Agent-Based Modelling shows that Operation of Fisher's Principle Does Not Deplete Heritability in Offspring Sex Ratio

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Abstract

The ratio of male to female births has garnered interest and debate for more than a century. According to Fisher's principle, offspring sex ratio remains approximately equal through a process of negative frequency-dependent balancing selection. That is, individuals whose alleles predispose them to produce the rarer sex will have greater fitness, causing these alleles to increase in frequency until the population sex ratio is even again and the allele is no longer advantageous. Recently, though, analysis of all Swedish births since 1932 revealed that offspring sex ratio is not heritable in humans, demonstrating that Fisher's principle cannot operate. Some have argued that Fisher's principle makes no prediction about the heritability of offspring sex ratio at equilibrium and therefore can still serve as a valid explanatory framework. We use agent-based modelling to simulate the operation of Fisher's principle and its effects on genetic variation in offspring sex ratio over 500 generations. Our simulations demonstrate that the operation of Fisher's principle at equilibrium maintains heritability, contrary to implicit assumptions in previous arguments. These results, combined with recent evidence that offspring sex ratio is not heritable in humans, suggest that Fisher's principle is not a valid explanatory framework for human offspring sex ratio.

Key words: offspring sex ratio, Fisher's principle, negative frequency-dependent balancing selection, agent-based model, genetic variation, sex allocation

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Offspring sex ratio – a parent's ratio of male to female births – has garnered interest and debate for more than a century. It is also the subject of Fisher's principle (1), which traces back to Darwin (2) and Dusing (cited in 3) and is sometimes referred to as Dusing-Fisher theory. Fisher's principle is an example of frequency-dependent balancing selection: all else being equal, individuals genetically predisposed to producing the scarce sex will tend to have greater fitness (more grandchildren), so those individuals' alleles will increase in frequency until the population sex ratio rebalances and the advantage of the allele disappears. According to the theory, this process keeps the sex ratio approximately even (under the condition that male and female offspring require equal parental investment).

Fisher's principle has been the primary framework by which human offspring sex ratio has been understood. Recently, though, using data from the whole Swedish population born 1932 or later (3,543,243 individuals and their 4,753,269 children), Zietsch et al. (4) showed that offspring sex ratio is not heritable in humans. That is, genetic differences do not influence the sex ratio of individuals' offspring, and therefore variation in offspring sex ratio cannot be inherited. Even within individuals there was no consistency at all in the sex of subsequent offspring, suggesting that offspring sex was determined by random Mendelian segregation of sex chromosomes. These observations are incompatible with the operation of Fisher's principle – offspring sex ratio must be heritable to respond to selection as Fisher described.

If Fisher's principle cannot operate in humans, how can it serve as a framework for understanding human sex ratio? Orzack et al. (5) and Lehtonen (6) argued that Fisher's principle makes no prediction about the heritability of offspring sex ratio at equilibrium (i.e. a

stable state reached through the operation of a process) and therefore can still serve as a valid explanatory framework. This position implies that the operation of Fisher's principle has eliminated the genetic variance in offspring sex ratio. However, the authors did not explain why this elimination would be expected under Fisher's principle or how it would occur. In fact, as explained by Zietsch et al. (7) in response, negative frequency-dependent selection (of which Fisher's principle is an example) is expected to actively *maintain* genetic variation, not eliminate it (8, 9). It is therefore difficult to see how zero heritability is compatible with Fisher's principle as an explanation of human offspring sex ratio.

The expectation that negative frequency-dependent selection actively maintains genetic variation is based on mathematical modelling where a given trait is influenced by variants at a limited number of genetic loci (10-12). To our knowledge there has been no modelling of the effect of Fisher's principle on genetic variation in offspring sex ratio. Given the complex underlying mechanisms of offspring sex ratio evolution, which are not always obvious, it is important to test this specific hypothesis. Here, we use agent-based modelling to simulate the operation of Fisher's principle and its effects on genetic variation at 20 loci in offspring sex ratio over 500 generations of evolution.

