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The Investigation of Stochastic Processes in Biology by Methods of Nonlinear Wave Dynamics

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The nonlinear equation for transitional probability among (x_0, t_0) and (x, t) variables of markov diffusion processes as well as for full probability of realization of (x, t) processes is proposed and solved.

1. Statement of problems of investigation of biological processes by methods of wave dynamics. For modern sciences it is typical the application of exact mathematical methods in their various regions. These methods are penetrating in economics, psychology and many other branches of science, including biology as well. In the last one the mathematics enters by different ways. By one aspect - there is using of modern computers technique for effective treatment of biological experiments results, by the other hand - the creation of mathematical models, describing various vital systems and processes in them. No more important also the "reverse relation", arising among mathematics and biology: the biology not only represents arena for application of mathematical methods, but also become more and more the essential source of new mathematical problems. It relates first of all to genetics and investigation of population dynamics. The mathematical genetics now undoubtly is sufficiently formed discipline. One must note that biological experiment is completed by mounting of experimental data, which are represented by graphs or tables. However, one must take into account that in biological experiments limited number objects are used and experiments are carried out in some time intervals. It means that one cannot speak about completely deterministic character of their results. From this point of view it is very actual mathematical calculation of probabilities of data of biological experiments. The majority of biological processes such as propagation of nerve impulse, of muscle shortening and so on [1], are described by nonlinear equations. In present paper the main attention is focused on examination of large variations of experimental curves of stochastic variables in different biological processes on the base of known linear equations for probabilities of markov diffusion processes of Kolmogorov-Einstein-Fokker-Plank, generalized in mentioned regions of strong disturbances of parameters by additional account of nonlinear term, which is done by analogy with nonlinear wave dynamics [2,3].

First the mathematical theory is applied to problem of determination of probability of genetical processes by examination of graph of frequency of birth-rate of children with Daun syndrome as function of age of mother [9]. One can note that trisomy 21 or Daun syndrome has frequency 1 on 700 births. The risk of birth-rate of children with Daun syndrome is raised with age mother due to increasing of probability of nondivergence of chromosomes: if for mother to 20 year birth-rate frequency of such children is 0,003%, for mothers older than 45 year this frequency is more than 4% [9]. It is interesting to determine these probabilities and to prognose them on greater times by methods of nonlinear gas and wave dynamics [3].

2. Stochastic processes and diffusion equations. For stochastic markov diffusion processes the transitional probability $p(t_0, x_0, t, x)$ from value of stochastic variable $\xi = x_0$ in initial moment t_0 to value $\xi = x$ in given moment t satisfies [5-8] to reverse and direct Kolmogorov equations

$$\frac{\partial p}{\partial t_0} = -a\frac{\partial p}{\partial x_0} - \frac{1}{2}b\frac{\partial^2 p}{\partial x_0^2}, \tag{2.1}$$

$$\frac{\partial p}{\partial t} = -\frac{\partial ap}{\partial x} + \frac{1}{2}\frac{\partial^2 bp}{\partial x^2}, \tag{2.2}$$

where, for example in (2.2), $a(x,t)$, $b(x,t)$ are written in form of integrals from p [7,8] taken over small vicinity of (x,t) point. a, b are called coefficient of pulling-down and diffusion, and a represents mean speed of variation of $\xi = x$ variable and by our terminology [3] linear wave speed. Instead of complex integral expressions [5-8] for a, b one can use more convenient method connected with graphs for mean values of $\xi = x(t)$. One can introduce [8] mean values for x, x^2a, b, ab

$$\overline{x} = \int\limits_{-\infty}^{\infty} xp(t_0, x_0, t, x)dx, \ \overline{x}(t_0) = x_0 \tag{2.3}$$

and so on, and obtain using (2.2)

$$\frac{d\overline{x}}{dt} = \overline{a(x,t)}, \ \frac{d\overline{x^2}}{dt} = 2\overline{a(x,t)x} + \overline{b(x,t)}. \tag{2.4}$$

