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Population and Mutagenesis or About Hardy and Weinberg One Methodical Mistake

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Abstract
The existing discrete form of the Hardy-Weinberg genetic law is applicable for a family tree. For population it is necessary to use a continuous time scale. The differential form of the Hardy-Weinberg law is offered. On the basis of this form of the law the demographic problem is considered where oncological diseases connected with the action of the stochastic mutagen factor. Genetic-mathematical aspects of hemophilia are considered in the assumption of the equivalent constant mutagen factor action.

Key words: Hardy-Weinberg law; Family tree; Population; Mutations; Selection

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INTRODUCTION
The Hardy-Weinberg law which was found by English mathematician Hardy and German doctor Weinberg in 1908 plays key role in the mathematical analysis of genetic processes. In the elementary kind the essence of this law will consist in the following.

In the elementary kind of two alleles of autosomal genes relative frequencies of genotypes in generations correspond to terms of binomial expansion $(p+q)^2$so $p+q=1$ where p and q is alleles frequencies. Relative frequencies of genotypes remain constant from generation to generation in case of the ideal population (number of species is very great, exist panmixia, there is no selection, mutations, migrations of species, etc.). Since founders of the law Hardy and Weinberg it is supposed that in such kind the law describes the processes in population (Vogel & Motulsky, 1990; Ayala & Kiger, 1984; Li, 1976; Weir, 1990; Volobuev, 2005; Brown & Rothery, 1994).

However founders of the law and the subsequent authors at use of the law make essential methodical mistake. The matter is that the population will consist of set of family trees which periodically contact among themselves. On Figure 1 the principle of population formation from separate family trees is shown. There the square means a male individual, a circle - female.

For example, three family trees are shown. For the family tree it is possible to consider the time of one generation change approximately $T\approx$25-30 years. For the population this time can be any t_1,t_2, etc. For the population continuous alternation of generations is characteristic and hence the form of the Hardy-Weinberg law should not have discrete character. In it there is essence of the basic methodical mistake of application of the Hardy-Weinberg law for the population. In used form the Hardy-Weinberg law is written down for the family tree.

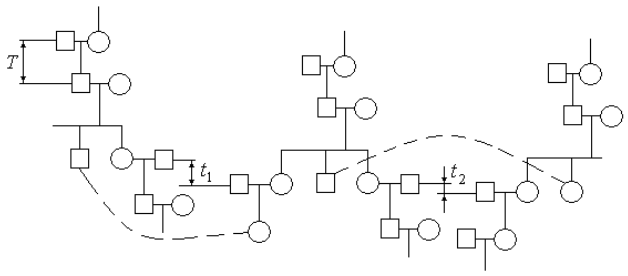

Figure 1
Formation of the Population From Separate Contacting Family Trees

1. HARDY-WEINBERG LAW FOR THE FAMILY TREE

For reception of necessary form of the Hardy-Weinberg law for population we shall start with the analysis of a separate family tree. It is obvious that in this case it is possible to use the given law in its standard form.

In the analysis the elementary case of two alleles of a gene linked to the *X*-chromosome is used. The frequency of dominant alleles *A* we shall designate at men p_m and at women p_f. For recessive alleles *a* it is accordingly q_m and q_f.

At reproduction in the first generation there is the ratio of women genotypes according to product $(p_f + q_f)(p_m + q_m)$ Thus:

$$(AA)\, p_f p_m : (Aa)(p_m q_f + p_f q_m) : (aa)\, q_m q_f \qquad (1)$$

Men have hemizygous the frequency ratio on genes in the *X*-chromosome determined by that the *X*-chromosome of the woman at reproduction passes to the man's offspring:

$$(A)\, p_f : (a)\, q_f \qquad (2)$$

Using distribution of genotypes (1) we shall find frequency of allele *a* at women in the following $(n+1)$ generation:

$$q_{f(n+1)} = \frac{1}{2}(p_{mn} q_{fn} + p_{fn} q_{mn}) + q_{mn} q_{fn} =$$
$$= \frac{1}{2}\left[(1 - q_{mn}) q_{fn} + (1 - q_{fn}) q_{mn}\right] + q_{mn} q_{fn} = \frac{1}{2}\left[q_{fn} + q_{mn}\right] \qquad (3)$$