Method

We created an agent-based model to test whether the operation of Fisher's principle depletes genetic variation in offspring sex ratio. This model was comprised of male and female agents, each possessing a small genome of 20 loci which influenced their tendency to produce male or female offspring. By allowing the agents to reproduce over 500 generations, we were able to see Fisher's principle influence the population sex ratio, as well as observe how selection affected agents' genetic predisposition to have male or female offspring and whether the heritability of this trait was depleted over generations. We used a model with males being the scarce sex and females being the surplus sex, but the results are identical the other way

around. In the following sections, we describe how agents were created and the rules by which they reproduced. We describe the model in more detail in the Supplementary Material and all code and output can be accessed in the Biorxiv Supplementary Material. All modelling was performed in R in R studio version 1.3.959 (13, 14).

Creating Initial Generation

An initial population of 2000 agents was generated, with 40% being males. In the reported simulation there were 20 loci that influenced offspring sex ratio, each with two alleles. Initial allele values were generated as either 0 or 1, which occurred with a probability that reflected the initial population sex ratio in any given simulation. In the reported model, the initial population sex ratio was 40% male, so the allele values were randomised with a 0.4 probability. In this format, 0 represents the low variant and 1 represents the high variant. Genotype was then calculated as *allele 1 + allele 2*, thereby giving agents genotype values of 0, 1, and 2 at each locus. Genetic score for offspring sex ratio was calculated by summing genotypes for all loci. In the reported simulation there were 20 loci influencing offspring sex ratio, so possible genetic scores ranged between 0 and 40.

Partner Selection

In the reported simulations, the following operations were performed five times to create five 'offspring rounds'. Before determining offspring sex ratio, partners needed to be selected for each agent. Agents were paired randomly, with some surplus-sex agents missing out on partnering and reproducing for that round. Mating success for the surplus sex therefore varied randomly between agents (ranging from 0-5), a result of the number of times they were randomly excluded from the mating round (due to not finding a partner). Partners' data were then merged with the agents' data so that values for both parents were available to determine offspring attributes.

Determining Offspring Sex

The following process emulated a genetic predisposition toward male or female offspring with additional environmental variance, such that offspring sex was determined 50% by genes and 50% by environmental factors. For each offspring, the parents' genetic scores were averaged and transformed to a proportion of the highest theoretical genetic score (i.e. 20 loci * 2 alleles = 40; e.g. a score of 10 would be transformed to 0.25). This proportionate genetic score was then halved and an additional random value ranging from 0 to 0.5 was added. Offspring sex was then determined by a threshold model; scores above and below 0.5 resulted in male and female offspring, respectively.

Reproduction

Alleles were passed down by a process of independent assortment. That is, at each locus, an offspring inherited one allele from each parent, determined randomly. The population matrix was then truncated (i.e. all parent information removed), leaving the offspring information to become the next generation. Offspring genetic scores were then calculated as described in the 'Creating Initial Generation' section. At this point, outcome measures were recorded for the current generation and the process repeated from the 'Partner Selection' section above. The reported model repeated this simulation for 500 generations or until the sample size (rarely) dropped below 100 agents.

Analysis Plan

We ran the model described above 100 times and averaged results over each generation. The outcome variables of interest were population sex ratio, mean genetic score, heritability, and genetic variance; each was recorded for every generation. Population sex ratio was recorded as the proportion of males. Mean genetic score was recorded as the mean of the raw genetic scores (with a possible range of 0-40). Given that our data was simulated

and we had complete genome information for each agent, we used simpler calculations of genetic variance and heritability than those normally used in the broader quantitative genetics literature. To calculate heritability, i.e. the proportion of phenotypic variance accounted for by genetic variance, we used the R^2 of genetic score predicting offspring sex ratio. To calculate genetic variance, we multiplied the total phenotypic variance by the heritability, giving us the variance in offspring sex ratio that is explained by genetic scores. We used correlations to assess trends in outcome variables over generations.

