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The model of correlation adaptometry and its use for estimation of obesity treatment efficiency

V. N. RAZZHEVAIKIN* and M. I. SHPITONKOV*

Abstract — Some approaches to mathematical modelling of mechanisms forming the base for methods of correlation adaptometry widely used in biology and medicine are presented. The construction is based on schemes lying in the base of the description of structured biological systems. An example of using the method in estimation of the efficiency of the obesity treatment is given.

1. Statement of the problem

The change in correlations between the physiological parameters of organisms under an external load on the population can be considered nowadays as a sufficiently established empirical fact [5]. The first attempts to construct an approach for explanation of this effect were undertaken in paper [1] of A. N. Gorban' with coauthors. These attempts were based on the usage of the evolution optimality and adaptation principles in polyfactorial conditions, where, along with pure theoretical results, some methods of correlation analysis of particular data were presented with examples. Consideration is based on adaptation models and their analysis with the help of the Haldane extreme principle. The approach we propose here is focused precisely on the mathematical modelling of the variations in correlation characteristics of physiological parameters of the population under a change of external factors, and not any other processes allowing one to give conceptual explanations of such variations. The base of such approach is the concept of a population as a set of individuals distributed in some domain in the space of parameters with appropriate redistribution laws. Thus, the model population is not an integral indivisible object, otherwise it would eliminate the possibility to use a correlation description for it. The population fills some domain in the space of parameters (domain of population homeostasis) so that in the absence of external factors there are no correlation dependences between the individuals (this is a naively obvious conjecture). In the presence of external factors, the individuals are shifted toward their resultant, it is clear that such shift increases the correlation.

*A. A. Dorodnicyn Computing Centre of the Russian Academy of Sciences, Moscow 119333, Russia

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In [4], we constructed and justified the diffusion model of correlation adaptometry of the form

$$\partial_t u = a\Delta u - (\mathbf{b}, \nabla u) \tag{1.1}$$

where $u = u(x,t)$, $x = (x_1, \dots, x_n) \in \Omega \subset R^n$, $t \in R_+$, $\nabla = (\partial_{x_1}, \dots, \partial_{x_n})$, $\partial_{x_i} = \partial/\partial x_i$, $\Delta = (\nabla, \nabla)$ is the Laplace operator with respect to x, $(\cdot,\cdot)$ is the scalar product in R^n, $\mathbf{b} \neq 0$ is an n-dimensional vector.

It is assumed that the bounded domain Ω has a sufficiently smooth boundary containing a single point $s(\mathbf{b}) \in \partial\Omega$ such that the vector of the outer normal to the boundary at that point coincides with the vector $\mathbf{b}$ both in its direction and the sign and the whole domain lies on one side of $s(\mathbf{b})$ in the direction $\mathbf{b}$.

Without loss of generality, assume that the orthogonal system of coordinates is chosen in R^n so that $s(\mathbf{b})$ is at the origin and $-x_n$ coincides with the direction of the vector $\mathbf{b}$, so that $\mathbf{b} = -be_n$, where $b > 0$ and e_n is the unit vector in the direction x_n.

Given the impermeability conditions

$$(a\nabla u - \mathbf{b}u, \nu)|_{\partial\Omega} = 0 \tag{1.2}$$

where ν is the normal to $\partial\Omega$, there exists a unique (up to the multiplication by a constant) stationary solution to problem (1.1) of the form

$$u(x) = v(x_n) = v_0 \mathrm{e}^{-bx_n/a}. \tag{1.3}$$

The fact that (1.3) is the solution is checked by its direct substitution into (1.1), (1.2), and the uniqueness follows from the constancy of the sign, which ensures its location in the proper subspace corresponding to the maximal eigenvalue of the operator L determined by the right-hand side of equation (1.1) with boundary conditions (1.2). This operator is self-adjoint and unbounded in the Hilbert space $L_2(\Omega)$ with the scalar product $\langle u, v\rangle = \int_\Omega \mathrm{e}^{-b/ax_n} u(x)v(x)\,\mathrm{d}x$. Its maximal eigenvalue is simple and the corresponding eigenfunction has a constant sign, because it provides the maximum of the form $\langle Lu, u\rangle / \langle u, u\rangle$. The necessity of the sign change in eigenfunctions corresponding to other eigenvalues follows from the orthogonality properties (with respect to the indicated scalar product) of eigenfunctions corresponding to different eigenvalues.

