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Foreword

This paper introduces a problem of parameterization in mathematical models of immuno-physiological processes. The assumption of similarity allows us to recalculate the model parameters for a given body through known parameters for the so-called basal organism or the "average" for a group of patients. The formal approach to the problem of parameterization and the method of parameter estimation for a given organism are discussed. The respective problems arise from applied motivations that come from biological and medical issues.

PARAMETERIZATION IN MATHEMATICAL MODELS OF IMMUNO-PHYSIOLOGICAL PROCESSES

A.L. Asachenkov[1], I.B. Pogozhev, S.M. Zuev[2]

1. Introduction.

Even though much progress has occurred in the theoretical immunology and mathematical modelling of disease, many problems are still unresolved. One of the essential problem is a parameterization of the disease model for a given patient. That is especially important then we try to use the model for the decision making, for example, choose the individual therapy or forecast of individual disease dynamic. The principle obstacle consists in estimating significant number of model parameters at the beginning of the disease, then the number of observations are not enough yet. To overcome this obstacle the idea about parameterization in the models of immuno-physiological processes was proposed by Marchuk in eighties years and developed by Pogozhev (1988), where the possibility of parameterization was confirmed by experimental data.

For the individual estimation of model parameters, we must have at least m measurements of the state vector, where m is the number of unknown parameters. For example, if we have a possibility to do measurements every day (a dream) we can evaluate the model parameters after m days. If $m \sim 10$, our forecast of disease course loses its significance. Here we discuss an approach for the solution of this problem which is based on the assumption (Pogozhev, 1988) of the micromovements of particles in the liquid media of an organism and their similarity for different bodies. Genuinely, during the immune response T- and B- lymphocytes, macrophages, viral particles, antibody, some organic molecules etc. interact with each other as well as with other cells and molecules of the

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organism. The value of model parameters $\alpha=(\alpha^1,\alpha^2,\ldots,\alpha^m)^T$ may be considered as functional depending on the micromovement intensity. So, we suggest that the difference between the similar organisms is conditioned by the differences in micromovement intensity. Therefore we can use the coefficient of similarity, HL, to recalculate the model parameters for an given patient through a known parameters for the so-called basal organism or "average" for a group of patient.

In this work the formal approach to the problem of parameterization and the method of parameter estimation for the given patient are proposed.

2. The problem of parameter estimation

Consider the disease model in the form

$$\begin{aligned} \frac{d}{dt}x_t &= f(x_t,\alpha), \quad t\in[0,T], \\ x_0 &= c, \quad x_t\in\mathbf{R}^n, \quad \alpha\in\mathbf{R}^m \end{aligned} \tag{1}$$

where $x_t\equiv x(t)$ is a vector of state variables (molecular concentrations, such as antibody, antigen, appropriate lymphokine or other molecular substances, and cellular populations, this might refer to B, T, and macrophage cell lineages etc.),

α is a vector of parameters,

f(.,.) is a vector function so that $\forall\alpha\in D\in R^m$ there exists an unique and asymptotically stable solution of the Cauchy problem (1).

Denote by

$$X_M = \left\{ x_t^i,\ t\in\Theta,\ i=1,2,\ldots,M \right\}, \quad \Theta = \left\{ t_1,t_2,\ldots,t_N \right\}\in[0,T], \tag{2}$$

observed data, where M is a number of patients,

X_M is a trajectories set of state vector, and assume that the vector x_t can be measured

in discrete instants of time $t \in \Theta$.

Example 1. Consider the dynamics of so-called generalized index of patient state severity (GI) [1,2,3], which is described by the equation

$$\frac{d}{dt}x_t = -\alpha x_t, \quad x_0 = 1, \quad t \geq 0, \quad \alpha > 0 \qquad (3)$$
$$x_t \in R^1, \quad \alpha \in R^1.$$

According to this model the decrease in organism damage due to infectious disease, for the patients with favorable disease dynamic, is an exponential in time.The parameter $\alpha > 0$ is an integral characteristic of the recovery process. Any deviation from this regularity suggest an unfavorable disease dynamics. For more detail see Marchuk, Zubikova, Pogozhev and other. If the values of GI in the instant of time $t_1, t_2, \ldots, t_N$ are connected by straight lines we have what we call a trajectory bunch. A typical situation is given on Fig. 1 and 2. One can see that the observed trajectories of GI, X_M, can be considered as a realizations of some random process

$$\tilde{x}_t = \{ \tilde{x}_x(w), \; t \in [0,T], \; w \in \Omega \} \qquad (4)$$

At the same time the model (3) is deterministic. Therefore, the trajectories from X_M do not belong to the set of model solutions. Following Zuev (1988) one make

Assumption 1. Assume that the model (3) describes the process in the average. It means that exists a vector α^* such that

$$x_t(\alpha^*) = E\,\tilde{x}_t = \int_{\Omega} \tilde{x}_t(\omega) dP(\omega), \qquad (5)$$

where $x_t(\alpha)$ is a solution of (3) for $\alpha = \alpha^*$,
and E is an operator of mathematical expectation.