At the deduction (3) the following obvious formulas p_{mn}=1-q_{mn} and p_{fn}=1-q_{fn} are used. The formula (3) can be copied in the following kind:

$$q_{fn} - 2q_{f(n+1)} + q_{mn} = 0 \qquad (4)$$

For convenience of the further analysis the formula (4) we shall write down with displacement on one generation back:

$$q_{f(n-1)} - 2q_{fn} + q_{m(n-1)} = 0 \qquad (5)$$

At the absent of mutagen influence the frequency of allele *a* at men is equal to the frequency of this allele at women of the previous generation $q_{m(n-1)} = q_{f(n-2)}$ Using the given condition from (5) we shall find:

$$q_{f(n-1)} - 2q_{fn} + q_{f(n-2)} = 0 \qquad (6)$$

The solution of the finite-differential equation (6) we search as $q_{fn} = a^n$ where in this case *a* is constant. Substituting this solution in the formula (6) we have:

$$a^{n-1} - 2a^n + a^{n-2} = 0 \qquad (7)$$

Let's divide the equation (7) on a^{n-2}:

$$a - 2a^2 + 1 = 0 \qquad (8)$$

We find two roots of the characteristic quadratic (8):

$$a_1 = 1 \quad \text{and} \quad a_2 = -\frac{1}{2} \qquad (9)$$

Hence, the general solution of the finite-differential equation (6) looks like:

$$q_{fn} = C_1 + C_2\left(-\frac{1}{2}\right)^n \qquad (10)$$

Constants of integration C_1 also C_2 we shall find on the basis of the initial conditions: at *n*=0, $q_{fn} = q_{f0}$ and at *n*=1 according to (3) $q_{fn} = q_{f1} = \frac{q_{m0} + q_{f0}}{2}$ Thus:

$$C_1 = \frac{2q_{f0} + q_{m0}}{3} \text{ and } C_2 = \frac{q_{f0} - q_{m0}}{3} \qquad (11)$$

Therefore the solution (11) finally looks like:

$$q_{fn} = \frac{2q_{f0} + q_{m0}}{3} + \left(\frac{q_{f0} - q_{m0}}{3}\right)\left(-\frac{1}{2}\right)^n \qquad (12)$$

2. POPULATION DYNAMICS OF GENOME

As it was already specified the Hardy-Weinberg law in the kind considered above there is concerns to separate family tree. Implicitly this law includes time since alternation of generations occurs through certain time *T*. Thus, Hardy-Weinberg law in form (1) has the expressed discrete character on time. The population will consist of family trees crossed among themselves and lives in continuous time. Alternation of generations of set of family trees results to the generations vary actually according to continuous time scale.

Let's transit to the continuous time scale *n*. Under size $n = \frac{t}{T}$ in this case we mean time of the population life normalized on average in the population time of the one generation life, i.e. actually dimensionless time.

Let's find out, whether there is the differential equation having the characteristic equation similar (7) or (8). For this purpose we shall consider the differential equation:

$$\frac{d^2 q_{f(n-1)}}{dn^2} + \eta \frac{dq_{f(n-1)}}{dn} = 0 \qquad (13)$$

where η is constant.

Let's transform the equation (13) to finite-differential form:

$$\frac{q_{fn}-2q_{f(n-1)}+q_{f(n-2)}}{\Delta n^2}+\eta\frac{q_{f(n-1)}-q_{f(n-2)}}{\Delta n}=0 \quad (14)$$

Uniting similar members and multiplying the equation (14) on -2 we shall find:

$$-2q_{fn}+2(2-\eta\Delta n)q_{f(n-1)}-2(1-\eta\Delta n)q_{f(n-2)}=0 \quad (15)$$

Let's try to identify the equations (15) and (6). For this purpose it is necessary to accept:

$$2(2-\eta\Delta n)=1 \quad (16)$$

$$-2(1-\eta\Delta n)=1 \quad (17)$$

Wonderful feature of the equations (16) and (17) is that they have one and too the solution:

$$\eta\Delta n=\frac{3}{2} \quad (18)$$

It means that the equation (6) and the differential equation (13) can have the same characteristic equation. Taking into account (18) the equation (13) can be copied as:

$$\frac{d^2q_{f(n-1)}}{dn^2}+\frac{3}{2\Delta n}\frac{dq_{f(n-1)}}{dn}=0 \quad (19)$$

The equation (19) can be integrated once:

$$\frac{dq_{f(n-1)}}{dn}+\frac{3}{2\Delta n}q_{f(n-1)}=C_1 \quad (20)$$

where C_1 is constant of integration.

