

UNDERSTANDING GENETIC LOAD

“Using Mendel’s Accountant to Simulate Mutation Accumulation and Genetic Load in Plants”

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THE PROBLEM:

For over 50 years many leading geneticists have expressed the concern that selection should not theoretically be able to stop the accumulation of deleterious mutations. But others have strongly disagreed. Is this problem real? Who is right? What factors affect the rate of mutation accumulation?

A NEW APPROACH:

We can not adequately understand biologically complex genetic processes using traditional mathematical modeling, because such modeling requires gross oversimplification of biological reality. The only way to analyze complex biological processes is to systematically account for all the components of the system simultaneously. Using advanced numerical simulation methods, this can now be done. The program *Mendel’s Accountant* (Mendel) was developed for this purpose and represents the most advanced forward-time population genetics program developed to date.

METHODOLOGY:

Mendel is a user-friendly and biologically realistic genetic simulation program which allows researchers to readily experiment with the parameters that affect mutation accumulation. This program can be tested and downloaded at mendelsaccountant.info. The researcher specifies the desired parameters, and initiates the experiment. The program creates a virtual population of potential mutations, which are then applied to a population of individuals. Mendel then selects the most phenotypically fit individuals, inter-mates them, and transmits their mutations to a new generation, in a proper Mendelian manner. This process is repeated for the specified number of generations and output data and figures are generated. In a typical run, Mendel will process millions of mutations. In the experiment shown here the key biological parameters were as follows:

Population: Size = 1000; Reproductive rate = 25; Fraction selfing = 0.9

Mutation: Non-neutral rate = 10; Fraction beneficial = .01; Fraction recessive = 0.8

Selection: Mode = pseudo-truncation; Heritability = 0.2

MUTATION ACCUMULATION:

Using biological realistic input parameters, we find that mutations invariably accumulate in a linear manner (figure 1)—even with intense selection. This is largely because of the problem of “nearly-neutral” mutations, which are effectively unselectable. This problem is greatly amplified when the mutation rate is high. We consistently see that the ratio of deleterious to beneficial mutations in only slightly altered by the selection process. For the most part, only the relatively high-impact mutations are affected by selection (Figure 2).

