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THEORETICAL PAPERS AND REVIEWS

Haldane's Rule and Somatic Mutations

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Abstract—Haldane's rule stating that viability and fertility in the heterogametic sex of hybrids are lower than in the homogametic sex is explained on the basis of the assumption that diploidy is aimed at protecting individuals having large body size and large genomes from somatic mutations. The presence of hemizygous sex chromosomes, which are effectively haploid in the heterogametic sex, results in the phenotypic expression of all deleterious somatic mutations arising in them. In the homogametic sex, somatic mutations that affect one out of two identical sex chromosomes are not expressed because the unaffected chromosome functions normally. Thus, the heterogametic sex is more sensitive to the harmful effect of somatic mutations. In hybrids, this difference may be critical. Consequently, when genetic distance between hybridizing species increases, the heterogametic sex of hybrids loses viability and fertility earlier than the homogametic sex, which agrees with Haldane's rule. On the basis of Haldane's rule and data on the small size of natural hybrid zones, restrictions on maximum heterozygosity compatible with viability were established.

INTRODUCTION

The well-known empirical rule formulated by Haldane [1–3] states that viability or fecundity in the heterogametic (e.g., XY) sex is lower than in the homogametic (XX) one. Consequently, if one sex in a hybrid is nonviable or sterile, this is the heterogametic sex. Haldane's rule holds for a wide range of organisms (mammals, birds, butterflies, *Drosophila*) irrespective of which sex is heterogametic [4] (for convenience, hereafter we refer to heterogametic sex as male). Among numerous explanations of Haldane's rule, none is generally accepted or encompass all available experimental evidence [3, 5]. Most explanations are based on various chromosome incompatibilities in the hybrid genome.

Concerted functioning of the X and Y chromosome is assumed to significantly affect male viability or fertility [6]. In this case, hybrid males are affected more than females because X and Y chromosomes from different species may be incompatible. Fitness of females is not impaired because females lack Y chromosomes. However, this explanation is not general because in some cases (e.g., in *Drosophila*), the contribution of the Y chromosome to viability is insignificant [7]. Moreover, in some cases, this chromosome has no effect on hybrid fertility [4].

Another explanation is based on the so-called dominance theory [5], which implies the concerted operation of autosomal and X-linked genes. It is assumed that products of many autosomal genes can participate in biochemical metabolic pathways only if the corresponding X-chromosome genes are expressed. Thus, some autosomal genes do not function in the absence of the X chromosome of their species. A lack of the X chromosome of a parental species in the heterogametic hybrid results in epistatic suppression of paternal autosomal genes [1]. In addition, it is assumed that defective genes that reduce hybrid viability and fertility are present in parental genomes. If alleles of defective autosomal genes of one species (species α) are recessive, it will lead to disruption of metabolic pathways in heterogametic hybrids. Consider crossing a female of species α with a male of species β. In hybrid females, chromosome set $\{X_\alpha A_\alpha X_\beta A_\beta\}$, where A stands for autosomes, will function normally because recessive defective autosomal genes A_α are not be expressed when their dominant counterparts A_β function in concert with genes of the X_β chromosome. In males $\{X_\alpha A_\alpha Y_\beta A_\beta\}$, dominant genes A_β will not function because the X_β chromosome of species β is absent, defective autosomal genes A_α will be expressed, and the fitness of heterogametic males will decrease [5, 8].

However, this explanation is in conflict with the fact that viable and fertile "unbalanced" hybrid *Drosophila* females were obtained that carry autosomes from different species and X chromosomes from the same species as well as the Y chromosome from another species or genome [4]. In our notation, their genotype is $\{X_\alpha A_\alpha X_\alpha A_\beta + Y_\beta\}$. These females carry the same set of genes and are expected to have the same fitness as males. In species, for which Haldane's rule holds for viability, both unbalanced females and males are not viable [9, 10]. If Haldane's rule holds for fertility, unbalanced females are fertile although hybrid males with analogous genomes are sterile [6]. To explain this, it is assumed that defective genes reducing hybrid fertility are sex-dependent, i.e. males and females have different genes and these genes function differently depending on the presence or absence of the Y chromosome [5, 8]. However, further experimental data are required to prove this scenario, because experiments

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with unbalanced females were carried out only on organisms with heterogametic males (*Drosophila*), whereas Haldane's rule holds for birds and butterflies, in which females are heterogametic.