Further integrating the equation (20) by method of separation of variables:

$$\int_{q_{f0}}^{q_{fn}}\frac{dq_{f(n-1)}}{C_1-\frac{3}{2\Delta n}q_{f(n-1)}}=\int_0^n dn \quad (21)$$

we shall find:

$$q_{fn}=\frac{2\Delta n}{3}C_1-\left(\frac{2\Delta n}{3}C_1-q_{f0}\right)e^{-\frac{3}{2\Delta n}n} \quad (22)$$

Identifying the solution (22) with the solution (12) we shall find:

$$\frac{2q_{f0}+q_{m0}}{3}=\frac{2\Delta n}{3}C_1 \text{ and}$$

$$\frac{q_{f0}-q_{m0}}{3}=-\left(\frac{2\Delta n}{3}C_1-q_{f0}\right) \quad (23)$$

As it was expected the formulas (23) do not contradict each other. Hence, the solution (22) can be written down as:

$$q_{fn}=\frac{2q_{f0}+q_{m0}}{3}+\left(\frac{q_{f0}-q_{m0}}{3}\right)e^{-\frac{3}{2\Delta n}n} \quad (24)$$

The formula (24) is correct for frequency of allele *a* only in even generations. This is consequence of transition to the continuous scale of generations *n*.

Comparing (12) and (24) for even generations we have $2^{-n}=e^{-\frac{3}{2\Delta n}n}$ or $\Delta n=\frac{3}{2\ln 2}$ Hence, (24) it will be transformed to the kind:

$$q_{fn}=\frac{2q_{f0}+q_{m0}}{3}+\left(\frac{q_{f0}-q_{m0}}{3}\right)e^{-n\ln 2} \quad (25)$$

that is identical to the formula (12) for even generations.

Taking into account (18) and $\Delta n=\frac{3}{2\ln 2}$ we find $\eta=\ln 2$. Thus, the differential equation (13) will be written down as:

$$\frac{d^2q_{f(n-1)}}{dn^2}+\ln 2\frac{dq_{f(n-1)}}{dn}=0 \quad (26)$$

As we used the continuous time the concept of generations actually does not play any role and the formula (26) it is possible to write down as:

$$\frac{d^2q_f}{dn^2}+\ln 2\frac{dq_f}{dn}=0 \quad (27)$$

The formula (27) it is Hardy-Weinberg law in case of continuous alternation of generations, i.e. for the continuous time scale at absence of mutagen influence on population. The equation (27) defines the time dependence of recessive allele *a* frequency $q_f(n)$ linked with the *X*-chromosome for women in the population.

The differential equation (27) as it is determined by the Hardy-Weinberg law reflects indifferent equilibrium of genome (Volobuev, 2005). Really, to the equation (27) satisfies the solution $q_f=const$, i.e. any constant value of allele frequency it is stable.

3. MUTATIONS

Extremely important topic of mathematical genetics there are mutations. The mutations explain genetically dependent hereditary diseases. Mutations allow explain process of the evolution of organisms. Mutations underlie of animals and plants breeding.

Mutations are spontaneous and induced (Vogel & Motulsky, 1990).

During induced mutations there is interaction of the mutagen factor and individual exposed mutation.

Process of the mutation has stochastic character. The individuals under action of the mutagen factor with some probability can be subjected to mutations, and can not be subjected.

During mutation the mutagen factor has the important role. It is possible classification mutagen factors into two groups: determined and stochastic.

The determined mutagen factors can be constant or functionally time-dependent.

For example, process of mutagenesis under action of the determined mutagen factor in due course reducing the intensity according to exponential law of disintegration of radioactive elements in the environment is considered (Volobuev, 2005).

3.1 Action of the Stochastic Mutagen Factor on the Population

Let's analyze influence of the stochastic mutagen factor by the example of the occurrence malignant newgrowths.

Among other kinds of diseases the occurrence of malignant newgrowths has some features. First of all, it is the big variability of the newgrowths site. It can practically arise in any place of the organism. Besides for oncological diseases there are typically a variety of the mutagen (cancerigenic) factors: poor-quality food, polluted environment, mode of life and professional work, smoking and many other factors.

All these cancerogenic factors finally affect on the mitogenetic function of a cell causing its malignant transformation.

Is generalized we shall consider that set of the reasons resulting to occurrence of the malignant newgrowths it is the influence on the organism of some stochastic mutagen factor.

Despite of the stochastic character of influence it is difficult to assume the situation at which the given stochastic mutagen factor completely would be absent. It concerns even completely isolated primitive societies. Especially such factor in any kind always is present at a modern civilized society.

As investigated model we shall consider homogeneous and stable in the demographic attitude a human society of very much advanced country with a high level of development of the medicine accessible to all population. In such countries death rate of the population basically should be caused by oncological diseases which start to play the role of the natural factor of inevitable alternation of generations. We shall name such countries demographic stationary.

It is possible to assume also that in similar societies the genetic-mathematical laws determining death rate of the population from oncological diseases should operate, i.e. as result of action of the stochastic mutagen factor.