Results

Sex ratio and genetic scores

To determine whether selection pressure via Fisher's principle results in evolution, we needed to establish whether genetic scores, and consequently sex ratio at birth, changed over time. Results demonstrated that the genetic scores for the second generation diverged sharply based on agent gender, with male agents having higher scores than female agents (see Figure 1A). This result was to be expected, given that a male is more likely to have been produced by male-making alleles, and thus will have inherited more male-making alleles themselves; likewise, females will have inherited more female-making alleles. We ran a simulation where the initial genetic scores for each sex reflected this natural separation between male and female genetic scores, and all results were comparable.

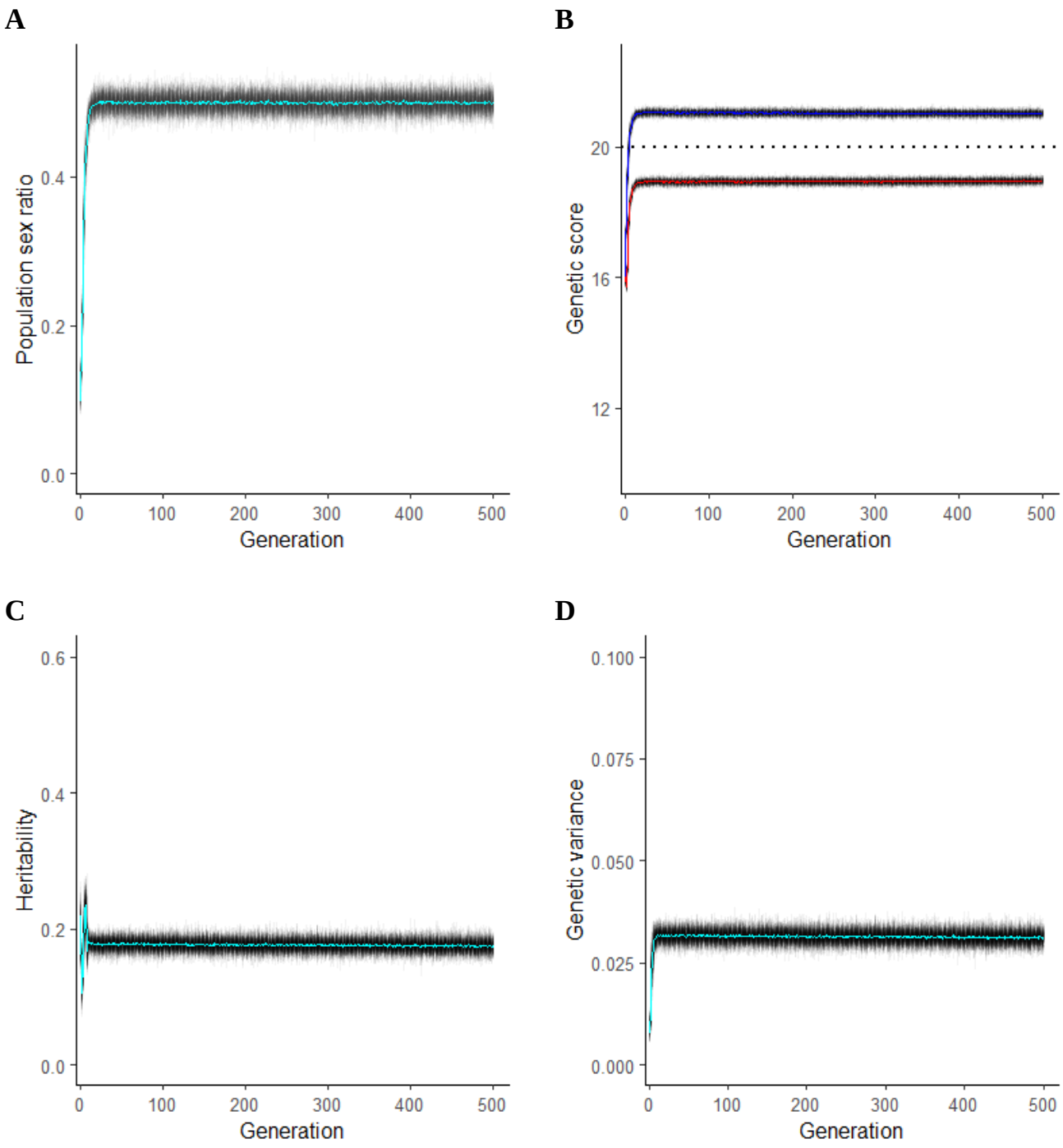
In addition to the divergence of genetic scores by sex, the mean genetic score also increased over time (from the initial mean genetic score which was biased towards female-making), such that alleles for having male offspring (i.e. the rarer sex) became more prevalent (Figure 1A). The rate of this increase slowed until the process reached an equilibrium at a 1:1 predisposition for offspring sex. The resulting population sex ratio also approached 1:1 over the generations (see Figure 1B).