Note that the stationary property of solution (1.3), which also means that the maximal eigenvalues of the operator L equal zero, also implies the stability of this solution up to proportional measurements. In what follows, without loss of generality, we assume $v_0 = 1$. The mathematical model of values measured in problems of correlation adaptometry consists of sets of linear functions

$$\varphi = \sum_{i=1}^{n} \varphi_i x_i, \qquad \psi = \sum_{i=1}^{n} \psi_i x_i \tag{1.4}$$

with a nonzero set of n components, and the model determining the valuable properties of adaptation of statistical characteristics is formed by their correlation coefficients with respect to distribution (1.3):

$$K(\varphi,\psi)=\frac{M[(\varphi-M\varphi)(\psi-M\psi)]}{(M[(\varphi-M\varphi)^2]M[(\psi-M\psi)^2])^{1/2}} \tag{1.5}$$

where

$$M(\varphi)=\frac{\int_\Omega \varphi(x)u(x)\,\mathrm{d}x}{\int_\Omega u(x)\,\mathrm{d}x} \tag{1.6}$$

is the mean value of the function $\varphi(x)$ with respect to the distribution of $u(x)$ in the domain Ω

The aim of this paper is the study of the dependence of expression (1.5) on the parameters of equation (1.1) subject to (1.4).

2. Estimation in the parabolic domain

In the case of the general position in the neighbourhood of the point $s(\mathbf{b})$ the boundary of the domain Ω can be represented in the form $\partial\Omega=\{x:x_n=\sum_{i=1}^{n-1}a_ix_i^2+o(x^2)\}$, where $a_i>0$, $i=1,\dots,n-1$.

The parabolic approximation of the domain Ω at the point $s(\mathbf{b})$ is said to be the parabolic domain of the form:

$$\Omega_p=\Big\{x:x_n\geqslant\sum_{i=1}^{n-1}a_ix_i^2\Big\}. \tag{2.1}$$

The calculation of correlation coefficients (1.5) for distribution (1.3) is performed for domain (2.1); therefore, in this section the integration in (1.6) is performed over the domain Ω_p instead of Ω.

We associate each function φ from (1.4) with the vector $\boldsymbol{\varphi}=(\varphi_1/\sqrt{a_1},\dots,\varphi_{n-1}/\sqrt{a_{n-1}},0)$. The angle between the vectors $\boldsymbol{\varphi}$ and $\boldsymbol{\psi}$ is denoted by $\angle\boldsymbol{\varphi\psi}$.

The following result is valid for parabolic domain (2.1) and functions from (1.4).

Theorem 2.1. (1) *For $b\to\infty$, $\boldsymbol{\varphi}\neq0$, $\boldsymbol{\psi}\neq0$ we have $K(\varphi,\psi)\to\cos(\angle\boldsymbol{\varphi\psi})$;* (2) *for $b\to0$ and $\varphi_n\psi_n\neq0$ we have $K(\varphi,\psi)\to\operatorname{sign}(\varphi_n\psi_n)$.*

Proof. Denote $N=\int_{\Omega_p}u(x)\,\mathrm{d}x$ and $M_{k,\mathbf{l}}=M(x_1^{l_1}x_2^{l_2}\dots x_{n-1}^{l_{n-1}}x_n^k)$, where $\mathbf{l}=(l_1,\dots,l_{n-1})$. If some l_i is odd, then we evidently have $M_{k,\mathbf{l}}=0$. Therefore, only $M_{k,2\mathbf{l}}$ can be of some interest. In particular, assume $M_k=M_{k,\mathbf{0}}$, $M_0=1$. For them we have (here and further $\gamma=b/a$)

$$NM_k=\int_{\Omega_p}x_n^k\mathrm{e}^{-\gamma x_n}\,\mathrm{d}x=\int_0^\infty x_n^k\mathrm{e}^{-\gamma x_n}S(x_n)\,\mathrm{d}x_n$$

where $S(x_n)$ is the $(n-1)$-dimensional volume of the cross-section of the domain Ω_p by the hyperplane $x_n = \text{const}$. If V_{n-1} is the volume of the unit $(n-1)$-dimensional ball, then $S(x_n) = V_{n-1}/Px_n^{n-1/2}$, where $P = (\prod_{i=1}^{n-1} a_i)^{1/2}$.