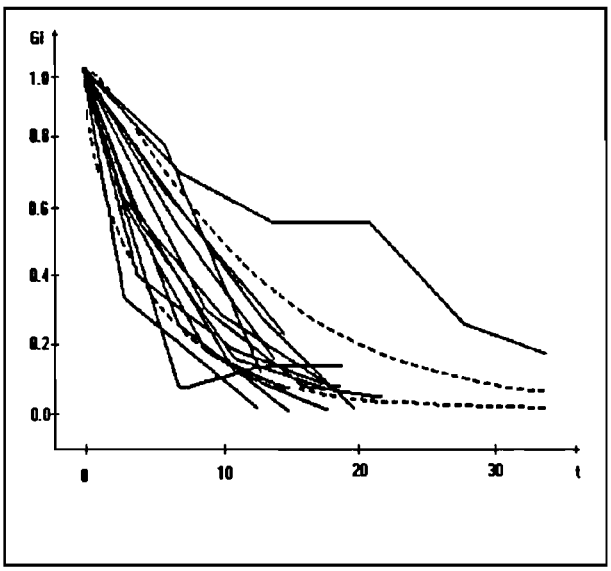

Figure 1 The trajectories of GI for the patients with viral hepatitis treated by drug A (the set X_M^A)(From Zuev, 1988).

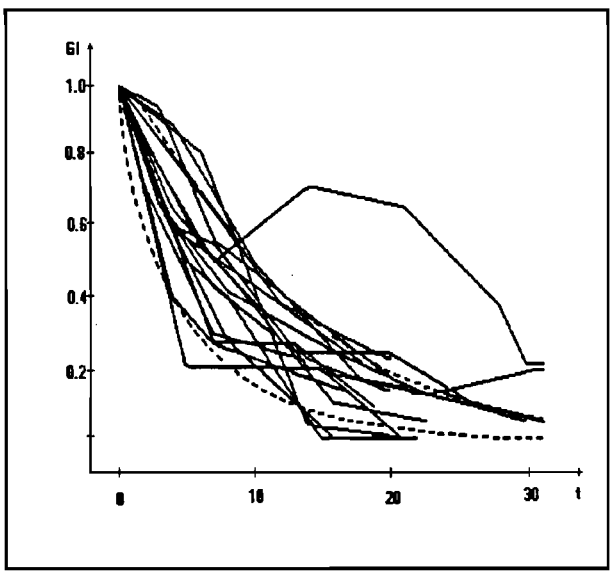

Figure 2 The trajectories of GI for the patients treated by drug B (From Zuev, 1988).

The problem is to estimate α^* by X_M. In the other words, we need to construct the estimate $\alpha_M=\beta(X_M)$ such that

$$\lim_{M\to\infty} \| \alpha_M - \alpha^* \| = 0. \tag{6}$$

2.1. Stochastic model for observed data.

To eliminate the discrepancy between the deterministic model and a random character of observed data we turn to the stochastic model of the process $\tilde{x}_t$ (for detail see Zuev,1988). This model is written in the form

$$\begin{aligned} \frac{d}{dt}x_t^\varepsilon &= f(x_t^\varepsilon,\ \alpha^*+\xi_{q\varepsilon}), \quad t\in[0,T], \quad x_0 = c, \\ \tilde{x}_t &= Qx_t^\varepsilon + \eta_t, \qquad t\in\theta \end{aligned} \tag{7}$$

The first equation is a continues model for the unobserved process x_t^ε, the second one is a measurement model, where Q is a constant $r\times n$ matrix and

$$\eta_t = \{ \eta_t(w),\ t\in\theta,\ w\in\Omega_1\} \tag{8}$$

is a random process, which is a model of measurement error (white noise with discrete time),

$$\begin{aligned} E\eta_t &= 0, \quad E\eta_t\eta_t^T = \Gamma_0, \quad \forall t\in\theta, \\ E\eta_t\eta_s &= 0, \quad \forall s\neq t, \quad s,t\in\theta \end{aligned} \tag{9}$$

A random process ξ_t in R^m has a piece-wise continue with the probability one trajectories, with

$$E\xi_t = 0, \quad E|\ \xi_2\ |^2 < \infty, \quad cov(\xi_t,\xi_{t+\tau}) \underset{\tau\to\infty}{\to} 0, \quad \forall t \tag{10}$$

A small parameter $\varepsilon>0$ has an order hours/day. It means that the random deviations of the trajectories from the deterministic dynamics are short-run compared to time of changing of state vector x_t. In other words, a random disturbances are fast. In [4] was shown that, for a small $\varepsilon>0$, the deviation

$$\delta x_t = x_t^{\varepsilon} - x_t(\alpha^*) \tag{11}$$

can be approximated by the linear model in the form

$$\begin{aligned} \frac{d}{dt}\delta x_t &= f_x(x_t(\alpha^*),\alpha^*)\delta x_t + f_\alpha(x_t(\alpha^*),\alpha^*)\frac{d}{dt}w_t \\ \delta x_0 &= 0, \qquad t\in[0,T], \\ \tilde{x}_t &= Q(\delta x_t + x_t(\alpha^*)) + \eta_t, \quad t\in\theta, \end{aligned} \tag{12}$$

where w_t is a gaussian process with independent increments and

$$Ew_t = 0, \quad Ew_t w_s^T = t\Gamma, \quad \forall t. \tag{13}$$

Here Γ is a matrix of intensity.

2.2. Estimating α^*

Let $\alpha^k \in D \subset R^m$, where D is a closed convex set, be a known initial guess for α^*, then

$$\alpha_M = \alpha^k + \delta\alpha \tag{14}$$

where $\delta\alpha$ is unknown and small as compared to α^k. Using (12) we write the model for the deviations in the form

$$\begin{aligned} \frac{d}{dt}\delta x_t &= f_x(x_t^k,\alpha^k)\delta x_t + f_\alpha(x_t^k,\alpha^k)\delta\alpha + f_\alpha(x_t^k,\alpha^k)\frac{d}{dt}w_t \\ \delta x_0 &= 0, \quad t\in[0,T], \\ \tilde{x}_t &= Q(\delta x_t + x_t^k) + \eta_t, \quad t\in Q, \end{aligned} \tag{15}$$

