

Nonlinear Genetics Inbreeding and Genetic Load

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Abstract

Comparison of concepts of occurrence and accumulation of the genetic load in result of inbreeding for a family tree and a population is given. It is shown that for the population the analysis of the genetic load concerns to area of nonlinear genetics. The nonlinear differential equation of the second order being the special case of the Hardy-Weinberg law at presence inbreeding for the population is found. The numerical decision of this equation allowed to find the law of increase of recessive allele frequency in the population is given. Some aspects of the traditional theory of the genetic load are considered.

Key words: Genetic load; Inbreeding; Hardy-Weinberg law; Nonlinear genetics

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INTRODUCTION

In (Volobuev, Romanchuk, & Malishev, 2013) it is shown that variation in during time of a population life of the recessive gene frequency linked to the X-chromosome in condition of the population balance is described by the linear differential equation of the second order. This equation is Hardy-Weinberg law for the panmixed

population. Also the linear differential equations of the second order describe, for example, the mutational process resulting in hemophilia (Volobuev, Romanchuk & Malishev, 2013) or mutational process under action of radiation (Volobuev & Petrov, 2011). Similar processes can be attributed to processes of linear genetics.

However in genetics there are the processes resulting in the nonlinear differential equations. These processes concern to nonlinear genetics. As an example of similar process we shall consider development of the population at presence of the inbreeding.

1. THE GENETIC LOAD IN RESULT OF INBREEDING IN A FAMILY TREE

The problem of inbreeding influence on the population is the important problem of genetics (Vogel & Motulsky, 1990). Now this problem yet has not received the final solution.

In the Hardy-Weinberg law the inbreeding in a family tree for the autosomal genome it is taken into account with the help of the inbreeding factor (Ayala & Kiger, 1984):

$$(AA)(p_n^2 + F_i p_n q_n) : (Aa)[2p_n q_n(1 - F_i)] : (aa)(q_n^2 + F_i p_n q_n), \quad (1)$$

where the standard designation of zygotes two-alleles genome AA , Aa and aa is used; p_n there is a frequency of the dominant allele A in generation n , q_n - the recessive allele a frequency, so $p_n + q_n = 1$, F_i - inbreeding factor for the family tree.

The ratio (1) refers to also as Wright's ratio. Wright's ratio shows that after consanguineous mating of individuals there are observed the following effects: there is increase in a fraction of homozygous in a family tree on $F_i p_n q_n$ and reduction in the fraction of heterozygous in $(1 - F_i)$ one in comparison with the panmixed population.

But already through generation the Hardy-Weinberg balance is restored, that specifies the small importance of separate consanguineous mating for a family tree:

$$q_{n+1} = \frac{1}{2} 2p_n q_n (1 - F_t) + (q_n^2 + F_t p_n q_n) = q_n \cdot \quad (2)$$

Obviously for a population as whole the separate act of consanguineous mating will have still smaller value than for a family tree.

The same effect of change of zygotes frequency is observed and for the sex-linked genes (Volobuev & Petrov, 2011):

$$\begin{aligned} (AA) \left[p_{fn} p_{mn} + (p_{mn} q_{fn} + p_{fn} q_{mn}) \frac{F_t}{2} \right] : (AA) [(p_{mn} q_{fn} + p_{fn} q_{mn})(1 - F_t)] : \\ (aa) \left[q_{mn} q_{fn} + (p_{mn} q_{fn} + p_{fn} q_{mn}) \frac{F_t}{2} \right], \end{aligned} \quad (3)$$

where p_{mn} there is allele A frequency at men and p_{fn} at women. For allele a it is accordingly q_{mn} and q_{fn} .

The recessive allele a frequency at the following generation women is equal:

$$\begin{aligned} q_{f(n+1)} &= \frac{1}{2} (p_{mn} q_{fn} + p_{fn} q_{mn})(1 - F_t) + q_{mn} q_{fn} + (p_{mn} q_{fn} + p_{fn} q_{mn}) \frac{F_t}{2} \\ &= \frac{1}{2} [(1 - q_{mn}) q_{fn} + (1 - q_{fn}) q_{mn}] (1 - F_t + F_t) + q_{mn} q_{fn} = \frac{1}{2} [q_{fn} + q_{mn}], \end{aligned} \quad (4)$$

that is corresponds with same frequency at absence inbreeding (Volobuev, Romanchuk, & Malishev, 2013), i.e. there is restoration the Hardy-Weinberg balance. Thus and for the genes linked to the X -chromosome the separate act of consanguineous mating for the family tree has no great value.