Since for $\nu > 0$, $\mu > 0$ we always have $\int_0^\infty x^{\nu-1} \mathrm{e}^{-\gamma x}\, \mathrm{d}x = \Gamma(\nu)/\gamma^\nu$, then

$$NM_k = \frac{\Gamma(\nu)V_{n-1}}{\gamma^\nu P}, \quad \nu = k + \frac{n+1}{2}. \tag{2.2}$$

Denote also $M_{0i} = M_{0,2\mathbf{l}_i}$, where $\mathbf{l}_i = (0,\dots,0,1,0,\dots,0)$ (1 stands at the ith place), so that

$$NM_{0i} = \int_0^\infty \mathrm{e}^{-\gamma x_n} \int_{-(x_n/a_i)^{1/2}}^{(x_n/a_i)^{1/2}} x_i^2 S(x_n, x_i)\, \mathrm{d}x_i\, \mathrm{d}x_n \tag{2.3}$$

where $S(x_n, x_i)$ is the $(n-2)$-dimensional volume of the cross-section of the domain Ω_p by the pair of hyperplanes $x_n = \text{const}$, $x_i = \text{const}$. Thus,

$$S(x_n, x_i) = \frac{V_{n-2}(x_n - a_i x_i^2)^{(n-2)/2} a_i^{1/2}}{P}. \tag{2.4}$$

From (2.3) and (2.4) we get

$$NM_{0i} = \mu_i \int_0^\infty \mathrm{e}^{-\gamma x_n} \int_0^{q_i} x^2 (q_i^2 - x^2)^m\, \mathrm{d}x_i\, \mathrm{d}x_n \tag{2.5}$$

where $q_i = \sqrt{x_n/a_i}$, $m = n - 2/2$, $\mu_i = (2a_i^{m+1/2} V_{n-2})/P$.

The inner integral in (2.5) is standard:

$$\int_0^q x^2 (q^2 - x^2)^m\, \mathrm{d}x = q^{2m+s} \int_0^1 y^2 (1 - y^2)^m\, \mathrm{d}y = I_m q^{2m+3}$$

here $I_m > 0$ is found by the change of variables $y = \sin\varphi$. This gives

$$NM_{0i} = \frac{\mu_i I_m}{a_i^{m+3/2}} \int_0^\infty \mathrm{e}^{-\gamma x_n} x_n^{m+3/2}\, \mathrm{d}x_n = \frac{2V_{n-2} I_m}{P a_i \gamma^\nu}(\nu) \tag{2.6}$$

for $\nu = m + 5/2 = (n+3)/2$.

Now calculate the correlation function of vectors (1.4). We have

$$\begin{aligned} M\varphi &= \varphi_n M_1 \\ M\varphi^2 &= \varphi_n^2 M_2 + \sum_{i=1}^{n-1} \varphi_i^2 M_{0i} \\ M\varphi\psi &= \varphi_n \psi_n M_2 + \sum_{i=1}^{n-1} \varphi_i \psi_i M_{0i} \end{aligned} \tag{2.7}$$

because

$$\varphi\psi = (\varphi_i x_i + \cdots + \varphi_n x_n)(\psi_1 x_1 + \cdots + \psi_n x_n) = \sum_{i=1}^{n} \varphi_i \psi_i x_i^2 + \sum_{i \neq j} \varphi_i \psi_j x_i x_j.$$

The terms of the second sum vanish in the integration, because they contain an odd degree of x_i, $i \leqslant n-1$, and the last summand in the first sum is separated with respect to representation (2.7).