Here $\delta x_t = x_t^\varepsilon - x_t^k$, and x_t^k is a solution of the system

$$\frac{d}{dt}x_t^k = f(x_t^k,\alpha^k), \quad t\in[0,T], \quad x_0^k = c. \tag{16}$$

The system (15) is linear by unknown parameter and to estimate the vector $\delta\alpha$ we can use the methods of the filtering theory. Let $\tau\in[t_i,t_{i+1}]$, t_i, $t_{i+1}\in\Theta$, and $R(t_{i+1},t_i)$ be fundamental matrix

$$\frac{d}{dt}R(\tau,t_i) = f_x(x_\tau^k,\alpha^k)R(\tau,t_i), \qquad R(t_i,t_i) = I. \tag{17}$$

Then the model (15) can be rewritten in the form

$$\begin{aligned} \frac{d}{dt}\delta x_{i+1} &= R_i\delta x_i + A_i\delta\alpha + W_i \\ \tilde{x}_i &= Q(\delta x_i + x_t^k) + \eta_i, \quad i = 0,1,2,..., \end{aligned} \tag{18}$$

where

$$\begin{aligned} \delta x_i &= \delta x_{t_i}, \\ x &= x_{t_i} \\ R_i &= R(t_{i+1},t_i) \\ A_i &= \int_{t_i}^{t_{i+1}} R(t_{i+1},\tau)f_\alpha(x_\tau^k,\alpha^k)d\tau, \\ W_i &= \int_{t_i}^{t_{i+1}} R(t_{i+1},\tau)f_\alpha(x_\tau^k,\alpha^k)dw_\tau \end{aligned} \tag{19}$$

Here W_i is gaussian random vector (integral of deterministic function by Wiener process) with zero mathematical expectation and a known covariance matrix. The filter equation for this model are well known, see for example [5]. Let $\delta\alpha_k$ be a solution of the filter problem, then for the next iteration we can use

$$\alpha_{k+1} = \alpha_k + \delta\alpha_k \tag{20}$$

This iterative scheme is equivalent one from [6]. Here we need to solve the filter problem on each iteration.

3. Parameterization

A traditional approach to the problem of parameter estimation based on the assumption that the number of observation N must be more than the number of unknown parameters m. If $N > m$, then, generally speaking, there are many well-known algorithms for parameter estimation, for example see [7,8], but then $N < m$, we cannot use any algorithms. Unfortunately that is a typical situation in the medicine then we want to estimate the model parameters at the beginning of therapy. To overcome this obstacle the idea about parameterization of the model parameters was proposed by Marchuk and developed by Pogozhev.

3.1. Basal and Studied organisms.

Consider two organisms, the first one we will call "basal" and a second one "studied" or "given". Suppose that the parameters of the basal organism are known. Consequently we have two models

$$\begin{aligned} &\frac{d}{dt}\underline{x}_t = f(\underline{x}_t,\underline{\alpha}), \quad t\in[0,T], \\ &\underline{x}_0 = \underline{c}, \quad \underline{x}_t\in\mathbb{R}^n, \quad \underline{\alpha}\in\mathbb{R}^m \end{aligned} \tag{21}$$

and

$$\frac{d}{dt}x_t = f(x_t,\alpha), \quad t\in[0,T], \qquad x_0 = c, \quad x_t\in\mathbf{R}^n, \quad \alpha\in\mathbf{R}^m \tag{22}$$

The first one describes a disease process in the basal organism, where $\underline{\alpha}$ is a known, and the second one in the given body, where α is unknown.

Assumption 2. Let the parameters α and $\underline{\alpha}$ be connected by the correlation of similarity

$$\alpha = v(\underline{\alpha},HL) \in R^m, \quad \underline{\alpha} \in R^m, \quad HL \in R^1 \tag{23}$$

where HL is a coefficient of similarity,

v(x,y) is a vector function such what

$$v(\underline{\alpha},1) = \underline{\alpha}. \tag{24}$$

Now, if the function v(x,y) and a vector $\underline{\alpha}$ are known then for estimating of unknown parameter α we must to evaluate only the coefficient of similarity. Clearly, the estimation of the one unknown parameter is a simpler problem.

Explanation. The state variables of the disease model are concentration of interacting particles (cells, molecules and etc.). These particles interact with each others by means of the movement of the liquid media in the organism (blood, lymph). By this means, the micromovement intensity of particles in the liquid media is an important factor influencing on the rate of biochemical processes in the body. Suppose that the model parameters are connected by means of some common factors G

$$\alpha = \tilde{v}(\underline{\alpha},G)\in R^m, \tag{25}$$

where $\underline{\alpha}$ is a known vector of parameters for so-called basal organism or "average" for the given group of patients, and for the evaluation of this parameter we can use the methods which was mentioned above, G is an unknown micromovement intensity of interacting particles.

Denote $\underline{G}$ micromovement intensity of interacting particles for the basal organism, then

$$\alpha = \tilde{v}(\underline{\alpha},G) = v(\underline{\alpha},HL), \qquad HL = \frac{G}{\underline{G}}. \tag{26}$$

So, the parameter HL we can interpret as normalized intensity of the micromovement of interacting particles in the liquid media of the organism. This means that for M patients we have to write M models

$$\frac{d}{dt}x_t^i = f(x_t^i, v(\underline{\alpha},HL^i)), \quad x_0^i = c^i, \qquad i = 1,2,...,M \tag{27}$$

which are distinguished only by the parameter HL.