There are populations where the principle of panmixed mating is essentially infringed. Usually it is geographically or socially be relative isolated small populations. In these populations the inbreeding, i.e. consanguineous mating of various orders (parent - child, siblings, cousin siblings, uncle - niece, etc.), can be spread widely enough. Therefore in such populations so-called the genetic load frequently connected to harmful mutations only recessive alleles passed to offspring is accumulates. The concept of the genetic load in the population was used for the first time the known geneticist Nobel laureate H. J. Muller (Muller, 1950). However, actually the theory of the genetic load has been developed only for a family tree.

As result of increase in recessive homozygous frequency in process of consanguineous mating in the population the increase of their harmful mutations is observed also. Therefore it is supposed that inbreeding is one of principal causes of occurrence and accumulation of the genetic load.

The genetic load can be expressed in lethal equivalents. The lethal equivalent is, for example, one lethal mutation resulting in death of an individual in all cases or two lethal mutations each of which resulting in death of the individuals in 50% cases, etc.

At research of inbreeding in populations the, action of selection we shall not take into account to not complicate the analysis. It is allowable since selection submits to other laws rather than occurrence of equation (Volobuev,

Romanchuk, & Malishev, 2013).

According to the genetic load theory the equation (3) needs to be transformed (Vogel & Motulsky, 1990):

$$\begin{aligned} (AA) \left[p_{fn} p_{mn} + (p_{mn} q_{fn} + p_{fn} q_{mn}) \frac{F_t}{2} \right] : \\ : (Aa) [(p_{mn} q_{fn} + p_{fn} q_{mn})(1 - F_t)(1 - sh)] : \\ : (aa) \left[q_{mn} q_{fn} + (p_{mn} q_{fn} + p_{fn} q_{mn})(1 - s) \frac{F_t}{2} \right], \end{aligned} \quad (5)$$

where s there is probability of the recessive homozygous destruction as consequence of the inbreeding, sh - probability of the heterozygous destruction as consequence of the inbreeding, h - so-called dominant degree of the mutation which have occurred owing to inbreeding. If $h=1$ there are heterozygous and recessive homozygous perish with the identical frequency, if $h=0$ the heterozygous are resistant to inbreeding. Dominant homozygous are assumed absolutely resistant to mutations. It is mutational model of process.

Let's notice that the ratio (5) concerns to a family tree as separate usually small making population.

Using (5) we shall find the recessive allele a frequency at women in the following generation:

$$\begin{aligned} q_{f(n+1)} &= \frac{1}{2} (p_{mn} q_{fn} + p_{fn} q_{mn})(1 - F_t)(1 - sh) \\ &\quad + q_{mn} q_{fn} + (p_{mn} q_{fn} + p_{fn} q_{mn})(1 - s) \frac{F_t}{2} \\ &= (p_{mn} q_{fn} + p_{fn} q_{mn}) \left[\frac{1}{2} (1 - F_t)(1 - sh) + (1 - s) \frac{F_t}{2} \right] + q_{mn} q_{fn} \\ &= \frac{1}{2} [(1 - q_{mn}) q_{fn} + (1 - q_{fn}) q_{mn}] [1 - sh - F_t + F_t sh + F_t - F_t s] + q_{mn} q_{fn} \\ &= \left(\frac{1}{2} (q_{fn} + q_{mn}) - q_{mn} q_{fn} \right) (1 - sh + F_t sh - F_t s) + q_{mn} q_{fn} \\ &= \frac{1}{2} (q_{fn} + q_{mn}) - \left(\frac{1}{2} (q_{fn} + q_{mn}) - q_{mn} q_{fn} \right) (sh - F_t sh + F_t s) \\ &= \frac{1}{2} (q_{fn} + q_{mn}) - \frac{1}{2} (q_{fn} + q_{mn}) (sh - F_t sh + F_t s) + q_{mn} q_{fn} (sh - F_t sh + F_t s) \\ &= \frac{1}{2} (q_{fn} + q_{mn}) (1 - sh + F_t sh - F_t s) + q_{mn} q_{fn} (sh - F_t sh + F_t s). \end{aligned} \quad (6)$$

In the following generation there is no restoration of the Hardy-Weinberg balance, i.e. accumulation of the genetic load in a family tree, and hence and in a population is observed.