Particularly for case $a(x,t)=a_0+cx$, $a_0, c=\mathrm{const}$ by denoting $x=\overline{x}+\Delta x$, one obtains [8] $\overline{a(x,t)}=a_0+c\overline{x}$, $\overline{b(x,t)}=(\Delta x)^2/\Delta t-2c(\Delta x)^2$ and for case $c=0$

$$\overline{a(x,t)}=a_0,\ \overline{b(x,t)}=(\Delta x)^2/\Delta t. \tag{2.5}$$

The same relations one obtains from Ito's equations [5-8]

$$\frac{d\xi}{dt}=a\{\xi(t),t\}+\sqrt{b\{\xi(t),t\}}\frac{d\eta}{dt}, \tag{2.6}$$

where $\eta(t)$ is Brownian processes. Here it is choosen the Ito's eqution form, which for considered stochastic biological processes is more available than Stratonovich form equation [11].

One can also write onedimensional probability $P(t,x)$ [8]

$$P(t,x)=\int_{-\infty}^{\infty}P_0(t_0,x_0)p(t_0,x_0,t,x)dx_0, \tag{2.7}$$

which also satisfies to (2.2), and to initial condition $P(t_0,x)=P_0(t_0,x)$.

Besides for the case $a(x,t)=a_0$, $b(x,t)=\mathrm{const}$ one can assume, that initial probability function $P_0(t_0,x_0)=P_0$ is constant, satisfies to equation (2.2), as well as transitional corresponding function $p_0(t_0,x_0,t,x)$, which can be written as Gaussian process [8] with $\overline{x}=a_0t$ and dispersion $\sqrt{bt}$, and then $P_0(t_0,x_0)=\mathrm{const}$. Furthermore one can introduce $P(t,x)=P_0+P'(t,x)$, where $P'(t,x)$ also satisfies to (2.2) linear equation.

One can see that (2.2) coincide with known linear wave equation of gas dynamics and wave dynamics [3] with addition of small dissipation term having b coefficient.

3. The investigation of nonlinear solution. By analogy with mechanics of continua [2,3] one can assume that the problem is weakly nonlinear and replace linear wave velocity a by nonlinear $a+\frac{1}{2}\gamma P'$, where coefficient γ, as well as a, b, is determined from graph of $x(t)$ by means of (2.4), (2.5), replacing $\frac{dx}{dt}\approx\frac{\Delta x}{\Delta t}$. Then one can write in a region of strong variations of inclination $\frac{dx}{dt}$, typical for biological problems [9], [10], nonlinear diffusion equation

$$\frac{\partial P'}{\partial t}+\frac{\partial P'a}{\partial x}+\gamma P'\frac{\partial P'}{\partial x}-\frac{1}{2}\frac{\partial^2 P'b}{\partial x^2}=0. \tag{3.1}$$

For typical case of constant $a=a_0, b$, connected with almost direct lines of graphs of $x(t)$, corresponding to linear solution P_0, taking place before nonlinear region of large variations of $\frac{dx}{dt}$, (3.1) one can write

$$\frac{\partial P'}{\partial t}+a_0\frac{\partial P'}{\partial x}+\gamma P'\frac{\partial P'}{\partial x}-\frac{1}{2}b\frac{\partial^2 P'}{\partial x^2}=0. \tag{3.2}$$

As in [2,3] one can introduce eiconal $\tau = t - \frac{x}{a_0}$, and, since in vicinity of wave, or direct part of $x(t)$, τ is small and for small P', $\frac{\partial P'}{\partial t} \sim 1$, and in main order (3.2) has the form [2,3]

$$\frac{\partial P'}{\partial x} + \frac{\gamma}{a_0^2} P' \frac{\partial P'}{\partial \tau} - \frac{1}{2} \frac{b}{a_0^3} \frac{\partial^2 P'}{\partial \tau^2} = 0, \tag{3.3}$$

where $\frac{\partial P'}{\partial x}$ is taken for constant τ and has order P', the same as other terms in (3.5) in vicinity of wave. For simplicity first one can take purely nonlinear case [2,3] and equation

$$\frac{\partial P'}{\partial x} + \frac{\gamma}{a_0^2} P' \frac{\partial P'}{\partial \tau} = 0. \tag{3.4}$$