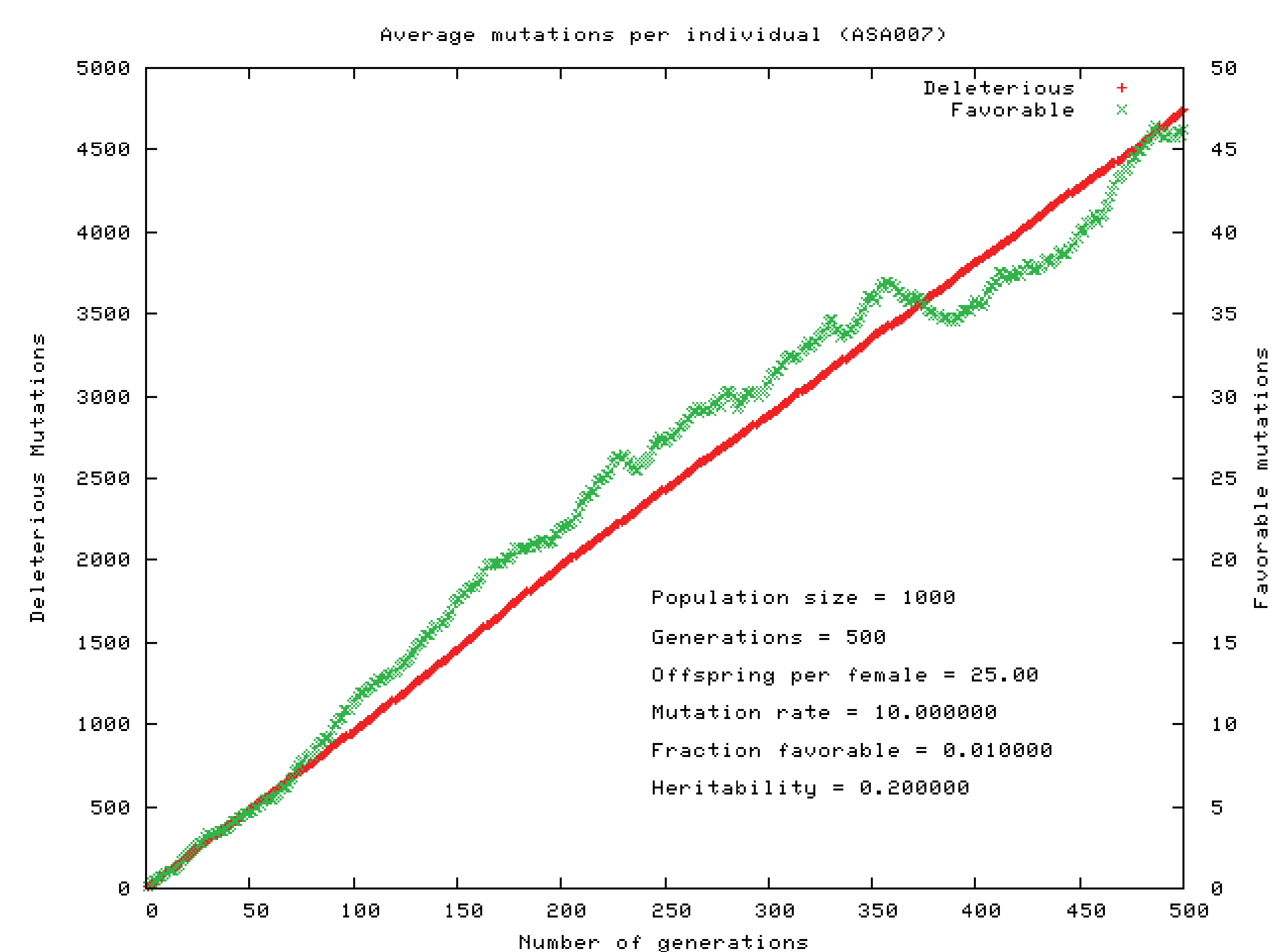


Figure 1: This figure shows the average mutation count per individual plotted over generations. Red represents deleterious mutation count per individual (scale on left), green represents the beneficial count (scale on right). Most deleterious mutations are not removed, even with intense selection. Beneficial counts are highly variable because they are very rare and are thus subject to drift/sampling error.