Let's enter the designation $F = sh - F_t sh + F_t s$ - factor of inbreeding for the population. We shall note that if the heterozygous are resistant to mutations owing to inbreeding $h=0$, and recessive homozygous are perish with probability $s=1$ the factors of inbreeding of the populations and family tree are equal $F = F_t$. Thus the equaton (6) can be written down as:

$$q_{f(n+1)} = \frac{1}{2} (q_{fn} + q_{mn}) (1 - F) + q_{mn} q_{fn} F. \quad (7)$$

Lack of the equation (7) is absence normalization on the general fraction of genes less than 1 the rest

after lethal mutations. However the standard way of normalization (Vogel & Motulsky, 1990) results in too complex formulas which do not allow to proceed to the analysis of the population.

For updating the equation (7) it is used the following logic. In the condition of balance of the family tree with inbreeding the equation (4) for calculation of the recessive allele a fraction is correct. The equation (4) is absolutely correct since is normalized on the general portion of genes equal 1.

Taking into account (4), and also $F \ll 1$ (Vogel & Motulsky, 1990) and small size of the second addend in the right part (7) it is possible to assume that for normalization (7) it is necessary to divide the right part into value $1-F$.

Therefore the corrected formula (7) looks like:

$$q_{f(n+1)} = \frac{1}{2}(q_{fn} + q_{mn}) + q_{mn}q_{fn} \frac{F}{1-F}. \quad (8)$$

The equation (8) allows find the recessive allele a fraction at women in the following generation of the family tree as the sum of equilibrium addend and gradually increasing owing to inbreeding the genetic load.

2. THE GENETIC LOAD AS RESULT INBREEDING IN THE POPULATION

We carry out now transformation from a family tree to the population by the technique offered in (Volobuev, Romanchuk & Malishev, 2013).

Taking into account that the man inherits the X-chromosome from mother i.e. $q_{mn} = q_{f(n-1)}$ it is possible to transform (7) to kind:

$$q_{fn} - 2q_{f(n+1)} + q_{f(n-1)} = -2 \frac{F}{1-F} q_{f(n-1)} q_{fn}. \quad (9)$$

The differential equation for change of frequency q_{fn} of recessive allele a in population we shall write down in general form:

$$\frac{d^2 q_{fn}}{dn^2} + \eta \frac{dq_{fn}}{dn} = \mu q_{fn}^2. \quad (10)$$

where the independent variable n there is in this case time of the population life normalized on average on family trees of population time of one generation change (approximately 25 years) i.e. actually continuous dimensionless time, η and μ - constants.

Let's pass in (10) to final differences:

$$\frac{q_{f(n+1)} - 2q_{fn} + q_{f(n-1)}}{\Delta n^2} + \eta \frac{q_{fn} - q_{f(n-1)}}{\Delta n} = \mu q_{fn}^2. \quad (11)$$

Let's collect the like terms:

$$q_{f(n+1)} - (2 - \eta \Delta n) q_{fn} + (1 - \eta \Delta n) q_{f(n-1)} = \mu \Delta n^2 q_{fn}^2. \quad (12)$$

Let's multiply (12) on -2 besides we shall replace $q_{fn}^2 = q_{f(n-1)} q_{fn}$ that is allowable for continuous in time of the generation alternation scale i.e. for a population:

$$-2q_{f(n+1)} + 2(2 - \eta \Delta n) q_{fn} - 2(1 - \eta \Delta n) q_{f(n-1)} = -2\mu \Delta n^2 q_{f(n-1)} q_{fn}. \quad (13)$$

Let's identify (13) and (9). In result we have system of three algebraic equations:

$$2(2 - \eta \Delta n) = 1, \quad (14)$$

$$-2(1 - \eta \Delta n) = 1, \quad (15)$$

$$\mu \Delta n^2 = \frac{F}{1-F}. \quad (16)$$

The solution of the given system looks like:

$$\eta = \frac{3}{2\Delta n}. \quad (17)$$

that similarly the equilibrium panmixed populations (Volobuev, Romanchuk & Malishev, 2013).

$$\mu = \frac{F}{\Delta n^2(1-F)}. \quad (18)$$

Hence, the differential equation (10) can be copied as:

$$\frac{d^2 q_f}{dn^2} + \frac{3}{2\Delta n} \frac{dq_f}{dn} = \frac{F}{\Delta n^2(1-F)} q_f^2. \quad (19)$$

The number of generation for the population does not play a role - the continuous time scale therefore an index n is omitted.