For concreteness one can consider typical problem on initial and boundary conditions. In initial point x_0, t_0 of nonlinear region on curve $x(t)$ are, introduced new coordinates $x - x_0$, $t - t_0$, which for convenience are denoted by x, t, so initial point will be $x = 0$, $t = 0$.

Then one has following conditions

$$t = 0,\ P'(x,t) = 0;\ x = 0; P'(x,t) = F(t). \tag{3.5}$$

Solution of (3.4) under (3.5) yields [3], $x \geq 0, t \geq 0$

$$P' = F(y_1),\ t - \frac{x}{a_0} + \frac{\gamma x}{a_0^2} F(y_1) = y_1, \tag{3.6}$$

where $y_1 = \mathrm{const}$ is equation of direct nonlinear characteristics.

In their intersection there is formed region of multivaluency of solution, which is avoided by introduction of shock wave [3], ahead of which $P' = 0$ in considered case, and behind of it [3]

$$F^2(y_1) = \frac{2a_0^2}{\gamma x} \int_0^{y_1} F(y_1) dy_1. \tag{3.7}$$

Particularly supposing that for prognosing value of probability of value $x_0 = 0$ in (3.5) $F(y_1) = A\sqrt{y_1}$, $A = \mathrm{const}$, one can from (3.6), (3.7), obtain on issuing from point $x = 0$, $t = 0$ shock wave

$$y_1^{\frac{1}{2}} = \frac{3}{4a_0^2} A\gamma x,\ P' = \frac{3A^2\gamma x}{4a_0^2},\ t - \frac{x}{a_0} + \frac{3A^2\gamma^2 x^2}{16a_0^4} = 0. \tag{3.8}$$

In linear region by (2.4), (2.5) $\frac{\Delta x}{\Delta t} = a_0$, $a_0 = \mathrm{const}$, which allows, by inclination of $x(t)$, determine a_0. And for nonlinear region of large variations $\frac{dx}{dt}$, for determination of constant coefficient γ, on account that on shock wave [3]

$$\frac{dx}{dt} = a_0 + \frac{\gamma}{2} P'$$

and P' is done by (3.8) one obtains

$$\frac{\Delta x}{\Delta t} - a_0 = \frac{3A^2\gamma^2 t}{8a_0}. \tag{3.9}$$

4. The case of strong disturbances. In §3 it is considered the case of small disturbed values P'. These considerations we in §5 apply to biological problem of [9], where on page 111 there is graph mentioned in §1, from which is obtained nonlinear coefficient. But from this curve one can see that $\frac{dx}{dt} - a_0$ in mentioned region is not small with respect a_0, and one must also, for comparison treat strong disturbances methods.

Then one can develop in stochastic problem the method [1] of not small nonlinear waves and write conservation equation for P'

$$\frac{\partial P'}{\partial t} + \frac{\partial q}{\partial x} = 0,\ q = aP',\ a = a(P'),\ P' = f(q), \tag{4.1}$$

where $P' = P - P_0$ here is disturbed probability, which in deterministic problem [1] corresponds to density ρ', and q in [1] is current, a is waves velocity. Equation on shock [1], ahead of which $P' = 0$,

$$\int_0^{y_1} q(y_1)dy_1 = -\{qf'(q) - f(q)\}x, \tag{4.2}$$

$$t = xf'(q) + y_1 \tag{4.3}$$

and, for example, assuming

$$a = a_0 + \frac{\gamma}{2}P',\ P' = A\sqrt{y_1} \tag{4.4}$$

where P' is not small, one can obtain on shock wave

$$\begin{gathered} \chi^2\frac{y_1^2}{2} + \frac{2}{3}a_0\chi y_1^{\frac{3}{2}} = \left(\xi - \frac{\xi^2 - \frac{a_0^2}{4}}{2\xi} - \frac{a_0}{2}\right)x, \\ t = x\frac{1}{2\xi} + y_1,\ \chi = \frac{\gamma}{2}A,\ \xi = \frac{a_0}{2} + \chi\sqrt{y_1}, \end{gathered} \tag{4.5}$$

whence for small $\frac{\gamma}{2}A$ can be obtained (3.8).