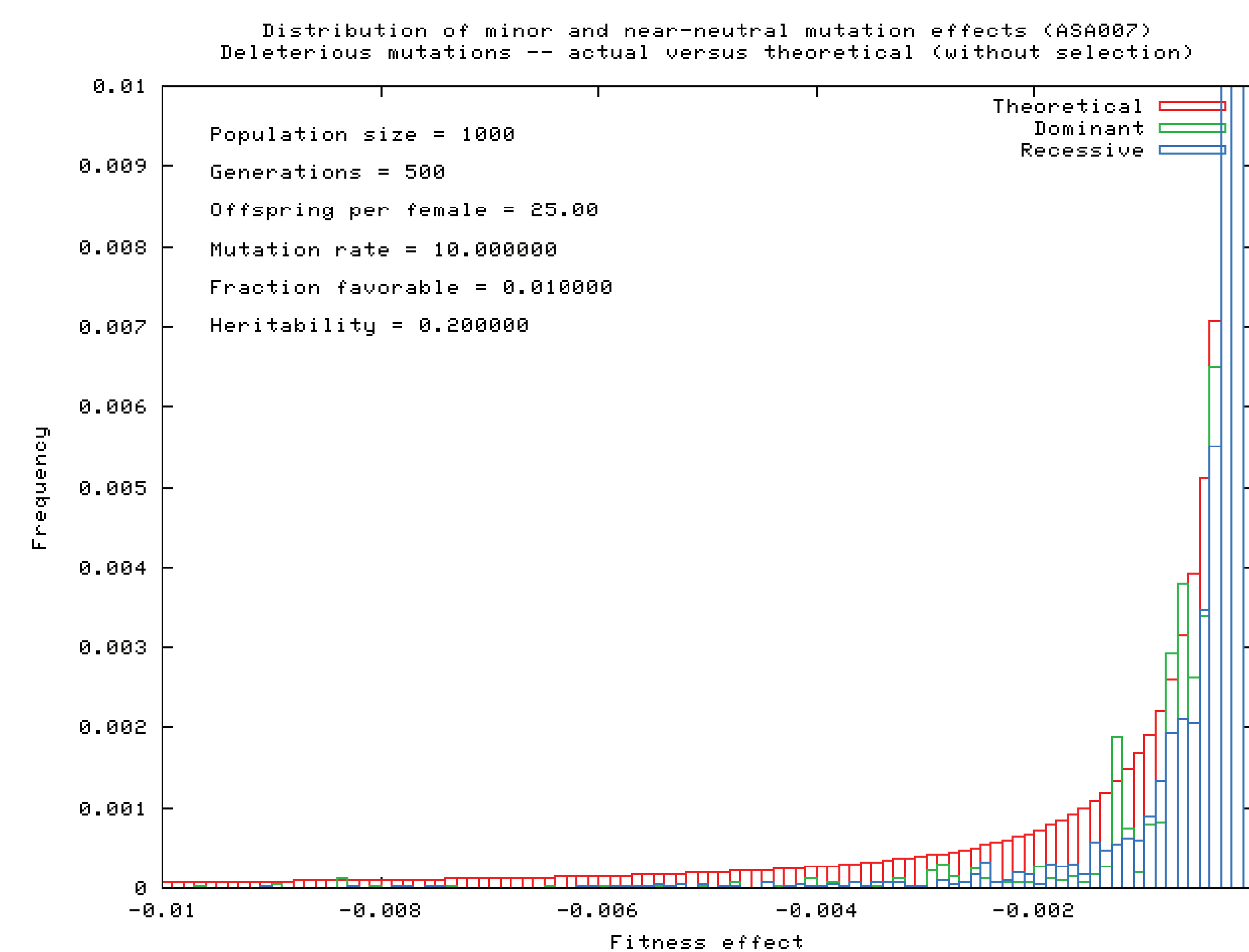


Figure 2: This figure shows the distribution of mutation effects – ranging from neutral (on right), to deleterious mutations which reduce fitness up to 1% (on left). Red is the distribution of mutations if there is no selection. Blue is the distribution of recessive mutations which are actually accumulating. Green is the distribution of dominant mutations that are actually accumulating. Because this experiment employs 90% selfing, recessives are being eliminated almost as fast as the dominant mutations. The distribution of dominants is more erratic because they are relatively rare (only 20%).

FITNESS DECLINE:

When the researcher inputs a much higher rate of deleterious mutations than beneficials, continuously declining fitness is observed (figure 3). This is because most of the deleterious mutations are not being eliminated by selection. The rate of decline is highly dependent on the mutation rate.