To understand how it is possible to take into account action of the stochastic mutagen factor we will address to other well investigated physical phenomenon—to the Brownian motion (Matveev, 1981). Brownian motion of a particle in a liquid at first sight should not exist. Really, on Brownian particle, for example, flower pollen impacts the molecules of the liquid which operation are counterbalanced from different directions. Therefore, the most probable condition of the particle is motionless. The particle should shiver only but should not have some constant displacement from a point of supervision. Einstein and Smoluchowski have shown that physically the Brownian motion is consequence of statistical properties of the second law of thermodynamics. If the researcher has relative small number of the molecules the essential deviation from the most probable state of system should be observed in this case the motionless state of the Brownian particles.

Let's note the main similarity of two phenomena: the Brownian motion and existence of the population in conditions of the stochastic mutagen factor action.

At the Brownian motion on the determined system - particle in the liquid – stochastic force acts from the molecules of a liquid.

In the researched case on the determined system - reproductive genome—some stochastic mutagen factor acts.

At the Brownian motion the equation of movement of the particle looks like:

$$m\frac{d^2S}{dt^2}+r\frac{dS}{dt}=F \tag{28}$$

where m there is mass of particle, S - displacement of the particle from initial position, r - factor of medium resistance to movement of the particle, t - time, F - stochastic force acting on the particle from the molecules of liquid. We shall note absence in the equation (28) the elastic forces which is determined returned the particle in initial position causing its oscillation around of the balance point.

The equation (27) is similar to the equation (28) for F=0.

If there is some stochastic mutagen factor $D(n)$ randomly time-dependent lives of the population the equation (27) by analogy with (28) it is necessary to copy as:

$$\frac{d^2q_f}{dn^2}+\ln 2\frac{dq_f}{dn}=D(n) \tag{29}$$

Using the result for the first time received by Einstein (Matveev, 1981) for the Brownian motion $\left\langle(\Delta S)^2\right\rangle\sim t$ we shall note that average square of the deviation of the allele frequency from norm (25) at action on the population of the stochastic mutagen factor is proportionally time of the population life $\left\langle\left(\Delta q_f\right)^2\right\rangle\sim n$. Angular brackets are mean averaging on individuals of the population.

Thus, during life of the population at action of the stochastic mutagen factor the mean square deviation of the allele frequency from the norm is proportionally to the root square from time of the population life $\sqrt{\left\langle \left(\Delta q_f\right)^2 \right\rangle} \sim \sqrt{n}$. At the certain level of the mean square deviation of the allele frequency from norm can lead to lethal outcome. For separate individual the lethal deviation is individually.

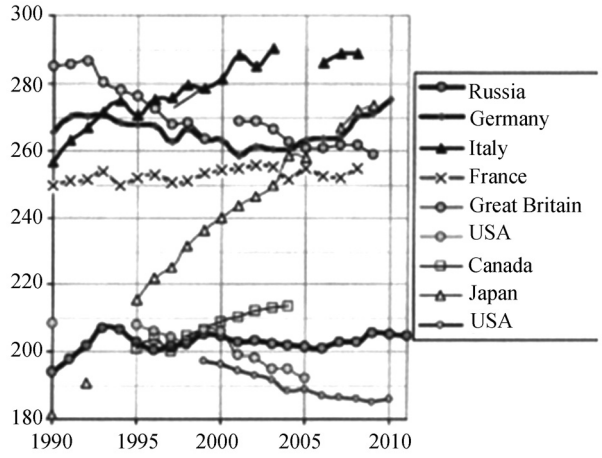

Figure 2
The Dynamics of Death Rates (Mortality Rate Coefficient) **of the Population in the Various Countries From Newgrowths** (Kalabekov, 2010)

The received result shows that during of the population life and alternation of generations at action of the stochastic mutagen factor the death rate inevitably grows (similarly to displacement of the Brownian particles from the point of initial supervision). This conclusion has completely general biology-mathematical character also is consequence of the second law of thermodynamics, i.e. consequence of inevitable growth of entropy in the population.

On Figure 2 the dynamics of death rates (mortality rate coefficient) of the population in the various countries from newgrowths is shown (Kalabekov, 2010). A mortality rate coefficient this ratio of quantity of died people in the country for the year to the average number of population in the given year multiplied on 1000.

Time interval 20 years during which death rate was investigated is small term but it is possible to make some conclusions.

In two countries Japans and Canada the law: death rate $\sim\sqrt{n}$ is obviously observed. Distinctive feature of these countries is, first, very high level of medicine, second, high uniformity of the population which is almost without exception uses these achievements of medicine. Some other social factors determining as whole a positive psychological climate in these countries influence also. In other words the situation with detection at the earliest stage and treatment of the newgrowths in these countries has approached to the stationary limit on the given level of development of the country. The not changes in this direction therefore the law - death rate $\sim\sqrt{n}$ therefore is carried out. The further decrease in death rate will take place at occurrence and universal application of essentially new methods of diagnostics and treatment of cancer. The similar development of a medical science demanding the big financial expenses and intellectual efforts is counteracting against growth entropy in the population.

