The Sex Ratio: A Biological and Statistical Conundrum

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At face value, questions about the sex ratio have always seemed to have straightforward answers, which on closer inspection turn out to be fiendishly complex. The familial distribution of male and female births is no exception.

A good place to start with the sex ratio is the binomial distribution — often explained with the example of a coin toss. In the long run, coin tosses should always result in an equal proportion of heads and tails. In human births, however, there are between 101 and 107 males per 100 females, depending on the population [1]. Is this evidence that there is a non-randomness at conception, perhaps evidence for genetic or facultative (physiological or epigenetic) variation in male and female births? It is necessary to look more closely at the distribution of the sexes between families to answer this question. In a study published in a recent issue of Current Biology, Long and Zhang [2] make a valuable contribution to the question of whether there is familial variation in the probability of producing a boy ($P_{boy}$), a crucial metric for determining the extent of any biological variability in the human sex ratio.

The binomial distribution tells us the combinations of males and females that we should expect to see within families across a population. To understand this, it is helpful to look at Pascal’s triangle (Figure 1), where the number of births in each family is the same as the row number, whilst the numbers in the hexagons represent the expected frequency of each combination — all-male (M) combinations to the left and all-female (F) combinations to the right. In families with two children: MM = 1 (25%), MF = 2 (50%), FF = 1 (25%), whereas in families with three children: MMM = 1 (12.5%), MMF = 3 (37.5%), MFF = 3 (37.5%), FFF = 1 (12.5%), and so on.

If there is underlying genetic variation in the sex ratio, then we would expect to see a super-binomial pattern, in which there is an above expected number of families with more children of one sex and fewer families with an equal number of each sex. This sounds straightforward, so why do we still not have a clear answer from this type of familial data as to whether there is any genetic or non-random variability, despite many previous studies? One reason may be — as Long and Zhang show, using UK Biobank survey data and Dutch genealogical data — that the opposite pattern may be found, i.e. a sub-binomial distribution, in which there is an excess of families with an equal number of each sex.

They explain this finding with what they call ‘coupon collection’ behaviour, based on the ‘coupon collector’s problem’ from probability theory, where the challenge is to collect all coupons in a collectible set. In this context, we see parents being statistically less likely to have another child if they already have one of each sex, suggesting a preference for a sex-balanced family. It is not altogether clear why this happens, but it is likely influenced by downward pressure on family sizes and may be due to greater appreciation of gender equality or the perception of sex-balanced families as the norm. The result of the behaviour is to skew the sex ratio distribution in the opposite direction to that which we would expect to see if there was genetic variability. A problem, yes, but surely the question of whether there is genetic variability in the human sex ratio does not hinge only on this type of analysis? Also, shouldn’t we assume that there must be genetic variability in the sex ratio (albeit disguised by coupon collection behaviour), otherwise how would the sex ratio be subject to natural selection? To answer these questions requires a bit of background.

A fundamental concept to understand is frequency-dependent selection. Darwin first outlined the concept in 1871 [3], explaining that imbalances in the ratio of males to females in the population might be corrected by natural selection acting on heritable variability in the number of male and female offspring that individuals producing as parents. If, for example, there are more males in the breeding population, then because every child has one mother and one father, females will, on average, gain higher reproductive success relative to males. Any heritable tendency to produce more females will then be transmitted to the next generation at a higher rate, leading to a correction of the sex ratio imbalance in the population.

This sounds straightforward, right? As the frequency of one sex increases over and above the other, this creates a selective pressure for an increase in production of the other sex. Not exactly. Nothing has proved to be straightforward when it comes to the sex ratio. In 1874 [4], Darwin claimed to have found fault in his previous thinking; he reasoned that natural selection favours individuals who produce more offspring (but the ratio of sons to daughters you produce does not affect that), also individuals who ensure the survival of their offspring (again, producing more sons or daughters does not affect that). He claimed to be perplexed by the problem and left its solution to the future [5].

In 1930, Fisher introduced the concept of genetic return for parental investment, arguing that natural selection will favour equal investment in each sex [6]. If, for example, male offspring are more likely to die during the period of parental care (as occurs in humans), then more males will be born in order to equalize the parental
resources invested in each sex. In its modern interpretation, this concept is the basis of ‘sex allocation’ theory, which is focused on how individuals facultatively adjust the sex ratio among their offspring to enhance their reproductive success and genetic return [7,8].