3.2. Estimating of HL.

Based on the previous results, let us study the problem of HL estimating by

$$X = \{ x_t,\ t\in\theta \}, \quad \theta = \{ t_1,t_2,...,t_N \} \tag{28}$$

According to (26) we have

$$\frac{d}{dt}x_t = f(x_t, v(\underline{\alpha},HL)) \tag{29}$$

or

$$\frac{d}{dt}x_t = F(x_t,\underline{\alpha},HL), \quad t\in[0,T], \quad x_0 = c \tag{30}$$

Appropriate stochastic model for observed data (see Section 2.1) is

$$\begin{aligned} \frac{d}{dt}x_t^\varepsilon &= F(x_t^\varepsilon,\underline{\alpha}+\xi_{t/\varepsilon},HL), \quad x_0^\varepsilon = c, \quad t\in[0,T], \\ \tilde{x}_t &= Qx_t^\varepsilon + \eta_t, \qquad t\in\theta. \end{aligned} \tag{31}$$

Repeating the manipulation from the Section 2.2 we can write the filter problem in the form

$$\begin{aligned} \frac{d}{dt}\delta x_{i+1} &= R_i\delta x_i + A_i\delta H + W_i, \quad \delta x_0 = 0, \\ \tilde{x}_i &= Q(\delta x_i + x_i^k) + \eta_i, \quad i = 0,1,2,..., \end{aligned} \tag{32}$$

For the estimation HL we have an iteration process again: $HL_{k+1}=HL_k + \delta HL_k$. But the analytical form for v(x,y) is an unknown yet. It call us to study the process in question on the microlevel.

4. The system of interacting particles.

Consider a system of interacting particles in the liquid media of the organism. Let us denote for the time t

$$q(t) = (q^1(t),q^2(t),...,q^s(t))^T \tag{33}$$

be generalized coordinates of the interacting particles system and

$$\frac{d}{dt}q(t) = \{ \frac{d}{dt}q_i(t),\ i=1,2,...,s \} \tag{34}$$

be corresponding generalized rate, where s is a number of degrees of freedom in the system of interacting particles. Using the generalized coordinate allows us, in principle, to describe complex progressive and revolving movement of the particles in the liquid media (blood and lymph). The number of degrees of freedom s has the order approximately 10^7 (a number of particles). Now, we can write, formally, the movement equation in the form

$$\frac{d}{dt}q(t) = \psi(\pi(t),\xi_{t/\varepsilon}),\quad t\geq 0,\quad q(0) = q_0, \tag{35}$$

where ψ is a generalized force, which describe the disturbance of the liquid media by the organs and tissues of a living body,

$\pi(t)$ is a disturbances with the characteristic time $\tau_1 \approx 1$ sec., which describe the movement of the liquid media due to heart beat. It should be mentioned that the variables q(t) and $\pi(t)$ have the same characteristic times.

$\xi_{t/\varepsilon}$ is a disturbances with the characteristic time $\tau_0 \approx 10^{-3}$ sec.(average time interval between contacts of the particles).

$\varepsilon > 0$ is a small parameter with order $\tau_0/\tau_1 \sim 10^{-3}$.

The movement of the system due to $\pi(t)$ we will call a trend and due to ξ a random movement. To describe a trend we need to do averaging by the fast variable. Suppose that the following limit exist

$$\bar{\psi}(\pi) = \lim_{T\to\infty} \frac{1}{T}\int_0^T \psi(\pi,\xi_t)dt. \tag{36}$$

More precisely, the following limit takes place, uniformly by τ, for any $\delta > 0$

$$\lim_{T\to\infty} P\left\{\left| \frac{1}{T}\int_{\tau}^{\tau+T} \psi(\pi,\xi_t)dt - \bar{\psi}(\pi)\right| > \delta\right\} = 0 \tag{37}$$

where P{A} is a probability of event A. Thus we have

$$\frac{d\bar{q}}{dt} = \bar{\psi}(\pi(t)) \tag{38}$$

Consider the normalized difference

$$\frac{1}{\sqrt{\varepsilon}}(q(t)-\bar{q}(t)) = \frac{1}{\sqrt{\varepsilon}}\int_0^T [\psi(\pi(s),\xi(s/\varepsilon)) - \bar{\psi}(\pi(s))]ds \tag{39}$$

Theorem 1. Assume that the random process ξ_t with the values in R^m has a piece-wise continues, with the probability one, trajectories and satisfy the condition of strong mixing with the coefficient $\gamma(\tau)$ such that

$$\int_0^\infty \tau[\gamma(\tau)]^{1/5}d\tau < \infty \tag{40}$$

and

$$\sup_{x,t} E \mid \psi(x,\xi_t) \mid^3 < R < \infty \tag{41}$$

Moreover, for all $\tau\in[0,T]$ and $C<\infty$

$$\left| \int_0^\tau [E\psi(\pi(s),\xi(s/\varepsilon)) - \bar{\psi}(\pi(s))]ds \right| < C\varepsilon \tag{42}$$

Then the process

$$\zeta_t^\varepsilon = \frac{1}{\sqrt{\varepsilon}}(q(t) - \bar{q}(t)) \tag{43}$$

as $\varepsilon \to 0$, weakly convergence on [0,T] to gauss process with the independent increments, zero mathematical expectation and covariate matrix

$$\begin{aligned} R &= \{ R^{ij}(t) \}, \\ R^{ij} &= \int_0^t A^{ij}(\pi(s))ds, \end{aligned} \tag{44}$$

where

$$\begin{aligned} A^{ij}(x) &= \lim_{T\to\infty}\frac{1}{T}\int_0^T\int_0^T A^{ij}(x,s,t)dsdt, \\ A^{ij}(x,s,t) &= \\ &= E[\psi^i(x,\xi_s) - E\psi^i(x,\xi_s)][\psi^j(x,\xi_t) - E\psi^j(x,\xi_t)] \end{aligned} \tag{45}$$