The found nonlinear differential equation (19) is the Hardy-Weinberg law for population with the account of inbreeding.

At $F=0$ (inbreeding is absent) the equation (19) it will be transformed to the kind:

$$\frac{d^2 q_f}{dn^2} + \frac{3}{2\Delta n} \frac{dq_f}{dn} = 0. \quad (20)$$

that corresponds to the equilibrium panmixed population (Volobuev, Romanchuk & Malishev, 2013).

We use in (19) new independent variable $t = \frac{n}{\Delta n} \sqrt{\frac{F}{1-F}}$. If to accept (Volobuev, Romanchuk &

Malishev, 2013) $\Delta n = \frac{3}{2 \ln 2}$ we shall find $t = \frac{2 \ln 2n}{3}$

$$\sqrt{\frac{F}{1-F}} \approx 0.462n \sqrt{\frac{F}{1-F}}.$$

For the new variable t the equation (19) depends only on one constant parameter ε :

$$\frac{d^2 q_f}{dt^2} + \varepsilon \frac{dq_f}{dt} = q_f^2 \quad (21)$$

where it is designated $\varepsilon = \frac{3}{2} \sqrt{\frac{1-F}{F}}$ At change of the inbreeding factor $0 \leq F \leq 1$ the size is $\infty \geq \varepsilon \geq 0$.

The nonlinear differential equation (21) can be solved only numerically.

Initial conditions first of all are necessary for the decision of the differential equation (21): initial frequency of the recessive allele a q_0 and initial speed of increase in this frequency $\left(\frac{dq_f}{dt}\right)_0$ or $\left(\frac{dq_f}{dn}\right)_0$

Initial frequency q_0 depends on time of the beginning of the population analysis. Therefore without reduction of the analysis generality at $t=0$ or $n=0$ we shall accept $q_0=0.6$.

Various variants of numerical calculations under the formula (21) show that the result of calculation at small initial speed of the frequency increase q_f practically does not depend on this speed. Therefore was accepted $\left(\frac{dq_f}{dt}\right)_0 = \left(\frac{dq_f}{dn}\right)_0 = 0$. The step of the variable t equal $\Delta t=0.001$ and numbers of steps 20,000 at calculation were used.

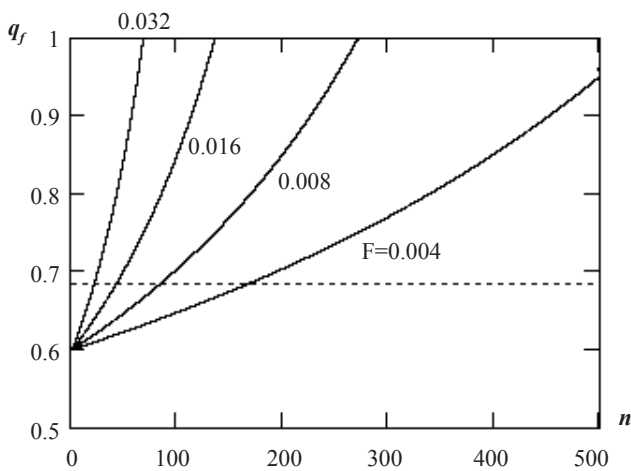


Fig.1.

Figure 1
Time Dynamics of the Recessive Allele a Increase in the Population for Various Inbreeding Factors. (For Japan $F=0.004$)

On Figure 1 the calculation of the population dynamics of recessive allele a on the basis of the equation (21) at various inbreeding factors F is shown. On the abscissa axis the size $n \approx \frac{t}{0.462} \sqrt{\frac{1-F}{F}}$ is plotted.

From graphs it is visible that at presence of inbreeding in the population there is continuous increase of the recessive allele a q_f frequency in which can arise lethal adverse (at association in homozygous) mutations i.e. there is the negative genetic load in the population.

Traditionally (Morton, Crow, & Muller, 1956) the genetic cargo is estimated on the basis of the analysis of deadborns or children's death rate with the help of two parameters A and B included in the approached equation for the fraction of the survived zygotes:

$$S = \exp(A + BF) \tag{22}$$

Unfortunately the data on experimental sizes of parameters A and B have very much variation of values. In (Vogel & Motulsky, 1990) cited the data on the population of France $B=1.5-2.5$ and $\frac{B}{A}=15.06-21.41$.