In order to calculate (1.5), we obtain

$$\begin{aligned} M(\varphi - M\varphi)^2 &= M\varphi^2 M\varphi)^2 \\ &= \varphi_n^2 M_2 + \sum_{i=1}^{n-1} \varphi_i^2 M_{0i} - \varphi_n^2 M_1^2 \\ &= \varphi_n^2 (M_2 - M_1^2) + \sum_{i=1}^{n-1} \varphi_i^2 M_{0i} \\ M[(\varphi - M\varphi)(\psi - M\psi)] &= M(\varphi\psi) - M\varphi M\psi \\ &= \varphi_n \psi_n M_2 + \sum_{i=1}^{n-1} \varphi_i \psi_i M_{0i} - \varphi_n \psi_n M_1^2 \\ &= \varphi_n \psi_n (M_2 - M_1^2) + \sum_{i=1}^{n-1} \varphi_i \psi_i M_{0i}. \end{aligned}$$

Further, for $\Gamma_l = \Gamma(l/2)$, taking into account $M_0 = 1$ and due to (2.2), we get

$$N = \frac{\Gamma_{n+1} V_{n-1}}{\gamma^{(n+1)/2} P}. \tag{2.8}$$

From (2.2) and (2.8) we get

$$M_k = \frac{\Gamma_{2k+n+1}}{\gamma^k \Gamma_{n+1}}, \quad k \geqslant 0. \tag{2.9}$$

Relations (2.6) and (2.8) imply

$$M_{0i} = \frac{2\Gamma_{n+3} V_{n-2} I_m}{\gamma^{\frac{n+1}{2}} \gamma P a_i} = \frac{2\Gamma_{n+3} V_{n-2} I_m}{\Gamma_{n+1} V_{n-1} \gamma a_i}. \tag{2.10}$$

From (2.9) we get

$$M' = M_2 - M_1^2 = \frac{\Gamma_{n+5}}{\gamma^2 \Gamma_{n+1}} - \frac{\Gamma_{n+3}^2}{(\gamma \Gamma_{n+1})^2} = \frac{\Gamma_{n+1}\Gamma_{n+5} - \Gamma_{n+3}^2}{\gamma^2 \Gamma_{n+1}^2} > 0. \tag{2.11}$$

For $K(\varphi,\psi)$ from (1.5) we obtain

$$K(\varphi,\psi)=\frac{M'\varphi_n\psi_n+\sum_{i=1}^{n-1}\varphi_i\psi_i M_{0i}}{\left[\left(M'\varphi_n^2+\sum_{i=1}^{n-1}\varphi_i^2 M_{0i}\right)\left(M'\psi_n^2+\sum_{i=1}^{n-1}\psi_i^2 M_{0i}\right)\right]^{1/2}} \tag{2.12}$$

Taking into account inequalities (2.10) and (2.11), we can define the vectors $\boldsymbol{\varphi}'=(\varphi_1/\sqrt{M_{01}},\dots,\varphi_{n-1}/\sqrt{M_{0,n-1}},\varphi_n/\sqrt{M'})$ and define $\boldsymbol{\psi}'$ similarly. Then (2.12) is rewritten in the form

$$K(\varphi,\psi)=\frac{(\boldsymbol{\varphi}',\boldsymbol{\psi}')}{\sqrt{(\boldsymbol{\varphi}',\boldsymbol{\varphi}')(\boldsymbol{\psi}',\vec{\psi}')}}=\cos(\angle\boldsymbol{\varphi}'\boldsymbol{\psi}'). \tag{2.13}$$

Since $M_{0i}/M'=\gamma C_i$, where C_i do not depend on $\gamma=b/a$, then the first $n-1$ components vanish in the vectors $\boldsymbol{\varphi}'$ and $\boldsymbol{\psi}'$ for $b\to 0$, and for $b\to\infty$ the last component vanishes. Multiplying the vectors $\boldsymbol{\varphi}'$ and $\boldsymbol{\psi}'$ by an appropriate positive constant (calculated from (2.10)), we get the first assertion of the theorem. The second assertion easily follows from the constructed asymptotics.

Corollary 2.1. For $n=2$ and $b\to\infty$ we have $K(\varphi,\psi)\to\operatorname{sign}(\varphi_1\psi_1)$.

3. Asymptotics for an arbitrary domain

In this section we show how the result obtained for the parabolic approximation of the domain Ω can be extended in the case $b\to\infty$ (or, equivalently, $\gamma\to\infty$) to this domain itself.