This is a simple variant of the Theorem 3.1 from (Ventcel at al, 1975). Using this Theorem, for small ε, we can rewrite of the movement equation in the form

$$\dot{q}(t) = \bar{\psi}(\pi(t)) + \sqrt{\varepsilon}B(t)\frac{d}{dt}w_t \tag{46}$$

where w_t is a wiener process, B(t) is a matrix such that

$$B(t)B^T(t) = R(t) \tag{47}$$

It is a known, that for the diffusion process x_t,

$$dx_t = A(x,t)dt + B(x,t)dw_t \tag{48}$$

the conditional probability density $p(x,t \mid x_0,t_0)$ satisfy to the Fokker-Planch equation

$$\begin{aligned}\frac{\partial}{\partial t}p(x,t) &= -\sum_i \frac{\partial}{\partial x_i}\left[A_i(x,t)p(x,t) \right] + \\ &+ \frac{1}{2}\sum_{i,j} \frac{\partial^2}{\partial x_i \partial x_j}\left[D_{ij}(x,t)p(x,t)\right], \\ p(x,t) &= p(x,t \mid x_0,t_0) \\ p(x,0) &= \delta(x-u(0)),\end{aligned} \tag{49}$$

where A is a shift vector, and

$D=BB^T$ is a diffusion matrix.

Thus for the system (46) we have

$$\begin{aligned}\frac{\partial}{\partial t}p(q,t) &= -\sum_i \bar{\psi}(\pi(t))\frac{\partial p(q,t)}{\partial q_i} + \\ &+ \frac{1}{2}\sum_{i,j} R_{ij}\frac{\partial^2 p(q,t)}{\partial q_i \partial q_j},\end{aligned} \tag{50}$$

By this means, in the system of interacting particles the shift of the particles together with liquid media due to heart beat and etc. is described by the vector $\vec{\psi}$ and the Browian movement by the covariance matrix R(t). It should be noted that for the centralized process

$$u(t) = q(t) - \bar{q}(t) \tag{51}$$

we have

$$\frac{\partial}{\partial t}p(u,t) = \frac{1}{2}\sum_{i,j} R_{ij}\frac{\partial^2 p(u,t)}{\partial u_i \partial u_j}, \tag{52}$$

Now consider the characteristic time τ_2 during which the separate micromovements of particles in the liquid media of the organism must be thoroughly mixed (this is approximately 1 min). It means that for the time interval more than τ_2 we can consider our stochastic process as a stationary stochastic process

$$R(t) = D, \tag{53}$$

where the matrix D is not dependent on time. Under this condition we can start to study the micromovement similarity for two organisms.

4.1. Similarity of the diffusion processes.

Definition 1. Two diffusion processes x(t) and y(t) are called stochastic equivalent if, for any t, their conditional density $p_x(u,t)$ and $p_y(u,t)$ are

$$p_x(u,t) = p_y(u,t) \tag{54}$$

almost everywhere u.

Compare two organisms. The first is a so-called basal one, the parameters of which are known $\underline{\alpha}=(\underline{\alpha}^1,\underline{\alpha}^2,\ldots,\underline{\alpha}^m)^T$. The parameters of the second organism $\alpha=(\alpha^1,\alpha^2,\ldots,\alpha^m)^T$ are unknown. Now we want to investigate its similarity. Let for $t>\tau_2$

$$\begin{aligned} q(t) &= \{\, q_i(t),\ i=1,2,\ldots,s \,\} \\ \underline{q}(t) &= \{\, \underline{q}_i(t),\ i=1,2,\ldots,s \,\} \end{aligned} \tag{55}$$

be generalized coordinates, and

$$\begin{aligned} \frac{d}{dt}q(t) &= \{\, \frac{d}{dt}q_i(t),\ i=1,2,\ldots,s \,\} \\ \frac{d}{dt}\underline{q}(t) &= \{\, \frac{d}{dt}\underline{q}_i(t),\ i=1,2,\ldots,s \,\} \end{aligned} \tag{56}$$

be generalized rate of the system of interacting particles.

Pogozhev's Hypotheses. From the thorough analysis made in [9] it follows that the general vital functions are approximately similar not only in different bodies but in many mammals as well. Organisms are much alike: they consist of cells of approximately equal size, however their total number defines each body size. The sizes of inter-cellular space, blood capillaries, erythrocytes, lymphocytes, macrophages and other particles interacting in the immune process are also almost the same as well as the volume fraction of an organ's liquid media such as blood plasma, lymph, intra-tissue fluid, their temperature and viscosity, concentration of lymphocytes, proteins, glucose and other interacting particles. Vital lung volume and heart mass vary with body mass, and about five systoles fall on one breathing cycle in humans and many other mammals.

The analysis of these and modern physiological data allows us to adopt the following assumption of similarity of interacting particle micromovements in liquid media of the organisms to be compared:

$$\frac{d}{dt}q(t) \doteq \frac{V_b}{\underline{V}_b}\frac{d}{dt}q(t\frac{\tau_c}{\underline{\tau}_c}), \tag{57}$$

where V_b, $\underline{V}_b$ are specific rate of blood circulation (calculated per mass unit);

τ_c, $\underline{\tau}_c$ are average durations of cardiac cycle of an organism in question and the basal one respectively;

symbol $\doteq$ in (57) and below is interpreted as stochastic equivalence of a corresponding random process [10].

A stochastic equivalence means that all available statistical information about the organism in question, which we can obtain in terms of generalized rates dq(t)/dt, we can recalculate using generalized rates for the basal organism. For this purpose we must multiply a generalized rate of basal organism on the quotation $V_b/\underline{V}_b$ and change the time scale $\underline{\tau}_0/\tau_0$. In other words for the different bodes we use its individual "physiological" time. This fact corresponds to main theses from (Shmidt-Nielson, 1987).