More detailed data are available on the population of Japan. In different prefectures the ratio $\frac{B}{A}$ 15.2–(–5). Negative value $\frac{B}{A}$ means that children's death rate in consanguineous marriages was lower than in non consanguineous marriages (Vogel & Motulsky, 1990). Average sizes on the country $A=0.1036$, $B=0.67$ and $\frac{B}{A}=6.7$.

It is possible to assume (Vogel & Motulsky, 1990) that there is some threshold of recessive homozygous genes allowable frequency compatible with a survival of individual.

Taking into account values A and B , and also inbreeding factor for Japan $F=0.004$ (Vogel & Motulsky, 1990) under the equation (22) we shall find the fraction of the survived zygotes $S=0.9$. Fraction of the perish zygotes there is $1-S=0.1$. The elementary estimation under the formula $1-S=q_f^2=0.1$ gives the fraction of lethal (parameter of selection is equal 1) at association in homozygous recessive alleles $q_f \approx 0.316$ (Ayala & Kiger, 1984). Hence the fraction of not mutant genes equal to threshold frequency of recessive alleles is $q_{f,max}=1-q_f=0.684$.

On Figure 1 dotted line shows the threshold frequency. For Japan this frequency is attained approximately in 167 generation.

The received result shows that accumulation of the genetic load it is process very slow. Achievement of threshold frequency for Japan to be carried out only in 167 generations or 4175 years at time of one generation change $T=25$ years.

In (Vogel & Motulsky, 1990) it is noticed that from the beginning of the population development with factor inbreeding $F=0.003-0.005$ up to achievement of equilibrium frequency which is established at action of selection should pass about 4500 years. In calculation the formula of linear increase of recessive alleles frequency was used at mutation speed $\mu=10^{-5}$. Increase of the mutant alleles number was compensated by selection against recessive homozygous with parameter of selection 0.5.

Therefore most likely that limiting values of the genetic load in a human population of many countries especially taking into account small sizes of inbreeding factor (Canada $F=45 \cdot 10^{-5}$, France $F=23 \cdot 10^{-5}$, Germany

$F=19 \cdot 10^{-5}$, Italy $F=16 \cdot 10^{-5}$ (Vogel & Motulsky, 1990), etc.) even at presence of selection till now are not achieved.

In our opinion with help of the offered method it is possible to examine not only harmful for the population genetic load related with inbreeding but also useful and indifferent genetic load (or attributes).

At early stages of mankind development the role of inbreeding was more in connection with smaller number of people and isolation of separate groups. Therefore accumulation of the genetic load was more intensively (the inbreeding factor was much more). Primeval people after the going out from Africa and moving in northern Europe began to live in conditions of smaller light exposure including in the ultra-violet part of spectrum. In result the skin with originally dark pigmentation started to have white color. It promoted occurrence of vitamin D which deficiency results in rickets (Vogel & Motulsky, 1990). Process of dark pigmentation reduction of skin can be examined as accumulation of the recessive useful genetic load. Natural selection fixed given phenotypic attribute at people in region.

To the indifferent genetic load in population it is possible to ascribe occurrence such recessive attribute as blond hair, for example, in northern part of Europe where apparently at early stages the inbreeding has been especially widespread. Color of hair does not play a role in survival of population. Fixed of this attribute was carried out by the sexual selection i.e. marriage preferences of people in region.

However it is traditionally accepted to examine accumulation of the genetic load in the population are determined by harmful mutations. Some fears of H. J. Muller are connected to this process about danger of the future biological degeneration of mankind (Muller, 1950).

CONCLUSIONS

Among processes of population genetics it is possible to allocate linear processes, for example, development of the

panmixed populations, the mutational process resulting in hemophilia, the mutational process under action of radiation which described by the linear differential equations of the second order. For nonlinear genetics processes which described by the nonlinear differential equations of the second order are typical, for example, development of a population at presence of inbreeding.

The concept of genetic load allows lead the analysis of the population with inbreeding, in particular to find the law of the recessive allele frequency increase in the population.

The existing theory of genetic load occurrence and accumulation is actually developed only for a family tree as small component of population.

Using the technique of transition offered by the authors from the analysis of a family tree to the analysis of a population the theory of the genetic load arising for the account inbreeding in a population is developed.

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