Theorem 3.1. *For an arbitrary bounded domain $\Omega\subset R^n$ having a sufficiently smooth boundary the assertion* 1 *of Theorem* 2.1 *is valid.*

Proof. Proof is based on the calculation of estimates of the deviations of $K(\varphi,\psi)$ from (1.5) calculated for the case $b\to\infty$ from the values of its parabolic approximation at the point $s(\mathbf{b})$ obtained in Theorem 2.1. Take $\varepsilon>0$ and consider the two domains $\Omega_1^\varepsilon=\Omega\cap\{x:x_n\leqslant\varepsilon\}$ and $\Omega_2^\varepsilon=\Omega\backslash\Omega_1^\varepsilon$. The corresponding partitioning of the parabolic approximation is denoted by $\Omega_{1p}^\varepsilon=\Omega_p\cap\{x:x\leqslant\varepsilon\}$, $\Omega_{2p}^\varepsilon=\Omega_p\backslash\Omega_{1p}^\varepsilon$. We show that, assuming $\varepsilon\to 0$ and choosing from it a sufficiently large value of b, we can achieve an arbitrarily small difference for each of the summands entering (1.5) calculated over Ω and over Ω_p, and the smallness of (x_n,ε) in the neighbourhood of the point $s(\mathbf{b})$ is achieved due to the closeness of the domains Ω_1^ε and Ω_{1p}^ε, i.e., due to the smallness of their symmetric difference $\Omega_s^\varepsilon=(\Omega_1^\varepsilon\cup\Omega_{1p}^\varepsilon)\backslash(\Omega_1^\varepsilon\cap\Omega_{1p}^\varepsilon)$.

Introduce the notation $I(\Omega, f, \gamma) = \int_\Omega f(x)\mathrm{e}^{-\gamma x_n}\,\mathrm{d}x$. The fact that all the components in the denominator of (2.12) are positive is the determinant factor in our ability to obtain estimates for $\gamma \to \infty$ with an appropriate choice of $\varepsilon \to 0$.

Integrating the expressions $I(\Omega_2^\varepsilon, x_n^k x_i^{2l}, \gamma)$, $I(\Omega_{2p}^\varepsilon, x_n^k x_i^{2l}, \gamma)$, $k, l \in I_+$, and taking into account the boundedness of the domain Ω and the parabolicity of Ω_p, we can estimate $|x_i|$ through $x_n^{1/2}$ and thus obtain upper estimates for them relative to $I(\Omega_p, x_n^k x_i^{2l}, \gamma)$ with the coefficient $(\gamma\varepsilon)^\nu \mathrm{e}^{-\gamma\varepsilon}$, $\nu = k + l$, vanishing for $\gamma\varepsilon \to \infty$.

This follows from the asymptotics of the Gamma function $\Gamma(a, z) \sim z^{a-1}\mathrm{e}^{-z}$ for $z \to \infty$ (see [3]). Concerning the crossed terms vanishing in the integration over the parabolic domain and thus not included into (2.12), those of them not equal to zero can be estimated in their absolute value by combinations of nonzero quadratic terms varying as members of the corresponding sums. The integrals over the domain Ω_s^ε of quadratic terms (and also of crossed ones majorated by them) can be estimated by the corresponding (see above) linear combinations of quadratic terms with a rough coefficient $o(\varepsilon)$ (specificity of the domain Ω_s^ε).

Summarizing all the corrections, we get the final coefficient $(1+o(\varepsilon)+o((\gamma\varepsilon)^{-1})$ for each of the sums entering the denominator in (2.12).

A slightly more difficult situation is that of the numerator in (2.12), in which the presence of summands with different signs is possible. Nevertheless, if this sum does not vanish, considering that all its terms are equal with respect to γ, it can be used for estimation (in this case the estimation coefficients depend on the form of the functions φ and ψ) according to the scheme described above for the integrals of both quadratic and crossed expressions with the same coefficient as above. If this sum is equal to zero, then under the presence of corrections related to the form of the domain the expression of the form $[o(\varepsilon) + o((\gamma\varepsilon)^{-1})]M_z$ stands in its place, here M_z is one of the sums entering the denominator in (2.12). For $\varepsilon \to 0$ and $\gamma\varepsilon \to \infty$ in this case we get $K(\varphi, \psi) \to 0$ exactly as in (2.12).