Genetic variation and heritability

Given previous arguments that offspring sex ratio might no longer be heritable due to the operation of Fisher's principle (5, 6), we next sought to test whether heritability was eliminated over generations. Heritability was unstable at first, before levelling out by generation 50 (see Figure 1C). Genetic variance increased at first, before also levelling out by generation 50 (see Figure 1D).

Although heritability and genetic variance appear to the naked eye, in the figures, to be stable beyond 50 generations, correlations revealed that they each subtly decreased over time (both analyses: $r = -0.68$, $p < .001$). Upon further exploration of the data, this decrease appears to be due to fixation of some alleles due to drift. An allele can fix at zero or 100% frequency due to chance fluctuations over many generations (i.e. drift), but once fixed it cannot change frequency (without mutation); that is, allelic variation can be lost but not replenished in our model, and so the occasional chance fixations will cause the genetic variation to decrease slightly over time. In analyses described in the Supplementary Material, we show the slight decreases in heritability detected in our model of Fisher's principle are less than those observed under no selection at all (and far less than observed under directional and stabilising selection). It is therefore clear that the operation of Fisher's principle is acting to maintain rather than deplete genetic variation.

Figure 1. A Population sex ratio, **B** mean genetic score, **C** heritability, and **D** genetic variance over 500 generations. Grey lines represent individual results from 100 simulations. Coloured lines represent the relevant mean across all simulations at each generation. In Figure B, the blue line represents male genetic scores and the red line represents female genetic scores.



Discussion

For more than a century, Fisher's principle has been widely accepted as the key explanatory framework for the 1:1 offspring sex ratio in humans (15, 16). However, a recent study demonstrated that offspring sex ratio is not heritable in humans (4), which is inconsistent with the current operation of Fisher's principle and undermines Fisher's principle as a framework for understanding human offspring sex ratio. Commenters argued that Fisher's principle could have operated in the past, is consistent with zero heritability of offspring sex ratio at equilibrium, and can therefore can still serve as a framework for understanding human offspring sex ratio (5, 6). This position implies that Fisher's principle operating in the past has eliminated the heritability of offspring-sex ratio – yet it is unclear how Fisher's principle would lead to this elimination (7). Previous models in limited contexts had demonstrated that negative frequency-dependent balancing selection, of which Fisher's principle is an example, is expected to maintain (rather than deplete) genetic variance (10-12). However, given the unique complexities of sex ratio evolution, we modelled the specific mechanism of Fisher's principle to assess whether it could have caused the elimination of genetic variation and heritability of offspring sex ratio over evolutionary time.

In the initial generation of our model, males were the scarcer sex and the population's alleles reflected this with a bias toward producing females. Over many generations, the sex ratio and genetic scores of the population approached equilibrium at a 1:1 offspring sex ratio. This pattern of results is consistent with Fisher's principle, which predicts that alleles that produce the scarcer sex will increase until they are no longer beneficial (once a 1:1 population sex ratio is reached). At this point, there is no selection for these alleles, which is consistent with our findings that population sex ratio and genetic scores remained stable after reaching equilibrium. While our model demonstrates that Fisher's principle is operationally sound, it does not support arguments that it could have eliminated offspring sex ratio

heritability over time. The reason is that Fisher's principle, in our simulations, maintained heritability at higher rates than for longer than directional selection and even neutral genetic drift (no selection). Thus, Fisher's principle cannot account for the current observable state of abundant heritability in virtually all variable traits that have been studied (both those under directional selection and no selection), and no heritability in offspring sex ratio.

