}{\partial r_1} = \frac{\partial k}{\partial r_2}$ when $f_1-r_1+\xi_1 = f_2-r_2+\xi_2$. Therefore from (A. 10) we obtain:

$$\begin{aligned}
\frac{\partial r_1}{\partial t} &= \frac{1}{3} \alpha \frac{\partial k}{\partial r} \\
\frac{\partial r_2}{\partial t} &= \frac{1}{3} \alpha \frac{\partial k}{\partial r_1} \\
\frac{\partial r_3}{\partial t} &= -\frac{2}{3} \alpha \frac{\partial k}{\partial r_1}
\end{aligned} \tag{A. 11}$$

or

$$\begin{aligned}
\frac{\partial r_1}{\partial t} &= \frac{1}{3} \alpha \frac{\partial k}{\partial r_1} \\
r_2 &= r_1+f_2-f_1+\xi_2-\xi_1 \\
r_3 &= R - 2r_1- (f_2-f_1)-(\xi_2-\xi_1)
\end{aligned} \tag{A. 12}$$

The following depends on concrete form of **k** but from the presence in (A. 12) both ξ_1 and ξ_2 we can see at once that the number of main components l=2 and the correlatedness less than in (A. 9).

We show it for example

$$\mathbf{K} \cong \frac{1}{2}[(f_1-r_1+\xi_1)^2+ (f_2-r_2+\xi_1)^2] \tag{A. 13}$$

when $f_1-r_1+\xi_1=f_2-r_2+\xi_2>f_3-r_3+\xi_3$.

From (A. 12 - A. 13):

$$\begin{aligned}
r_1 &= f_1+\xi_1-C' \exp(-1/3\alpha t) \\
r_2 &= f_2+\xi_2-C' \exp(-1/3\alpha t) \\
r_3 &= R-f_1-f_2-\xi_1-\xi_2+2C' \exp(-1/3\alpha t).
\end{aligned} \tag{A. 14}$$

We suppose that at $t<0$: $f_1-r_1+\xi_1>f_2-r_2+\xi_2$ and (A. 7) works and at $t>0$ (A. 14) works. By sewing (A. 14) and (A. 7) at $t=0$ we have:

$$C' = \frac{1}{3}f_1+\frac{2}{3}f_2-\frac{2}{3}C+\frac{1}{3}f_1+\frac{2}{3}\xi_2. \tag{A. 15}$$

From (A. 15)

$$<<C'\xi_1>> = <C'\xi_1>=\frac{1}{3} \tag{A. 16}$$
$$<<C'\xi_2>> = <C'\xi_2>=\frac{2}{3}$$
$$<<C'^2>> = <C'^2> =\frac{5}{9} .$$

Here $<<AB>> = <(A-<A>)(B-<B>)>$.

We obtain now from (A. 14)-(A. 16) that correlatedness decrease in cours e of time.

Indeed, at $\alpha t<<1$, for example, we have

$$\lambda_1= 3 - \frac{9}{8}\alpha^2 t^2, \lambda_2= \frac{9}{8}\alpha^2 t^2, \lambda_3= 0 \tag{A. 17}$$

And it is evident that $l=2$ and f_2, f_3, f_6 calculated from (A. 9).

Begining from certain moment

$$f_1-r_1+\xi_1=f_2-r_2+\xi_2=f_3-r_3+\xi_3 \tag{A. 18}$$

and (A. 11) stop working and r_1, r_2, r_3 stop changing. From (A. 18) and (A. 2):

$$r_1=\frac{R}{3}+\frac{2}{3}f_1 - \frac{1}{3} f_2- \frac{1}{3} f_3+ \frac{2}{3} \xi_1- \frac{1}{3} \xi_2- \frac{1}{3} \xi_3$$
$$r_2=\frac{R}{3}-\frac{1}{3}f_1+ \frac{2}{3} f_2- \frac{1}{3} f_3- \frac{1}{3} \xi_1+ \frac{2}{3} \xi_2- \frac{1}{3} \xi_3 \tag{A. 19}$$
$$r_3=\frac{R}{3}-\frac{1}{3}f_1- \frac{1}{3} f_2+ \frac{2}{3} f_3- \frac{1}{3} \xi_1- \frac{1}{3} \xi_2+ \frac{2}{3} \xi_3 .$$

We have from (A. 19) $l=3$ and

$$R_{ij}=\begin{pmatrix} 1 & -1/2 & -1/2 \\ -1/2 & 1 & -1/2 \\ -1/2 & -1/2 & 1 \end{pmatrix}, \tag{A. 20}$$

$\lambda_1= \lambda_2= \frac{3}{2}, \lambda_3= 0.$

Thus we see that system (A. 1) ensure increasing of correlations between r_i (and therefore between the physiological parameters) when the number of relevant factors increases in the case of Libig' s factor system.

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