Let us now use the idea of transformation (57) and consider the following relation.

$$u(t) \doteq a\underline{u}(bt), \tag{58}$$

where a and b are unknown constant $a,b \in R^1$. To find them let us consider the process

$$\tilde{u}(t) = a\underline{u}(bt). \tag{59}$$

on the time interval more than τ_2 and establish the condition of stochastic equivalence $u(t) \doteq \tilde{u}(t)$. The conditional densities for u(t) and $\underline{u}(t)$ are

$$\begin{aligned} \frac{\partial}{\partial t}p(u,t) &= \frac{1}{2}\sum_{i,j} D_{ij}\frac{\partial^2 p(u,t)}{\partial u_i \partial u_j}, \\ \frac{\partial}{\partial t}\underline{p}(u,t) &= \frac{1}{2}\sum_{i,j} \underline{D}_{ij}\frac{\partial^2 \underline{p}(u,t)}{\partial u_i \partial u_j}, \end{aligned} \tag{60}$$

Now, we can write the analogous equation for the process $\tilde{u}(t)$. Clearly, that

$$\begin{aligned} \tilde{P}(u,t) &= \underline{P}(ax \le u,t) \\ &= \underline{P}(x \le u/a,t) = \underline{P}(u/a,t) \end{aligned} \tag{61}$$

Then from (60) we have

$$\frac{\partial}{\partial t}\tilde{p}(u,t) = \frac{1}{2}\sum_{i,j} a^2 b\underline{D}_{ij}\frac{\partial^2 \tilde{\underline{p}}(u,t)}{\partial u_i \partial u_j}, \tag{62}$$

Using (62) and Definition 1, for the stochastic equivalence of the process u(t) and $\tilde{u}(t)$ the following relation must be hold

$$D = a^2 b\underline{D} \tag{63}$$

Differentiating (58) we have

$$\frac{d}{dt}u(t) = ab\frac{d}{dt}\underline{u}(bt) \tag{64}$$

Comparing previous relations we have

$$b = \frac{\tau_c}{\tau_c}, \qquad a = \frac{V_b\tau_c}{\underline{V}_b\underline{\tau}_c} \tag{65}$$

Thus

$$D = \frac{V_b^2\tau_c}{\underline{V}_b^2\underline{\tau}_c}\underline{D} \tag{66}$$

and if

$$HL = \frac{V_b^2\tau_c}{\underline{V}_b^2\underline{\tau}_c} \tag{67}$$

then we have

$$D = HL\underline{D} \tag{68}$$

which was called by Pogozhev as a relationship of similarity. Now, it should be mentioned that for the diffusion processes the following relationship is hold

$$u(\beta t) = \sqrt{\beta}u(t) \tag{69}$$

and for (58) we have

$$\begin{aligned} u(t) &= \sqrt{HL}\,\underline{u}(t) \\ &= \underline{u}(HL,t) \end{aligned} \tag{70}$$

Repeating previous calculations we can write the equations for densities

$$\begin{aligned} \frac{\partial}{\partial t}p(q,t) &= -\sum_i \underline{\Psi}(\pi(t))\frac{\partial p(q,t)}{\partial q_i} + \\ &+ \frac{1}{2}\sum_{i,j} \underline{D}_{ij}\frac{\partial^2 p(q,t)}{\partial q_i \partial q_j}, \\ \frac{\partial}{\partial t}p(q,t) &= -\sum_i \sqrt{HL}\,\underline{\Psi}(\pi(t))\frac{\partial p(q,t)}{\partial q_i} + \\ &+ \frac{1}{2}\sum_{i,j} HL\underline{D}_{ij}\frac{\partial^2 p(q,t)}{\partial q_i \partial q_j}, \end{aligned} \tag{71}$$

This means that for the shift vector we have a transformation

$$\overline{\Psi} = \sqrt{HL}\ \underline{\Psi} \tag{72}$$

and same results can be obtained for the non-stationary case.

4.2. Parameterization of the model.

Let us now return to the model (29) Now we have to define an analytical form of the function v($\underline{\alpha}$,HL). Let $\eta(\tau)$ and $\underline{\eta}(\tau)$ be the number of interactions of particles during the period τ in the given and basal organisms respectively. These values are functionals of the trajectory of the interacting particles system

$$\begin{aligned} \underline{\eta}(\tau) &= J(\underline{q}(t),\ 0 \le t \le \tau) = \underline{\mu}\tau \\ \eta(\tau) &= J(\underline{q}(t),\ 0 \le t \le \tau) = \mu\tau \end{aligned} \tag{73}$$

To explain this proposition we can consider the number of interactions as a random process

of the events, which is stationary with the intensity μ. In this case, the probability of z interactions is

$$P(z=k) = \frac{(\mu\tau)^k}{k!} e^{-\mu\tau} \tag{74}$$

Then the average number of contacts is $\mu\tau$. Using the relation of similarity we have

$$\begin{aligned} \mu\tau = \eta(\tau) &= J(u(t),\ 0 \le t \le \tau) = \\ &= J(\ \underline{u}(tHL),\ 0 \le t \le \tau) = \\ &= J(\ \underline{u}(s),\ 0 \le s \le \tau HL) = \underline{\mu}\tau HL. \end{aligned} \tag{75}$$

or

$$\mu = \underline{\mu} HL \tag{76}$$

The vector of parameters α in the model (29) is proportional to intensity of interactions μ and

$$\alpha = \mu\gamma \tag{77}$$

where γ is a constant vector. From (76), for the given organism, we have

$$\alpha = \underline{\alpha} HL \tag{78}$$

In such manner

$$\nu(\underline{\alpha}, HL) = HL\underline{\alpha} \tag{79}$$

4.3. Similarity of the homeostasis levels.

The reaction of the homeostatic system to perturbations is described by the linear system

$$\frac{d}{dt}x_t = Ax_t + B, \quad x_0 = c, \tag{80}$$

Here c is a vector of disturbances,

A is a matrix of parameters,

B is a vector, which is interpreted as a rate of influx of particles into zone of interacting. Therefore this vector is proportional to the shift vector $\vec{\psi}$.