From (4.5) are obtained y_1 by t, χ, and further P'. From graph of $x(t)$ on nonlinear part one has

$$\frac{\Delta x}{\Delta t} = a_0 + \frac{\gamma}{2}P', \tag{4.6}$$

where $P' = A\sqrt{y_1}$, and one can express y_1 by χ, place in (4.5) and obtain χ.

The solution of (4.5) can be obtained numerically. To simplify consideration one can assume that due to graph [9] p.111 $\frac{dx}{dt} \gg a_0$ and choosing $P'(0,t) = A_1\sqrt[4]{t}$ from (4.2) obtain on shock wave

$$P' = t^{1/4}A_2\frac{3^{1/4}}{5^{1/4}}, \tag{4.7}$$

which does not depend from $\frac{\gamma}{2}$, $\frac{\gamma}{2}A_1$ can be obtained by (4.6). In the case of arbitrary boundary condition $F(y_1)$ the shock wave is arised in first point [13]

$$y_1 = 0,\ t_* = \frac{a_0 + \gamma F(0)}{F'(0)},\ \frac{x_*}{a_0 + \gamma F(0)} = t_* \tag{4.8}$$

and for $F(y_1) = A\sqrt[4]{y_1}$, $t_* = 0$, $x_* = 0$.

5. Biological stochastic processes consideration by methods of wave dynamics. Let us consider graph of dependence of frequency x of birth-rate of children with Daun syndrome from age of mothers [9] p.111, see fig.1.

On initial almost direct line on t (15; 35) years takes place variation on x (0.003; 0.14)%, whence linear wave velocity

$$a_0 = \frac{\Delta x}{\Delta t} = 0.007\frac{\%}{\text{year}} \tag{5.1}$$

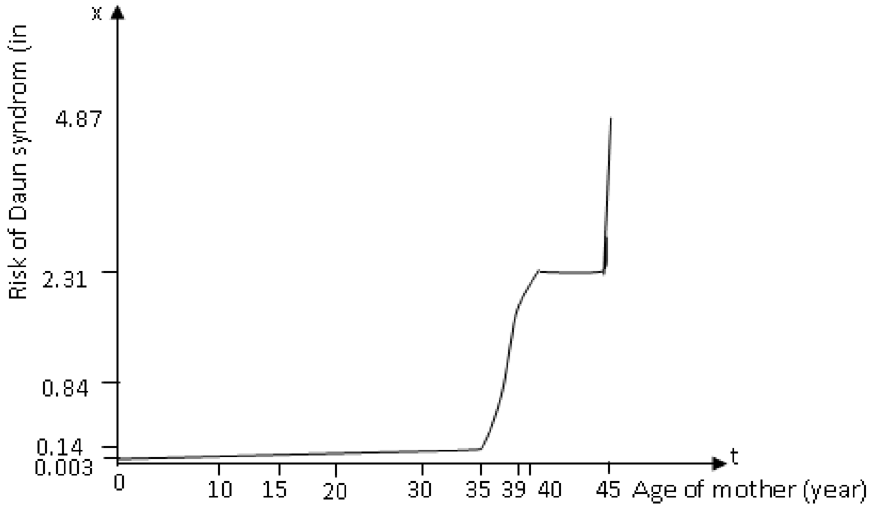

Fig. 1

Further there is large increasing of $\frac{dx}{dt}$ on nonlinear part of $x(t)$ (0.14; 2.31)%, t (35; 40) year, and from fig.1 one can obtain