Note that in all previous arguments we have considered only the sums entering (2.12), but not the expression containing M' as a multiplier. Concerning the latter, first, all above arguments can be applied to them taking into account that $M' > 0$ (in the simpler case without crossed terms), and second, these expressions themselves become not interesting (for $\gamma \to \infty$, due to a higher asymptotics with respect to γ^{-1} compared to the considered sums (see (2.10), (2.11)).

In the end of the proof, note that assuming, for example, $\varepsilon = \gamma^{-1/2}$, we can get the correction coefficient $(1 + o(\gamma^{-1}))$ for the expression in (2.12) that is valid for the domain Ω itself.

4. Obesity treatment

Generally, the criterion of the intensity of the population adaptation to an external exposure is calculated by introducing the correlation estimate for the analyzed parameters by the weight of the correlation graph $G = \sum_{|r_{i,j}| \geqslant 1/2} |r_{i,j}|$. Here $r_{i,j}$ are pairwise correlation coefficients between the measured parameters. It was shown in [6]

Table 1.
The weights of the correlation graphs for the three groups of obesity patients.

Patient group	before treatment	after treatment
group 1	7.29	6.63
group 2	9.93	7.49
group 3	12.99	10.03

that the method of correlation adaptometry gives satisfactory results in estimation of the efficiency of the Vilyui encephalomyelitis treatment by various medicines, where one can judge the efficiency by the weight decrease of the correlation graph after treatment.

We studied treatment efficiency by the method of correlation adaptometry for patients with different degrees of obesity. The study involved 70 patients at the age from 18 to 60 years suffering from obesity of the 1st–3rd degrees. All the patients were divided into 3 groups depending on the degree of obesity and on the character of concominant pathologies. The first group mainly included patients with the first degree of obesity and also the second degree without concominant pathologies. The second group was formed by patients suffering from obesity of the 2nd–3rd degrees with functional abnormalies of various organs and systems of the organism (dyskinetic disorders of the digestive system, hypertension of the 1st degree, asthenic syndrome, etc.). The third group included patients with organic diseases caused by obesity of the 2nd and 3rd degrees (ulcer, hypertension of the 3rd degree, post-infarction and post-insult states, etc.). All patients got the traditional treatment course for 30 days intended for decreasing the body weight and correcting metabolic and organic disorders, including dietotherapy, individual treatment procedures, physio- and hydroprocedures, and symptomatic and pathogenetic pharmacotherapy adequate to the existing pathology. The diets used in the course had a reduced calorie content (1200–1500 kcal) and contained 60–70 g of protein, 60–70 g of fat, 120–150 g of carbohydrates with exclusion of monosaccharides, and restriction of cholesterol, purine bases, and table salt. The treatment of the patients from the 1st group included only dietotherapy, for the 2nd group it additionally prescribed symptomatic medicines, for the 3rd group it included pathogenetic medicamental therapy.

The following characteristics of patients were monitored: body weight, fat mass, meager mass, total water content, and also the content of the urea, creatinine, cholesterol, and triglycerides in the blood. Then the weights of the correlation graphs were calculated $G = \sum_{|r_{i,j}|\geqslant 1/2} |r_{i,j}|$ for the three groups of obesity patients before and after the treatment. The obtained results are presented in Table 1.

The analysis of data from the table shows that the weight of the correlation graph G monotonically increases from group 1 to group 3, i.e., from less ill to seriously ill patients. A similar pattern is observed for patients before and after treatment. With dietotherapy carried out, the weight of the correlation graph G is lower after the treatment than before the treatment, and this is observed for all three groups of patients. In this case the differences between the groups are slightly less evident.

The results obtained here show that the weight of the correlation graph is a sufficiently sensitive indicator in the groups of patients with different degrees of obesity. The estimation of the weights of the correlation graphs gives us ability to perform a simple comparison of different methods of dietotherapeutic treatment and to choose the most efficient ones.

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