This allows us to consider the vector B as a lineal functional of $\vec{\psi}$, and we can write

$$B = G(\overline{\psi}) = G(\sqrt{HL}\ \overline{\psi}) = \sqrt{HL}\ G(\overline{\psi}) = \sqrt{HL}\ \underline{B} \tag{81}$$

According to the model (80) the homeostasis level is

$$x^{\infty} = A^{-1}B \tag{82}$$

Then, taking into account our previous results, for the given organism we have

$$\frac{d}{dt}x_t = HL\ \underline{A}x_t + \sqrt{HL}\ \underline{B} \tag{83}$$

where $\underline{A}$ and $\underline{B}$ are the parameters of the basal organism. So, we obtain

$$x^{\infty} = \frac{1}{HL}\ \underline{A}^{-1}\ \underline{B}\sqrt{HL} = \frac{\underline{x}^{\infty}}{\sqrt{HL}} \tag{84}$$

These transformations of parameters are sufficient for this work. The reader can find others

in (Pogozhev, 1988). For example, for the effective volume we have

$$W = \underline{W}HL^{3/2}.$$

5. The model of carbohydrate metabolism.

To conform our theory consider the model of carbohydrate metabolism which is known as Bolier model

$$\begin{aligned}
\frac{d}{dt}y(t) &= -\alpha_1 y(t) \\
\frac{d}{dt}x_1(t) &= \alpha_2 y(t) - \alpha_3 x_1(t) - \alpha_4 x_2(t) \\
\frac{d}{dt}x_2(t) &= \alpha_5 x_1(t) - \alpha_6 x_2(t) \\
y(0) &= c, \qquad x_1(0) = x_2(0) = 0,
\end{aligned} \tag{86}$$

where y_t is the quantity of glucose in the intestines, $x_t^1 = G_t - G^*$ and G_t is the concentration of glucose in the blood; $x_t^2 = I_t - I^*$, I_t is a concentration of insulin in the blood, G^* and I^* are related homeostasis levels. Let $\underline{\alpha}^i$, $i=1,2,\ldots,6$, $\underline{G}^*$ and $\underline{I}^*$ correspond to the basal organism. Using the previous results for the individual one we have

$$\begin{aligned}
\frac{d}{dt}y(t) &= -HL\underline{\alpha}_1 y(t) \\
\frac{d}{dt}x_1(t) &= HL^{-1/2}\underline{\alpha}_2 \frac{y(t)}{\underline{W}} - HL(\underline{\alpha}_3 x_1(t) + \underline{\alpha}_4 x_2(t)) \\
\frac{d}{dt}x_2(t) &= HL(\underline{\alpha}_5 x_1(t) - \underline{\alpha}_6 x_2(t)) \\
y(0) &= c, \qquad x_1(0) = x_2(0) = 0, \\
x_1(t) &= G_t - \frac{G^*}{\sqrt{HL}}, \\
x(t)^* &= I_t - \frac{I^*}{\sqrt{HL}}, \\
W &= \underline{W}HL^{3/2}
\end{aligned} \tag{87}$$

In the model the parameter HL takes into account the individual character of the metabolism process in the given organism. For the group of M patients we have H^1, $HL^2,\ldots,HL^M$ individual parameters.

Here, we discuss some practical examples following Pogozhev. In Fig. 3. the dynamics of the sugar in the blood are presented. Every sugar curve corresponds to a single age group of healthy persons and describes the average sugar dynamics in this group after glucose loading. These curves we can consider as curves, which were obtained from the eight different patients with

$$X_M = \{ x_t^i,\ t\in\Theta,\ i=1,2,\ldots,8 \} \quad \textbf{(88)}$$

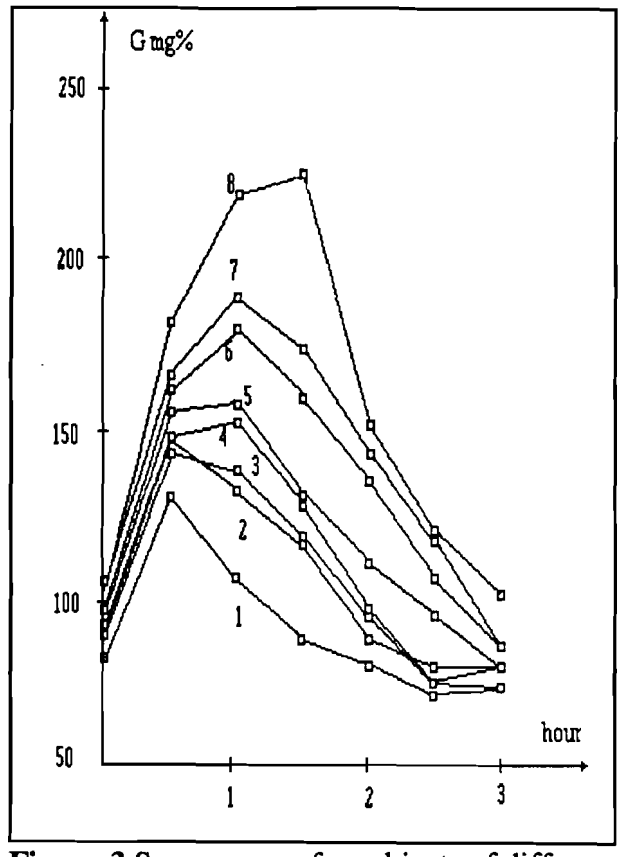

Figure 3 Sugar curves for subjects of different age (observation data). G - blood sugar in, t- hours after glucose load. Age groups (years); 1- up to 10; 2- 10-20; 3- 20-30; 4- 30-40; 5- 40-50; 6- 50-60; 7- 60-70; 8- more than 70.