In the present work, Haldane's rule is explained on the basis of the assumption that diploidy is aimed at preserving cells of a multicellular organism from somatic mutations. In a homozygous locus of the diploid genome lacking deleterious hereditary substitutions, new harmful mutations of one allele arising in somatic or germline cells are compensated by normal functioning of the other allele [11]. In a heterozygous locus, of which one allele contains a deleterious substitution and does not function normally, new mutations of the other normal allele are phenotypically expressed. This implies the existence of critical heterozygosity levels: if these levels are exceeded, individual viability declines. We argue that the heterozygosity level is crucial for explaining Haldane's rule.

DIPLOIDY

So far, there is no generally accepted explanation of the fact that genomes of most organisms are diploid [12]. Diploidy increases genetic polymorphism of viable individuals in a population. This is usually regarded as a factor accelerating evolution and adaptation of the population to changing environments [13].

A fundamentally different approach to understanding diploidy is based on the effect of somatic mutations in multicellular organisms [11, 14–16]. In a multicellular organism, genetic information pertaining to individual development and complex concerted action of its cells and organs must be stored. Consequently, such organisms have large genomes with the minimum size of 10^8 bp; most multicellular animals have genomes of 10^9 to 10^{10} bp [17].

The problem of somatic mutations is related to the large genomic and body size in multicellular organisms. Deleterious germline mutations are eliminated from the population by selection. However, deleterious somatic mutations cannot be thus eliminated because cells of different organs in a multicellular organism are highly differentiated and associated and cannot substitute each other like individuals in a population. Thus, a multicellular organism carries a load of somatic mutations. In what follows, we demonstrate that this load is proportional to the genomic and body size. It is assumed that, if the critical genomic and body sizes are exceeded, the existence of a multicellular organism in the haploid phase is impossible and the organism becomes diploid. Diploidy ensures protection from the deleterious mutation effects [11]: the allele that is not mutationally affected can compensate defective functioning of the mutant allele.

The mean number of somatic mutations μ per cell of an organism with the genomic size G and body weight M can be estimated as follows. The mutation rate per one base pair (bp) per cell division (d) is $\nu \sim 10^{-10}$ (bp)$^{-1}$ d^{-1} [11]. We can estimate the number of cell divisions in a somatic line K_s using the dichotomous approximation, i.e., assuming that all cell divisions are dichotomous. In this case, an organism that consists of n cells will have $K = \log_2 n$ somatic cell divisions. The value of n can be estimated as $n = M/m_{cell}$, where M is the body weight, and m_{cell} is the mean weight of cells of the organism. Taking mean weight of an eukaryotic cell to be 10^{-9} g and converting logarithms from binary to natural ones, we obtain

$$K_s = \log_2 10 \log(M/m_{cell}) = 3.3(\log M + 9), \quad (1)$$

where M is the body weight in grams. Thus,

$$\mu = \nu G K_s = 3.3\nu G(\log M + 9). \quad (2)$$

For small organisms having body weight of about 0.1 g and the genome size not exceeding that of haplodiploid insects ($G_1 \approx 2 \times 10^8$ bp) [18, 19], we obtain from (2)

$$\mu_1 = 3.3 \times 10^{-10} \times 2 \times 10^8 (\log 0.1 + 9) \approx 0.5 < 1. \quad (3)$$

This means that the mean number of somatic mutations arising in each cell during development of the organism is less than unity, i.e. somatic mutations are absent or rare. This value of μ_1 can be regarded as the critical value, which determines the transition to diploidy, because males of haplodiploid insects apparently are the largest haploid animals having the largest genome.

Note that some haploid algae are large in size. This is explained by a weak association between their cells because algae lack the vascular system. The appearance of cells with an unacceptable number of somatic mutations results in the death of these cells but the normal functioning of other cells is not impaired. In animals, which have strongly associated cell systems, this course of events is impossible because the death of cells of any specialized organ will lead to the death of the individual. Consequently, in algae, the correlation radius (the area within which the death of given cells results in the death of all cells associated with them) is small, not exceeding the size of strongly correlated small haploid organisms. Thus, relationship (3) apparently holds for all haploid algae.