In the given countries death rate from newgrowths is the basic natural factor of alternation of the generations.

3.2 Action of the Constant Mutagen Factor on Population

We research action of the constant mutagen factor on the population of two-alleles genome, linked with the *X*-chromosome by the example of hemophilia.

Distribution (1) can be used also for the description of blood system ABO. In spite of the fact that to this system corresponds three-alleles ensemble of the genes the two alleles *A* and *B* are dominant and their general frequency can be designated at men p_m and at women p_f. Alleles O has in this case frequency at men q_m at women q_f. The ratio (1) for blood system ABO is not frequency distribution of blood genotypes but the genotype frequency *aa* (or a genotype OO), and also phenotype frequency corresponding to a blood group I it the ratio reflects truly.

The basic demonstration of existence *X*-linked recessive inheritance for the blood system ABO consists that the destruction at disease of blood, for example, hemophilia are men and daughters phenotypic are healthy (Vogel & Motulsky, 1990).

For the first time the mathematical genetics laws has applied Haldane to a problem of hemophilia on basis of Danforth idea about the equilibration of frequency of mutations and selection. Occurrence of hemophilia there is usually concern to spontaneous mutations. However formally meaning balance of mutations and selection, and also constancy of the population mutation occurrence (otherwise illness quickly would disappear) it is possible to calculate the problem of hemophilia assuming action on the blood system of some equivalent constant mutagen factor. Action of selection will be appreciated further.

The analysis we shall make on the basis of Hardy-Weinberg law written down as:

$$\frac{d^2 q_f}{dn^2} + \ln 2 \frac{dq_f}{dn} = \alpha \tag{30}$$

where the value α there is characterizes some equivalent constant mutagen factor causing hemophilia.

The equation (30) can be integrated once:

$$\frac{dq_f}{dn} + \ln 2 q_f = \alpha n + C_3 \tag{31}$$

where C_3 there is constant of integration.

The equation (31) is integrated in quadrature. The general solution looks like:

$$q_f = \frac{\alpha n}{\ln 2} - \frac{\alpha}{(\ln 2)^2} + \frac{C_3}{\ln 2} + C_4 e^{-n\ln 2} \quad (32)$$

where C_4there is constant of integration.

In connection with that the basic results for genetic research of hemophilia have been earlier received at use of discrete alternation generations principle at the given of analysis stage, for use of the previous researchers results, it is convenient to return to the discrete scale of generations.

Change of alleles *a* frequency for one generation is equal:

$$\Delta q_{f(n-1)} = q_{fn} - q_{f(n-1)} = \frac{\alpha(n+1)}{\ln 2} - \frac{\alpha}{(\ln 2)^2} + \frac{C_3}{\ln 2} + C_4 e^{-(n+1)\ln 2} - \left(\frac{\alpha n}{\ln 2} - \frac{\alpha}{(\ln 2)^2} + \frac{C_3}{\ln 2} + C_4 e^{-n\ln 2} \right) = \frac{\alpha}{\ln 2} - \frac{1}{2} C_4 e^{-n\ln 2} \quad (33)$$

At increase in number of generations $n \to \infty$ the change of alleles frequency is $\Delta q_{f\infty} = \frac{\alpha}{\ln 2}$.

Frequency of the mutations for hemophilia in different countries (into the population) changes from $4.4 \cdot 10^{-5}$ (Switzerland) up to $6.4 \cdot 10^{-5}$ (Denmark), i.e. the gene of hemophilia have from 44 up to 64 women on one million (Vogel & Motulsky, 1990). The frequency of the mutations it is ratio of number of anomaly cases display to the double number of the examined individuals the corrected sizes of mutations frequencies therefore are used (multiplied on 2).

Let for $n \to \infty$ the size is $\Delta q_{f\infty} \approx -6 \cdot 10^{-5}$. I.e. 60 girls which birth on one million have the gene of hemophilia. In this case the equivalent constant mutagen factor $\alpha = \Delta q_{f\infty} \ln 2 \approx -4.16 \cdot 10^{-5}$.

The uncertain size in dynamics of change of alleles frequencies (33) is the constant C_4. According to (33) we shall find the law of genic frequency decrease:

$$q_{fn} = q_{f(n-1)} + \frac{\alpha}{\ln 2} - \frac{1}{2} C_4 e^{-n\ln 2} \quad (34)$$

We use the initial condition: for $n = 1$ according to (3) $q_{f1} = \frac{q_{m0} + q_{f0}}{2}$.