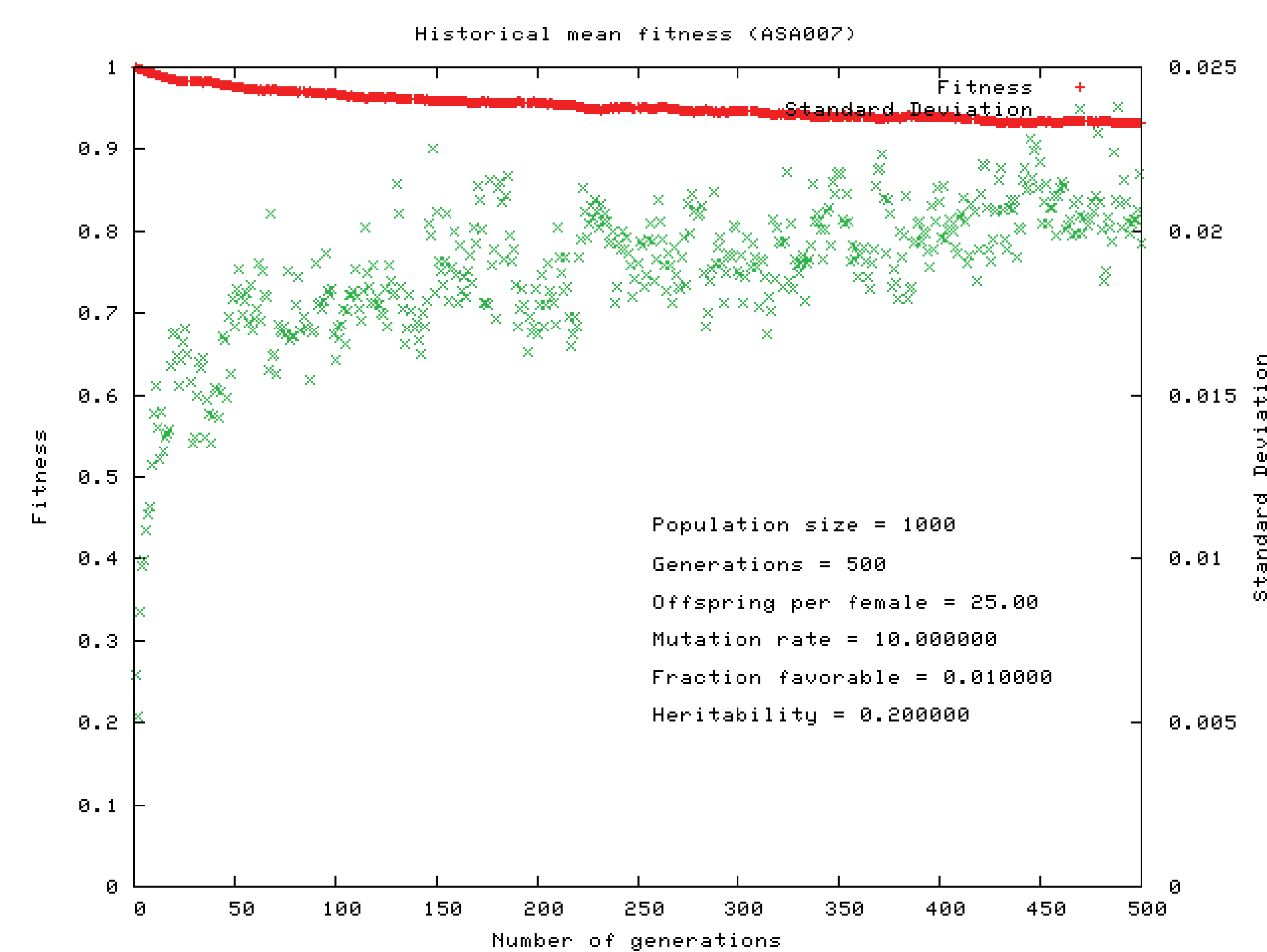


Figure 3: This figure shows the mean fitness of the population plotted over generations. Mean fitness is shown in red (scale of left), fitness standard deviation is shown in green (scale on right). Because most mutations are deleterious, and because most deleterious mutations are not removed by selection (see figures 1, 2, and 4), fitness consistently declines with time. This is the essence of the genetic load problem. The fitness decline is surprisingly similar in experiments involving strict outcrossing.

LINKAGE BLOCK DEGENERATION:

When biologically realistic input parameters are employed and deleterious mutations are accumulating faster than beneficials by several orders of magnitude, essentially all linkage blocks are incurring genetic damage (figure 4). The only exception to this which we see is where high-impact beneficials are specified. In such cases, a single beneficial mutation can counteract many linked deleterious mutations, so this special linkage block can have a net gain in fitness.