Large animals, e.g., mammals of about 10 kg (10^4 g) in weight, which have the haploid genome size $G_2 \approx 4 \times 10^9$ bp [20], would have contained about 20 expressed somatic mutations in each cell, if the genomes of these cells were haploid. This is 40 times higher than the corresponding value for haploid insects μ_1 (3):

$$\mu_2 = 3.3 \times 10^{-10} \times 4 \times 10^9 (\log 10^4 + 9) \approx 20 \gg 1. \quad (4)$$

It is known that about 1% of the genome in a population is not polymorphic [21]. This means that any mutations in this part of the genome lead to lethality or sterility of their carriers. Thus, if the mean number of mutations per cell is higher than 1 (4), up to 1% of cells

of an individual would contain mutations in impermissible regions, which would result in mortality of large haploid organisms having large genomes. Thus, diploidy seems to be a necessary prerequisite for the existence of large organisms with large genomes. The fact that $\mu_1 \ll \mu_2$ quantitatively demonstrates the possible significance of diploidy in the protection of an organism from deleterious somatic mutations.

This role of diploidy is confirmed by the results of experiments on irradiation of haploid males and diploid females of haplodiploid insects [18]. In haploid males, cells of many organs are known to acquire polyploidy in ontogeny. In adult males, most cells have ploidy of 2, 4 and more. However, at early stages of development, most somatic cells in these males remain haploid. In females, somatic cells have ploidy of 2 or higher throughout their life. When males and females are exposed to radiation at early developmental stages, males whose cells are still haploid die far more often than females. At later stages of development, this difference in mortality rates decreases and ultimately disappears when diplo- and polyploidization of most male cells is completed. After irradiation of adult males and females, their mortality is equal. Thus, diploidy of somatic cells can have a substantial effect on individual viability.

Using expressions (1) and (2) for estimation of the mean number of somatic mutations per cell requires explanation. The rate of mutation accumulation is proportional to the cell metabolic rate. In anabiosis, metabolism is depressed but not completely absent; consequently, mutations occur even in dormant plant seeds. The rate of cell division is also proportional to the rate of cell metabolism, which changes by several orders of magnitude when temperature and body size change [22]. Consequently, the rate of mutation accumulation per cell division, which does not depend on metabolism, i.e., temperature and body size, is uniform in large taxa. This parameter is widely used for estimating mutation accumulation rates in various organisms [11, 23, 24].

Estimation of the deletion number K_s in the somatic line on the basis of dichotomous approximation (1) is not exact because of the fact that after termination of individual development, stem cells in many tissues continue to divide and old cells are substituted by new ones although the organ and the entire body do not grow. On average, the number of stem cell divisions occurring in the lifetime of an individual can be several times higher than the estimated number of dichotomous divisions occurring during growth. However, only part of the genome, which is several times smaller than the total genome size, functions in all specialized organs. Totipotency, i.e., functioning of the entire genome required for development of the organism, is preserved only during the first cleavage divisions. Consequently, the order of magnitude of the mean number of mutation substitutions in somatic cells [(3) and (4)] is preserved when this value is estimated on the basis of stem cell divisions in an adult individual.

Finally, the main argument in favor of using dichotomous approximation (1) is low variation of K_s in different organisms. The genome of multicellular animals varies in different taxa by several orders of magnitude (from 10^8 bp in sponges to 10^{11} bp in some fish species and anurous amphibians) [17]. By contrast, the minimal number of cell divisions in somatic line K_s, which is proportional to the logarithm body weight (1), changes in these organisms by less than an order of magnitude (from $K_s = 10$ in the smallest to $K_s = 50$ in the largest multicellular animals). Thus, the primary relationship is that between μ (2) and the genome size G, whereas the bias in the K_s estimation is not significant.

In diploid organisms, somatic mutations are expressed only in the case when they simultaneously occur in the same site of the two copies of the diploid genome. The probability of this double event is proportional to the product of the probabilities of the single events (ν^2), i.e., this probability is very small. Thus, the appearance of diploidy opened the possibility for constructing organisms as large as is wished.