$$a = \frac{\Delta x}{\Delta t}. \tag{5.2}$$

Here t, x are coordinates of §3, and $t = 35$ year, $x_0 = 0,14\%$, and introducing new coordinates $t - t_0$, $x - x_0$, denoted anew by t, x, one can take in new values of t (3.9). For large disturbances using (4.2) and (4.4), one has on strong shock wave

$$\frac{\gamma P'}{2} = -\frac{2a_0}{9} + \sqrt{\left(\frac{2a_0}{9}\right)^2 + \frac{1}{6}A^2\gamma^2 t},\ \frac{\gamma P'}{2} \approx A\gamma\sqrt{\frac{t}{6}} \tag{5.3}$$

whence, since the very large increasing of $x(t)$ on (39,40) year part of fig.1 is doubtfully, taking mean value of new coordinate $t = 4$ year, on equating (4.6), (5.3) to $\frac{\Delta x}{\Delta t} = 0.0021\frac{1}{\text{year}}$, one obtains

$$A\gamma = 0.0024\frac{1}{\text{year}^{3/2}}. \tag{5.4}$$

The same calculations are made for fig.2, taken for the mentioned Daun syndrome graph from [14].

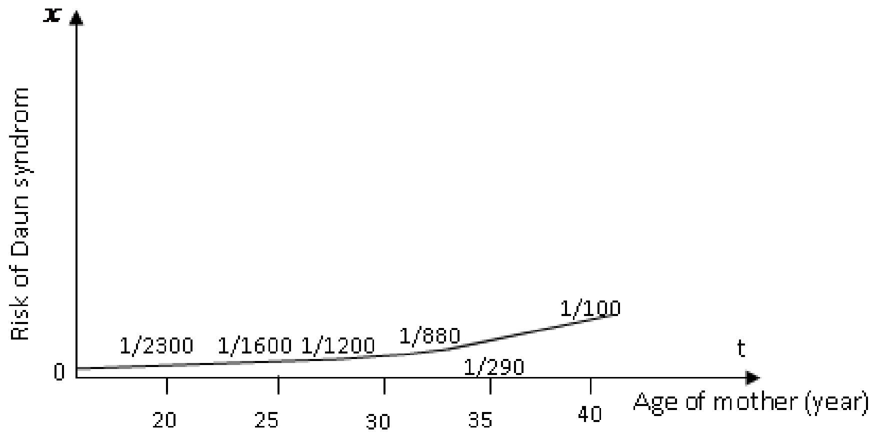

Fig. 2

Instead of (5.1) on linear part (0;35) year of fig.2 one obtains $a_0 = 0.0001\frac{1}{\text{year}}$, and from nonlinear part of curve (35;40) year, one obtains $a_0 = 0.0013\frac{1}{\text{year}}$, $a - a_0 = 0.0012\frac{1}{\text{year}}$. Then from (4.6), (5.3), taking anew as mean point $t = 4$year, one obtains

$$0.0012 = A\gamma\sqrt{\frac{2}{3}},\ A\gamma = 0.00144\frac{1}{\text{year}^{3/2}}. \tag{5.5}$$

To calculate approximate experimental values of probability $P(x,t)$, one can, by comparison of curves $x = x_1(t)$ of fig.1 and $x = x_2(t)$ of fig. 2, obtain, denoting $1 - P \approx \frac{|x_2 - x_1|}{x_2 + x_1}$,

$$t = 0 \div 35\,\text{year},\ P = P_0,\ 1 - P_0 = 0.5;\ t = 39\,\text{year},\ 1 - P = 0.1. \tag{5.6}$$

Thus, since on linear part of curves fig.1, fig.2 $P \approx 0.5$, on nonlinear part $P \approx 0.9$ one can note, that there is transition from stochastic linear region to almost deterministic nonlinear region, as in known [11] cases of generation of coherent radiation in lasers or passage from stochastic mutations to high level vital forms.