Hence, using (34) we shall find:

$$q_{f1} = q_{f0} + \frac{\alpha}{\ln 2} - \frac{1}{4} C_4 = \frac{q_{m0} + q_{f0}}{2} \quad (35)$$

From (35) we find constant C_4:

$$C_4 = 2(q_{f0} - q_{m0}) + \frac{4\alpha}{\ln 2} \quad (36)$$

Substituting (36) in (33) we shall find:

$$\Delta q_{f(n-1)} = \frac{\alpha}{\ln 2} - \left((q_{f0} - q_{m0}) + \frac{2\alpha}{\ln 2} \right) e^{-n\ln 2} \quad (37)$$

Believing for definiteness of calculation $q_{f0} = q_{m0}$ we shall receive:

$$\Delta q_{f(n-1)} = \frac{\alpha}{\ln 2}\left(1 - 2e^{-n\ln 2}\right) = \frac{\alpha}{\ln 2}\left(1 - 2^{-(n-1)}\right) \quad (38)$$

For n=0 we find initial change of alleles O frequency which is equal $\Delta q_{f(-1)} = -\frac{\alpha}{\ln 2}$. Taking into account $\alpha \approx -4.16 \cdot 10^{-5}$ we find $\Delta q_{f(-1)} \approx 6 \cdot 10^{-5}$. We shall note that the value $\Delta q_{f(-1)}$ has rated character. Change of genic frequency at mutagenesis is real begins from time coordinate n=1 at which according to (38) is $\Delta q_{f(n-1)} = \Delta q_{f(0)} = 0$ .It concerns to Figure 3 and Figure 4.

On Figure 3 the dependence of genic alleles O frequency change $\Delta q_{f(n-1)}$ at women on the time of the population life plotted under the formula (38) is shown.

The analysis Figure 3 allows to assume that under action of the equivalent constant mutagen factor α there is average on individuals of the population the mutation (practically constant after n>8) resulting in average on the population to continuous reduction of healthy alleles O frequency at women and during too time to increase at them of destructive alleles O frequency i.e. to the hemophilia.

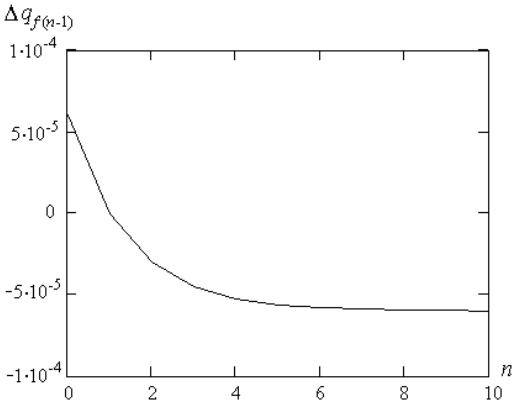

Figure 3
Dependence at Hemophilia of Genic Alleles O Frequency Change $\Delta q_{f(n-1)}$ for Women on the Dimensionless Time *n* of the Population Life

The law (32) of decrease in frequency of blood alleles O at mutations with the account (36) also $q_{f0} = q_{m0}$ can be written down as:

$$q_f = \frac{\alpha n}{\ln 2} - \frac{\alpha}{(\ln 2)^2} + \frac{C_3}{\ln 2} + \frac{4\alpha}{\ln 2} e^{-n \ln 2} \quad (39)$$

Using the initial condition: for n=0, $q_f = q_{f0}$ we shall find:

$$C_3 = q_{f0} \ln 2 + \frac{\alpha}{\ln 2} - 4\alpha \quad (40)$$

With account (40) the formula (39) we shall write down as:

$$q_f = q_{f0} + \frac{\alpha n}{\ln 2} - \frac{4\alpha}{\ln 2}\left(1 - e^{-n \ln 2}\right) \quad (41)$$

On Figure 4 (curve 1, the left scale of the ordinates axis) the graph plotted under the formula (41) for initial allele frequency $q_{f0} = 0.605$ (Vogel & Motulsky, 1990).

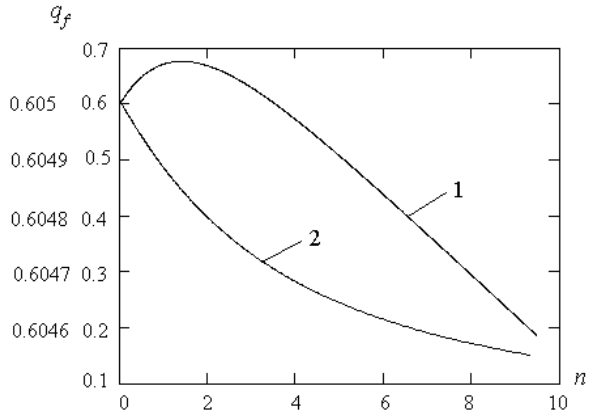

Figure 4
Graph of Dependence of Decrease in Allele Blood O Frequency q_f on Dimensionless Time *n* of the Population Life at Hemophilia 1 (Left Scale of the Ordinates Axis) **and at Selection 2** (Right Scale of the Ordinates Axis)

4. ACTION OF THE SELECTION ON POPULATION

For the analysis of the selection action on the population, with the purpose of the previous researches use, we shall return to the separate family tree. In the family tree where the hemophilia is observed the selection resulting in decrease of genic frequencies in particular of allele O blood operates.