Equation (2) holds for the coding region of the genome G_p:

$$\mu_p = \nu G_p K_s = 3.3\nu G_p(\log M + 9), \qquad (5)$$

where μ_p is the mean number of somatic mutations in the coding region of the genome. According to the data reviewed in [25], the number of the coding part of the genome increases with the total genome size following the relationship $G_p \sim G^{0.6}$ (the table). Because of this, the difference between μ_p values estimated from (3) and (4) for large and small organisms having respectively large and small genomes, persists in being approximately $1.8 \times 20^{0.6} \approx 10$. Thus, these values differ approximately ten times: by a factor of 1.8 due to the difference in K_s and 6 due to the change in the coding genome regions, which corresponds to the 20-fold change in the total genome size:

$$\frac{\mu_{p_2}}{\mu_{p_1}} = \frac{G_2^{0.6} K_{S_2}}{G_1^{0.6} K_{S_1}} = \frac{(4 \times 10^9)^{0.6}}{(2 \times 10^8)^{0.6}} \times \frac{(\log 10^4 + 9)}{(\log 0.1 + 9)}$$

$$\approx 20^{0.6} \times 1.8 \approx 10.$$

In the estimation of the effectively haploid part of the genome presented below, we use values corresponding to the coding genome regions (autosomal and hybrid heterozygosities) since heterozygosity in the noncoding part of the genome is studied in less detail.

AUTOSOMAL AND SEX HETEROZYGOSITY

In all diploid organisms, a small portion of the genome can be haploid because of the chromosomal determination of sex. Heterogametic males in mammals (and females in butterflies and birds) carry unmatched (haploid, sex) X and Y (in birds and butterflies, W and Z) chromosomes. In mammals, these chromosomes constitute 5% of the total genome [20].

The relationship between the size of coding part of the genome and the total genome size in animals

Organism	Genome size ($G \equiv 1$ C) (10^9 bp)	Relative size of the coding genome part, % ($G_p/G \times 100$)	Absolute size of the coding genome part G_p (10^9 bp)
Bacterium (*E. coli*)	0.004	100	0.004
Yeast (*Saccharomyces*)	0.009	70	0.0063
Nematode (*Caenorhabditis*)	0.09	25	0.0225
Fruit fly (*Drosophila*)	0.18	33	0.0594
Newt (*Triturus*)	19.0	3	0.57
Human (*Homo sapiens*)	3.5	18	0.63
Fish (*Protopterus*)	140.0	0.8	1.12

Note: Data from Table 2 of [25]. Values were approximated by the power function $G_p = aG^b$, which gave $b = 0.58 \pm 0.06$ ($r = 0.98$, $P < 0.001$).

In addition to sex chromosomes, the genome contains a small random heterozygous part, in which alleles of the diploid set of matching chromosomes (autosomes) do not coincide because of accumulated mutation substitutions. This part of the genome can be described by the observed protein heterozygosity H_a. Comparing effects of somatic mutations in the hemizygous sex part and the heterozygous autosomal part of the genome, it should be taken into account that the observed protein heterozygosity H_a corresponds to the presence of mildly deleterious mutation substitutions [26] that passed through the "selection sieve." Consequently, deleterious somatic mutations in heterozygous autosomal loci have a weaker phenotypic expression than corresponding mutations in the effectively haploid hemizygous part of the genome. This fact can be accounted for by introducing a coefficient $\alpha (0 \le \alpha \le 1)$ before H_a in all expressions, i.e., H_a should be replaced by αH_a. However, as this substitution does not alter any of the conclusions and results of this paper, we omit coefficient α in all further intermediate calculations, i.e., for simplicity we consider $\alpha = 1$.

We define total effective individual heterozygosity H, which characterizes the effectively haploid part of the genome, as the number of noncoinciding sites of the diploid genome related to the total genomic site number. In this case, noncoinciding sites of unmatched chromosomes are supplemented by null sites. The total effective heterozygosity H is equal to the sum of random autosomal heterozygosity H_a and fixed sex heterozygosity H_0:

$$H = H_a + H_0.$$

Sexual heterozygisity (hemizygosity) H_0, associated with unmatched sex chromosomes, exists only in heterogametic sex, i.e., in males of mammals and females of butterflies and birds [1, 27]. In homogametic sex, $H_0 = 0$, total effective heterozygosity H coincides with traditional heterozygosity and is determined by accumulation of deleterious recessive substitutions in autosomes and the X chromosome. In mammals, autosomal heterozygosity H_a is on average 4% [28], whereas the relative length of the X and Y chromosomes is on average 5% of the haploid genome [20].

Thus, the total effective heterozygosity H is at least twice as low in the homogametic as in the heterogametic sex:

$$H = (H_a + H_0) \le 9\%$$

for the heterogametic sex and

$$H \approx H_a \le 4\%$$

for the homogametic sex. Here, we neglected the contribution of X-chromosome heterozygosity, which provides a correction of about 5%. Thus, the homogametic sex is at least twice better protected from the effect of deleterious somatic mutations than the homogametic one. This can account for the fact that mammalian males have a higher mortality rate than females [29]. In birds, females (heterogametic WZ sex) should have higher a mortality rate than males, which is actually observed [30–32].