For X_M we have the model (86), and the parameter HL takes into account peculiarity of every curve. In our example, as a basis for calculation of HL we consider the group of patients from 20 to 30 years old as a basal trajectory. Using this curve we can estimate $\underline{G}\infty$, $\underline{I}\infty$, and $\underline{\alpha}$. Now for our example, we recalculate the parameters of the model (85) for each curve using the relationships

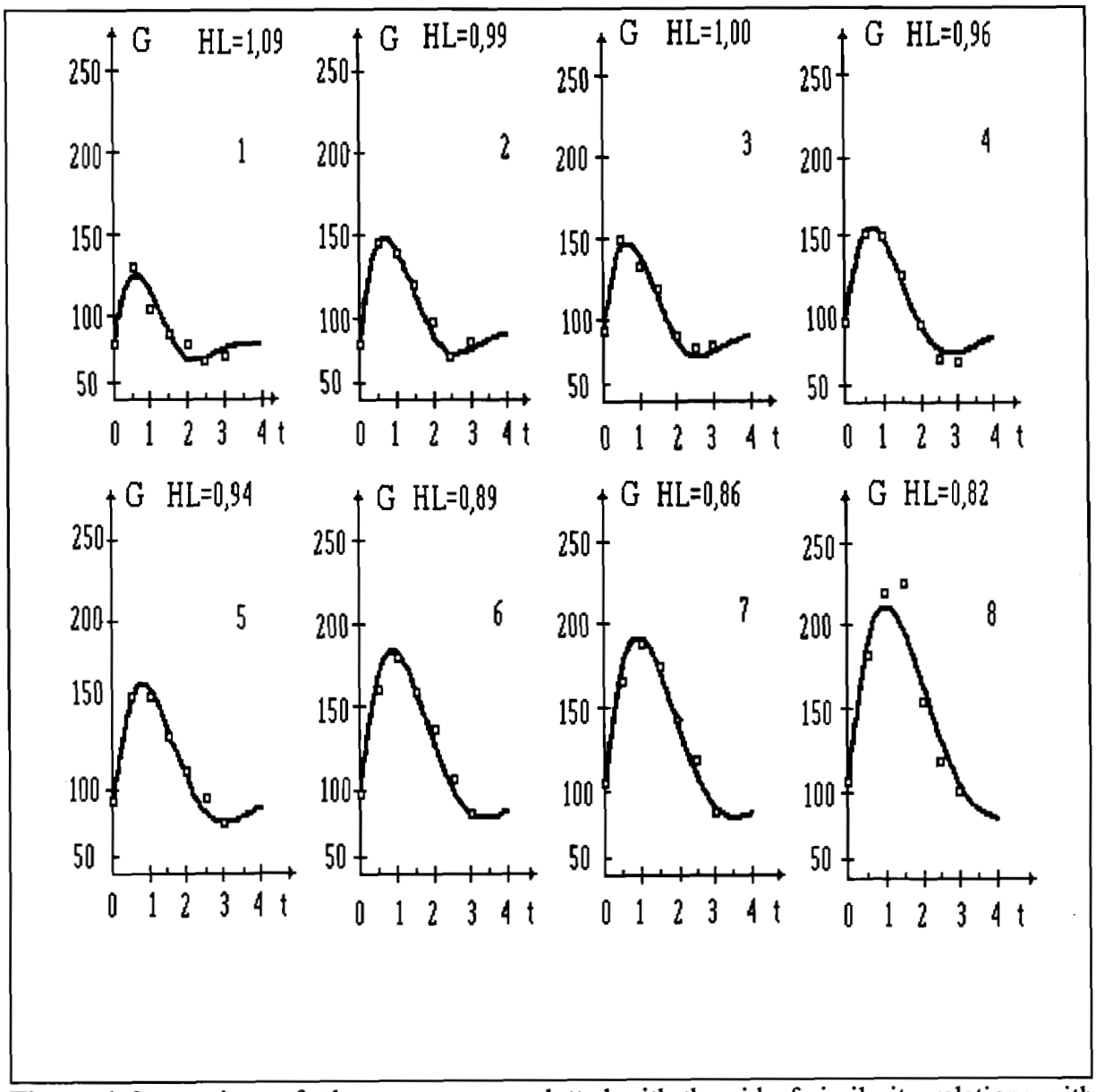

Figure 4 Comparison of the sugar curves plotted with the aid of similarity relations with respect to "norm". Number of charts and values oh HL parameter corresponds to age groups in Fig. 3.

$$\alpha = \underline{\alpha} HL,$$
$$G_{\infty} = \frac{G^*}{\sqrt{HL}}, \qquad (89)$$
$$I_{\infty} = \frac{I^*}{\sqrt{HL}}.$$

Here HL is an unknown parameter. For the group of patients from 20 to 30 years HL=1.The results are presented in Fig. 4.

From the graphs it can be seen that the distinction between curves are completely described by the parameter HL. All these results show that the approach, which is proposed here, for the model parameterization do not contradict the data of observations. Of course this approach should be tested with other models and data.

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