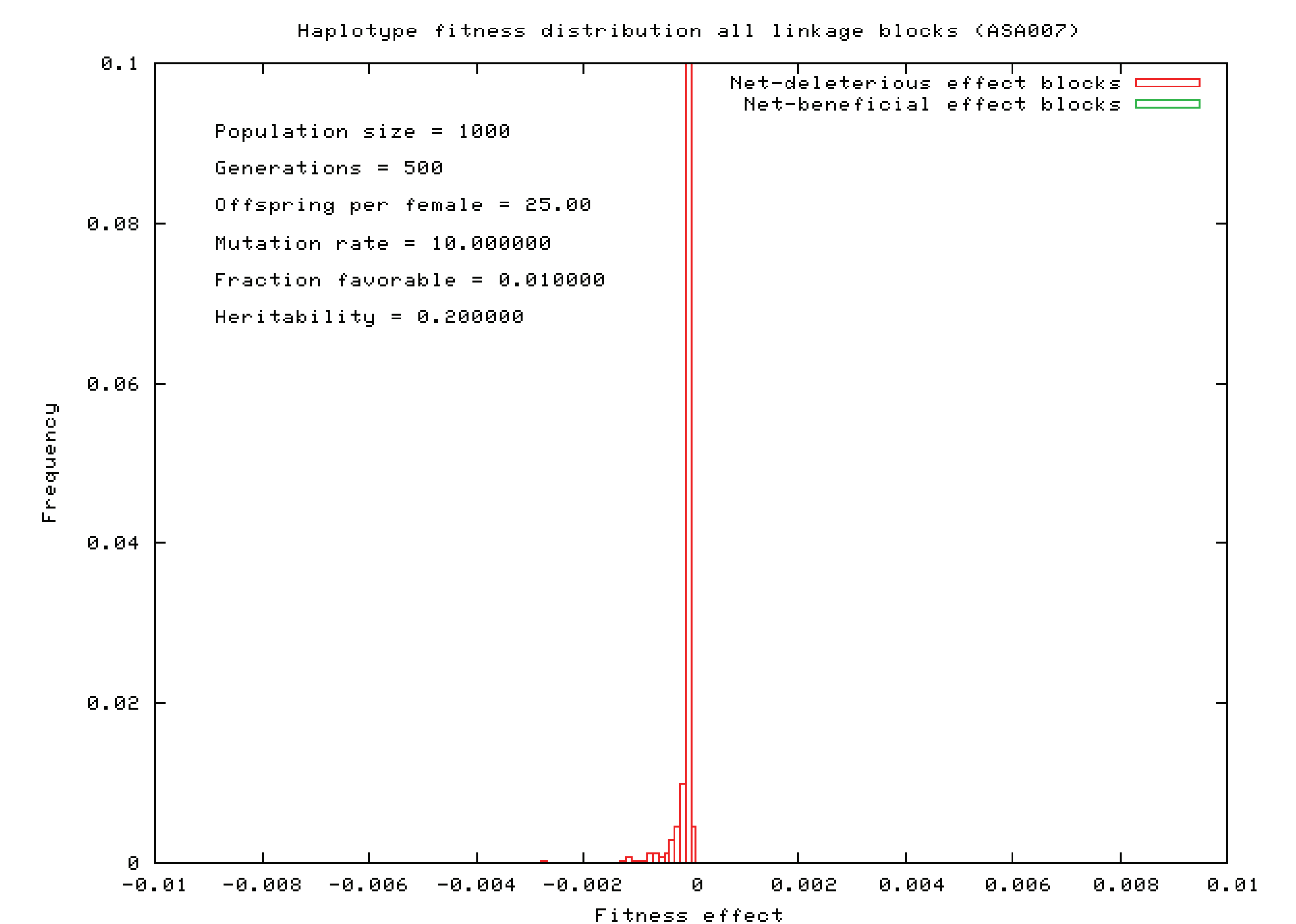


Figure 4: This figure shows the distribution of linkage block effects. Linkage blocks with a net deleterious effect are in red and are shown to the right of the neutral mark. Linkage blocks with a net beneficial effect are in blue and are to the left of the neutral mark. Although an un-realistically high rate of beneficial mutations were employed in this experiment, no linkage blocks had a net beneficial effect—due to the strong predominance of deleterious mutations in each linkage block.

CONCLUSIONS:

Mendel’s Accountant is the only biologically accurate forward-time population genetics program. This program clearly demonstrates that the “genetic load” problem is real. This suggests that existing theoretical paradigms may need to be re-examined.

For more information go to mendelsaccountant.info.

Also, see the publications below:

Sanford, J., Baumgardner, J., Gibson, P., Brewer, W., ReMine, W. (2007a). Mendel’s Accountant: a biologically realistic forward-time population genetics program. *SCPE 8(2)*, 147–165. <http://www.scpe.org>.

Sanford, J., Baumgardner, J., Gibson, P., Brewer, W., ReMine, W. (2007b). Using computer simulation to understand mutation accumulation dynamics and genetic load. In Shi et al. (Eds.), *ICCS 2007, Part II, LNCS 4488* (pp.386–392), Springer-Verlag, Berlin, Heidelberg.