THRESHOLD HETEROZYGOSITY VALUES AND HALDANE'S RULE

In large animals having large genomes, the effective haploid part of the diploid genome characterized by the total effective heterozygosity H cannot increase indefinitely due to the rapid accumulation of deleterious mutational substitutions in ontogeny. The larger the animal, the more cell divisions required for its development, and the more new mutational substitutions contained in each cell of its body.

Hence, there are two threshold values of heterozygosity: H_c (threshold ability to compete with other individuals in the population) and H_L (lethality threshold). All individuals with total effective heterozygosity H that does not exceed H_c are equally competitive in a natural population. Individuals whose total effective heterozygosity H is higher than H_c have a low competitive ability and are eliminated from the population. However, their viability is retained at the level $H_L > H_c$. Outside their natural environment and under noncompetitive conditions, the number of these individuals can

increase (e.g., domestic animals with $H < H_L$ are viable, but in natural environments, they are competitively replaced by wild related species whose $H > H_c$). All individuals with heterozygosity $H > H_L$ are nonviable or sterile, i.e., their genomes are eliminated from the population.

The existence of the threshold heterozygosity H_L explains Haldane's rule, according to which heterogametic sex in interspecific hybrids is often absent, nonviable, or sterile [1, 9]. The diploid genome of an interspecific hybrid contains two haploid genomes of parental species. In this case, autosomal heterozygosity is determined not only by random substitutions accumulated in each species but also by differences in normal parental genomes that appears in strictly defined locations irrespective of the presence or absence of random intraspecific substitutions. This can be termed hybrid heterozygosity H_h in contrast to random heterozygosity H_a of each species.

The total effective heterozygosity of a homogametic hybrid, which is equal to the sum of hybrid and autosomal heterozygosities, in this case is higher than autosomal heterozygosity of homogametic individuals of each species and can be close to the lethality threshold H_L:

$$H = H_a + H_h \le H_L.$$

The addition of relative contribution of sex chromosomes H_0 to the total autosomal heterozygosity can move the total effective heterozygosity of the heterogametic hybrid beyond the lethal threshold and cause hybrid lethality:

$$H = H_a + H_h + H_0 > H_L, \quad (6)$$

which corresponds to Haldane's rule.

Taking into account that H_a enters into expression (6) instead of αH_a, note that the result holds true also with $\alpha = 0$, since Haldane's rule is determined by H_0 describing the difference between total heterozygosities of the hetero- and homogametic sexes, while αH_a is equal for both sexes.

ESTIMATION OF LETHAL AND HYBRID HETEROZYGOSITIES

On the basis of the absence (or, more precisely, relatively low abundance [33]) of hybrids in natural environments and Haldane's rule for artificially obtained hybrids, we estimated values of threshold heterozygosities H_c and H_L. Under natural conditions,

$$H_0 + H_a \le H_c < H_L.$$

In nature, the absence of hybrids of both homo- and heterogametic sexes (the hybrids are competitively eliminated) is equivalent to the inequality

$$H_h + H_a > H_c.$$

From these two inequalities, we obtain

$$H_h \ge H_0. \quad (7)$$

This means that in all hybridizing species, hybrid heterozygosity exceeds the relative length of sex chromosomes (sex heterozygosity). Hybrid heterozygosity H_h can be estimated from data on Nei's genetic distance D. For two species 1 and 2, according to [34], we have

$$D = -\ln[(1 - H_{12})/\sqrt{(1 - H_1)(1 - H_2)}],$$

where $H_{12} = H_h$ measures fixed (regular) differences in genomes of the two species (hybrid heterozygosity), and H_1 and H_2 are the random differences in individual genomes within each population (H_a). With $H_1 = H_2 = H_a$, we have

$$H_h = 1 - e^{-D}(1 - H_a).$$

Interestingly, the mean value of H_h estimated for 101 pairs of *Drosophila* species was 0.60 [35] whereas mean relative length of sex chromosomes in *Drosophila* is 0.25, i.e., $0.65 > 0.25$ as in (7). In mammals, H_h for 144 pairs of species was 0.29 [36] whereas sex heterozygosity H_h was 0.05 [$0.29 > 0.05$, which agrees with inequality (7)].