One can denote disturbed value of probability in nonlinear region $P' = P - P_0$, then for $t = 39$year or in new variables $t = 4$ year, since by (4.6) $P' = A\sqrt{y_1}$, from (5.3) one obtains $\sqrt{y_1} = 2\sqrt{\frac{2}{3}}\,\text{year}^{\frac{1}{2}}$, $P' = A \cdot 1.6$, whence one obtains

$$A = 2.5\frac{1}{\text{year}^{\frac{1}{2}}} \tag{5.7}$$

Using (5.7), one can from (5.4) and (5.5) for cases of fig.1 and fig.2 obtain nonlinear coefficient

$$\gamma = 0.1\frac{1}{\text{year}} \quad \text{and} \quad \gamma = 0.06\frac{1}{\text{year}}. \tag{5.8}$$

We assume, that value of γ due to fig.2 is preferable. For obtained values of $P(x,t)$ one can also make prognosis of curve $x(t)$ to larger t, or to solve filtration problem [6].

By the same method are investigated regions of large variations of $\frac{dx}{dt}$ for curves of [10] fig. 90, I, IV. They give variational pulsogramm. Fig. 90 I. In linear region of graph $t(0.72; 0.75)$sec. $\Delta x = 15p$(pulsations), $a_0 = 500p/\sec$. Nonlinear region $t(0.75; 0.8)$sec; $\Delta x = 45p$, $a = 900p/\sec$. From (3.9), where t is new variable, $t = 0.05$sec,

$$A\gamma = 3200p/\sec^{3/2}, A = 5/6\sec^{-1/2},\ \gamma = 4000p/\sec, P' = 0.1. \qquad (5.9)$$

and assuming $P_0 = 0.5$, one obtains $P = 0.6$ and disturbances are small.

Excessive variational pulsogramm. Fig. 90 IV. Linear region $t(0.75; 0.78)$sec., $\Delta x = 15p$, $a_0 = 500p/\sec$. Nonlinear region $t(0.78; 0.81)$sec, $\Delta x = 43p$, $a = 1433p/\sec$. $t = 0.03$sec, $A\gamma = 1260p/\sec^{3/2}$, $\gamma = 7400p/\sec$, $P' = 0.25$, $P = 0.65$.

For problems of [10] fig. 90 it is enough theory of small nonlinearities.

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The Investigation of Stochastic Processes in Biology by Methods of Nonlinear Wave Dynamics

The nonlinear equation for stochastic processes probability among two states and for full probability of considered state of Markov diffusion processes is derived and solved.

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Исследование стохастических процессов в биологии методами нелинейной волновой динамики

Предлагается нелинейное уравнение для переходной вероятности между состояниями и для полной вероятности осуществления данного состояния марковских диффузионных процессов.

Коэффициенты сноса, диффузии и нелинейности этого уравнения определяются с помощью осредненных кривых ряда биологических процессов и уравнения Ито. Определяются указанные вероятности в рассматриваемой области сильных изменений наклонов указанных графиков, где существен учет нелинейности.

Գ.Ա. Մարփիրոսյան, ՀՀ ԳԱԱ թղթակից անդամ Ա.Գ. Բագդոև

Ստոխաստիկ մարկովյան պրոցեսների ուսումնասիրությունը կենսաբանության մեջ ոչ գծային ալիքային դինամիկայի եղանակներով

Առաջարկվում է ոչ գծային հավասարումը մարկովյան դիֆուզիոն պրոցեսների անցումային հավանականության եւ լրիվ հավանականության համար տվյալ վիճակի իրականացման դեպքում:

Անցկացման, դիֆուզիայի եւ ոչ գծայնության գործակիցները նշված հավասարման համար որոշվում են մի քանի կենսաբանական պրոցեսների միջինացված կորերի եւ Էպոյի հավասարման միջոցով:

Նշված հավանականությունները որոշվում են գրաֆիկների թեքումների ուժեղ փոփոխությունների փիրույթներում, որտեղ կարեւոր է ոչ գծայնությունը:

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