The operation of Fisher's principle requires offspring sex ratio to be heritable. This is clearly specified in Fisher's own description (1). Moreover, we demonstrate in the Supplementary Material that Fisher's Principle does not operate in a model with no offspring sex ratio heritability (i.e. where offspring sex is determined entirely by environmental factors). Thus, for Fisher's principle to be a valid explanation of the 1:1 offspring sex ratio in humans, offspring sex ratio must have been heritable at some point in our evolutionary past. However, our results demonstrate that heritability could not have been eliminated through the long-term operation of Fisher's principle, and therefore Fisher's principle simply cannot account for the current observable state (lack of sex ratio heritability; 4).

Our findings challenge recent arguments made by commentors (5, 6), and support Zietsch et al.'s (4) original contention that Fisher's principle is untenable as a framework for understanding human offspring sex ratio. We suggest that human offspring sex ratio theory needs to be overhauled, given that Fisher's principle has had a foundational and lasting influence in the field, as described by West (15, p.14):

> *'Fisher's theory of equal investment provides the basic null model for sex allocation theory, but it is also the foundation for all subsequent theoretical developments.'*

Hardy (16, p.2, emphases added) also acknowledges that Fisher's principle underpins extensive subsequent research:

> *'Darwin, Düsing, Fisher, and Shaw and Mohler established the* ***fundamental principle that members of the minority sex tend to have higher fitness than members of the majority sex****. They also outlined how various ecological, demographic and genetic variables might affect the details of sex-allocation strategies by modifying both the constraints and the fitness functions.* ***Modern sex-allocation research is devoted largely to the exploration of such effects****, which connect sex ratios to many other aspects of the biologies of many species'*

Our simulation is a simplified representation of the real world, and as with any model, there are limitations. For example, our agents and their genomes of 20 loci cannot comprehensively represent true human genetic architecture. However, we have no reason to expect that complexities involving linkage disequilibrium or minor allele frequencies would substantively affect our findings, especially since Fisher's description of his principle does not implicate any of these factors. It is worth noting again that the discrete generations in our model are a simplified representation of mating environments, which in reality have overlapping generations.

We also did not consider factors such as group size and environmental fluctuations in sex ratio. For instance, we did not explore what would happen if many males in a small population were eliminated due to war. However, we believe that random environmental fluctuations in sex ratio would not impact sex ratio evolution. For example, a generation with more females due to the elimination of many males would have more female-making genes, but each individual in the following generation would have inherited genes from one surviving female and one surviving male, resulting in a 1:1 offspring sex predisposition based on existing genetic scores. During the development of our model, we found that setting the initial genetic scores to reflect the uneven population sex ratio was crucial for sex ratio evolution. For example, if the initial generation had 40% males, but the initial genetic scores

were set at a 50% predisposition for male offspring (instead of 40% to match the population sex ratio), we observed no sex ratio evolution; the second generation immediately returned to a 1:1 sex ratio per the genetic scores.

Our models' findings, combined with recent evidence that offspring sex ratio is not heritable in humans (4), suggest that Fisher's principle is not a valid explanatory framework for variation in the offspring sex ratio in humans. Moreover, the inconsistency of offspring sex ratio within people (4) suggests that there is no predisposition for offspring sex at an individual level. Instead, a random Mendelian process may determine the offspring sex ratio in humans, although it is unclear what evolutionary processes have led to this outcome. Orzack and Hardy (5) proposed that natural selection for a 1:1 sex ratio could be linked to the Mendelian process of sex determination, but Fisher's principle does not account for such selection. It remains unclear whether individual or group selection for a 1:1 offspring sex ratio could lead to fixation of a mechanism that produces a random sex ratio at the individual level. We encourage readers to explore the previous papers on this issue for more theoretical discussion of these possibilities (4, 5, 7, 17). We anticipate that new theoretical models will be necessary to reconstruct our understanding of sex ratio evolution in humans, and we look forward to seeing progress in this field.

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