The existence of homogametic hybrids and absence of heterogametic hybrids in conditions different from natural ones (Haldane's rule) corresponds to inequalities

$$H_h + H_a \le H_L, \quad (8)$$

$$H_L \le H_h + H_a + H_0, \quad (9)$$

which on average gives for mammals ($H_h \approx 0.29$, $H_a \approx 0.04$, $H_0 \approx 0.05$):

$$0.3 \le H_L \le 0.4.$$

The lower and upper limits are obtained when αH_a is substituted for H_a in (8) with $\alpha = 0$ and in (9) with $\alpha = 1$, respectively. Note that the true value of α do not significantly affect the obtained result, because the main summand in (8) and (9) is H_h, $H_h \gg H_a$. The substitution of α results only in larger error of H_L.

DISCUSSION

In this paper, we explain Haldane's rule from the statistical point of view on the basis of the assumption that diploidy of multicellular organisms is aimed at the protection from accumulation of somatic mutations. The validity of Haldane's rule depends on the total effective heterozygosity $H = \alpha H_a + H_0$, where H_a is the autosomal heterozygosity, H_0 is the length of sex chromosomes of the hemizygous part of the genome, and α is the ratio of phenotypic expression of somatic mutational substitutions in autosomal heterozygous and homozygous parts of the genome ($0 < \alpha < 1$). The results of this study do not depend on the value of α. According to the assumption above, two critical values of heterozygosity H must exist: the observed total effective heterozygosity (H_c) maintained by competitive interaction of individuals and heterozygosity $H_L > H_c$, which determine viability of individuals outside their

natural environments and in the absence of competition. When H exceeds H_c, the individual loses its competitive ability and is eliminated from the natural population. When H exceeds H_L, the individual loses viability or fertility.

Based on Haldane's rule, we can estimate the heterozygosity of lethality threshold H_L and hybrid heterozygosity H_h from the observed natural heterozygosity H_c and effective sex heterozygosity H_0 (relative length of the X and Y chromosomes).

Our explanation of Haldane's rule does not require the assumption of epistatic gene interactions in autosomes and the X chromosome (i.e. incompatibility of autosomes and sex chromosomes of different species) and sex-dependent regulation of fertility [5, 8]. The explanation holds in the case when the functioning of autosomal and sex-linked genes is completely independent. The fertility of unbalanced hybrid females, which carry two identical X chromosomes from one of the parental species [4] is also explained: a substitution of the X chromosome of one species for its counterpart of the other species decreases total heterozygosity but maintains the number of deleterious loci at the level controlled by male competitive ability and fitness.

Our explanation accounts for some specific cases of Haldane's rule. For instance, in the mouse *Mus musculus* and *M. spretus* [37], the observed sterility of X0 hybrid females and fertility of X0 females belonging to these species results from an increase of heterozygosity due to the contribution of hybrid heterozygosity in the interspecific hybrid.

The absence of viability differences between male and female hybrids of the species that have one inactivated X chromosome in somatic cells (e.g., mammals) is also explained. The X-chromosome inactivation results in equivalence of somatic cells in males and females if Y-linked genes do not function in the somatic lineage. Consequently, hybrid males and females are equally viable or nonviable. In this case, Haldane's rule is manifested in lower fertility of the heterogametic sex than in the homogametic one, since both X chromosomes function in ontogeny.

The following fact also supports the proposed explanation. In interspecific *Drosophila* crosses, species carrying large sex chromosomes (up to 40% of the haploid genome size), conform to Haldane's rule upon smaller genetic distances than species having relatively small sex chromosomes (20%) [38]. Let us suppose that pairs A and B of intercrossed species have respectively $H_{0A} = 0.4$ and $H_{0B} = 0.2$. Autosomal heterozygosity H_a in (6) is neglected. To conform to Haldane's rule, hybrid heterozygosity of pair A should be lower than of pair B:

$$H_{hA} = H_L - 0.4 < H_{hB} = H_L - 0.2,$$

which is actually observed [38].

Our concept explains the small size of X and Y chromosomes in species having large genomes and large body sizes (mammals, birds), in which the total length of sex chromosomes does not exceed 5 to 10% of the length of the haploid genome while in insects having small genomes (*Drosophila*), the X chromosome can attain 40% of the total genome [38]. This can be attributed to the fact that small organisms having small genomes have a lesser load of somatic mutations and thus can have larger effectively haploid hemizygous parts of the genome.

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