Action of selection is intensive enough. For example, the life duration of the men who were ill by hemophilia makes 1/3 from the life duration of healthy people (Vogel & Motulsky, 1990), male fertility i.e. chances to have posterity in comparison with healthy men is reduced. Therefore not all men of the given family tree participate in reception of posterity and damaged alleles O eliminated from the family tree.

Let's consider selection against homozygotes *aa* (or OO).

Genotypes before selection, for example, in generation n-2 are distributed according to (1).

We accept fitnesses of genotypes (Vogel & Motulsky, 1990):

$$1:1:(1\text{-}s), \quad (42)$$

where s there is reduction of the homozygotes fraction of recessive allele as a result of selection (parameter of selection).

Genotypes after selection we shall write down for the following generation (n-1):

$$\begin{aligned} &(AA)\, p_{f(n-1)} p_{m(n-1)} : \\ &(Aa)\,(p_{m(n-1)} q_{f(n-1)} + p_{f(n-1)} q_{m(n-1)}) : \\ &(aa)\, q_{m(n-1)} q_{f(n-1)} (1-s) \end{aligned} \quad (43)$$

Taking into account, that

$$\begin{aligned} &p_{f(n-1)} p_{m(n-1)} + (p_{m(n-1)} q_{f(n-1)} + \\ &p_{f(n-1)} q_{m(n-1)}) + q_{m(n-1)} q_{f(n-1)} = \\ &\left(p_{f(n-1)} + q_{f(n-1)}\right)\left(p_{m(n-1)} + q_{m(n-1)}\right) = 1 \end{aligned}$$

we find the sum of genotypes frequencies: $1 - q_{m(n-1)} q_{f(n-1)} s$

Further, using a standard rule of an alleles frequency finding in the following generation (half of heterozygotes frequency plus of homozygotes frequency) and the formula (43) we calculate the frequency of recessive alleles *a* at women in generation n it is similar (Vogel & Motulsky, 1990) where such calculation is made for autosomal genome:

$$q_{fn} = \frac{\frac{1}{2}\left(p_{m(n-1)} q_{f(n-1)} + p_{f(n-1)} q_{m(n-1)}\right) + q_{m(n-1)} q_{f(n-1)} (1-s)}{1 - q_{m(n-1)} q_{f(n-1)} s} \quad (44)$$

Let's transform the formula (44), using $p_{m(n-1)} = 1 - q_{m(n-1)}$ and $p_{f(n-1)} = 1 - q_{f(n-1)}$:

$$q_{fn} = \frac{\frac{1}{2}\left(q_{f(n-1)} + q_{m(n-1)}\right) - q_{m(n-1)} q_{f(n-1)} s}{1 - q_{m(n-1)} q_{f(n-1)} s} \quad (45)$$

We believe that alleles *a* frequency at the men is equal to alleles *a* frequency at the women of the previous generation $q_{m(n-1)} = q_{f(n-2)}$. Hence:

$$q_{fn} = \frac{\frac{1}{2}\left(q_{f(n-1)} + q_{f(n-2)}\right) - q_{f(n-2)}q_{f(n-1)}s}{1 - q_{f(n-2)}q_{f(n-1)}s} \qquad (46)$$

Mutagenesis and selection operate in one direction. If arisen for the account mutagenesis the damaged alleles will be with the same velocity due to selection eliminated from a family tree the balance to be kept. A quantity of the damaged genes is kept in the family tree but this quantity will not increase.

The change of allele *a* frequency in the family tree using (46) it is possible to calculate under the formula:

$$\Delta q_{f(n-1)} = q_{fn} - q_{f(n-1)}$$

$$= \frac{\frac{1}{2}\left(q_{f(n-1)} + q_{f(n-2)}\right) - q_{f(n-2)}q_{f(n-1)}s}{1 - q_{f(n-2)}q_{f(n-1)}s} - q_{f(n-1)}$$

$$= \frac{\frac{1}{2}\left(-q_{f(n-1)} + q_{f(n-2)}\right) - q_{f(n-2)}q_{f(n-1)}s + q_{f(n-2)}q^2_{f(n-1)}s}{1 - q_{f(n-2)}q_{f(n-1)}s} \qquad (47)$$

At transition to the continuous time scale we believe difference in genic frequencies of two generations following one after another infinitesimal, i.e. $q_{f(n-2)} \approx q_{f(n-1)}$ Hence, the formula (47) will be transformed to the kind similar autosomal genome (Vogel & Motulsky, 1990):

$$\Delta q_{f(n-1)} = -\frac{q^2_{f(n-1)}s\left(1 - q_{f(n-1)}\right)}{1 - q^2_{f(n-1)}s} \qquad (48)$$

For transition from the family tree to the population we shall take the method offered by Vogel and Motulsky (1990) for calculation of allele *a* frequency at the big number of generations. We shall copy (48) as:

$$\frac{dq_f}{dn} = -\frac{q^2_f s\left(1 - q_f\right)}{1 - q^2_f s} \qquad (49)$$

Number of generation in the index of allele frequency for the population we do not write, *n* it is dimensionless time. We shall integrate (49):

$$\int_{q_{f0}}^{q_f} \frac{dq_f}{q^2_f s\left(1 - q_f\right)} - \int_{q_{f0}}^{q_f} \frac{dq_f}{\left(1 - q_f\right)} = -\int_0^n dn \qquad (50)$$

In result we shall find:

$$\frac{q_{f0} - q_f}{q_{f0}q_f} + \ln\frac{q_{f0}}{q_f}\left(\frac{1 - q_f}{1 - q_{f0}}\right)^{1-s} = sn \qquad (51)$$

For the blood system ABO as before initial allele *a* frequency we shall accept according to Vogel and Motulsky (1990) $q_{f0} = 0.605$.

The estimation of fitness (1-*s*) is enough challenge. One of possible ways to calculate fitness to find it is as the ratio of an average of survived children of the falling one parent which is sick of hemophilia to average of survived children on one healthy parent. For example, in the fitness at hemophilia calculated thus it is equal 1-*s*=1.75/2.5=0.7 (Li, 1976). But further proceeding from some supervision the most comprehensible needs size 1-*s*=0.29. For calculation we shall use the size of parameter of selection *s*=0.71.

On Figure 4 (curve 2, the right scale of the ordinates axis) the graph of dependence of decrease in blood allele O frequency q_f on dimensionless time *n* at the selection plotted under the formula (51) is shown.

Decrease in blood alleles O frequency occurs for the account of the mutants alleles elimination. This process is rather intensive at least it much more intensively mutational process at hemophilia, Figure 1 (curve 1, the left scale of the ordinates axis). Thereof concerning Haldane and Danforth ideas some words are necessary to tell about the balance of frequencies of mutations and selection at hemophilia.

Such equilibration is hardly feasible. Physiologically, it is two different processes. The law of occurrence of mutations (41) is absolutely not similar to the law of alleles elimination in population at selection (51). But actually equilibrations also it is not necessary. It is necessary only that velocity of mutations occurrence did not exceed the velocity of selection.

CONCLUSION

At the first record of the Hardy-Weinberg law the methodical mistake has been admitted connected by that this law was applied to the analysis of a population in the form correct only to the family tree. For the analysis of population it is necessary to use continuous time scale and the mathematical section of the differential equations.

Exception of the given methodical mistake allows to expand the numbers of the problems solved with the help of the Hardy-Weinberg law in particular in the demographic problem it permit to clear genetic-mathematical laws of generations alternation in the countries with a high level of medicine development and the homogeneous population also more clearly to understand the interrelation of mutagenesis and selection, for example, at hemophilia.

REFERENCES

Ayala, F., & Kiger, J. Jr. (1984). *Modern genetics* (Volume 3, p.335). California: The Benjamin/Cummings Publishing Company, Inc.

Brown, D., & Rothery, P. (1994). *Models in biology: Mathematics, statistics and computing* (p.688). Chichester, New York, Brisbane, Toronto, & Singapore: Jon Wiley & Sons Ltd.

Kalabekov, I. G. (2010). *Russian reforms in digits and facts* (p.498). Moscow, RUSAKI.

Li, C. C. (1976). *First course in population genetics* (p.556). Pacific Grove, California: The Boxwood Press.

Matveev, A. N. (1981). *Molecular physics* (p.400). Moscow, Higher School.

Vogel, F., & Motulsky, A. (1990). *Human genetics* (Volumes 1 & 2, p. 1068). Berlin: Springer-Verlag.

Volobuev, A. N. (2005). Population development of genome in conditions of radiating environment. *Moscow, Mathematical modeling*, *17*(7), 31-38.

Weir, B. S. (1990). *Genetic data analysis* (p.400). Sunderland, Massacusetts: Sinauer Associates, Inc Publishers.