In a system of facultative sex ratio control, individuals may make an adjustment to produce more sons when the operational sex ratio (sex ratio in the breeding population) is biased toward females, or more daughters when it is biased toward males. In such a system, we might not see any heritability or a consistent super-binomial pattern in familial sex ratio data. In a system characterised by ‘hard-coded’ genetic variation, on the other hand, individuals will have no control over the sex of their offspring and there will be a generational delay in the response to selective pressure. In this system, we will expect to see evidence of heritability and super-binomial variation. There is arguably a blurring of the line between facultative and genetic control of sex ratio in the literature, which is a source of confusion that needs to be addressed. If we assume that sex ratio evolution can be resolved with the existence of facultative control, then should we expect to find genetic variation correlated with sex ratio? Likewise, when evidence of genetic variability is found (e.g. [9,10]), should we expect to also observe facultative control, or expect parental resource investment to be of any consequence to the transmission of allelic variants affecting sex ratio [11]?

In the context of the human sex ratio, it may be argued that there has been a failure of empirical evidence to confirm the existence of either facultative or genetic control. A recent study of over 3.5 million births in Sweden since 1932 found no evidence of heritable variation [12], in contrast to previous studies [13–15]. A comprehensive analysis of embryonic karyotypes found that the sex ratio at conception is 50:50, indicating that random segregation of chromosomes and prenatal mortality might provide the best explanation for sex ratio variation [16,17]. The two genomic studies that have looked for genetic variation related to sex ratio have found conflicting results [18,19]. The evidence for correlation of sex ratio with social and financial status is mixed and is probably not significant when taking into account publication bias [20]. The hormonal system of sex ratio control, argued for by William James in publications spanning five decades, has not been tested in a randomised controlled way that would draw a line under questions about sample sizes, publication bias and confounding variables.

The jury is still out on the presence of genetic variability in the human sex ratio. It is possible that genomic research will resolve the question, with breakthroughs possibly transferring from research in other species. This doesn’t negate the importance of demographic research, which has the potential to resolve theoretical questions and guide and supplement the genomic research. The importance of using diverse, and indeed historical datasets, should also not be dismissed, because sex preferences have been shown to differ over time, between regions and according to cultural trends. An interesting finding from the Long and Zhang study is that preference for a sex-balanced family (coupon collection behaviour) was a mid- to late 20th century development in the UK and Netherlands, possibly concurring with the arrival of modern contraceptive methods and more-precise family planning. In the Netherlands, their analysis shows a significant super-binomial distribution in the sex ratio throughout the 17th to 19th centuries, which is what we would expect to find with underlying genetic variability in the probability of having a boy or girl. It seems that questions about the fundamental biology of the sex ratio remain, but in this increasingly data-rich age, we can expect to see more empirical studies of sex ratio distribution at this level of detail, which will no doubt edge us closer to solving the conundrum.

REFERENCES

Brain States: Sensory Modulations All the Way Down

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From wakefulness to sleep, and from moment to moment, the arousal state of the brain is a powerful internal context that shapes our perception and actions. Using cutting-edge imaging methods, two new studies show that arousal already sculpts visual information as it first enters the brain.

In the traditional model of sensory systems, information flows forward along neural pathways, up through a hierarchy of brain regions that encode increasingly abstract representations of the sensory environment. In the visual pathway, for example, the retina encodes low-level information (such as relative position and motion and spatial frequency), and downstream structures extract features (such as contours), followed by objects (such as sofas). It is well-established that this model is too simple; feedback, or ‘top-down’ influences on sensory processing are widespread. These feedback pathways impart diverse contextual effects, such as attention to a particular region of visual space, or expectations about upcoming stimuli. Although well-appreciated, top-down influences are by-and-large studied in the cortex [1]. Cortex-centric models of top-down processing typically assume that the sensory periphery provides reliable building blocks for downstream feedforward and feedback processing. This assumption simplifies models, but is it true?

The arousal state of the brain imparts a powerful context on sensory processing. During sleep, for example, cortex is largely cut off from sensory input and we are ignorant of our surroundings. Arousal also fluctuates much more dynamically. For example, during a boring lecture we may tune out the speaker and gradually doze off, while nonetheless remaining upright and coarsely responsive to the environment. Over the past decade, the effects of diverse waking states on sensory processing have been extensively explored, including in head-fixed rodents on treadmills. These studies have used pupil size or locomotor status as metrics of brain state, and revealed diverse effects on sensory processing, particularly in cortex [2].

Two new studies [3,4], one reported by Liang et al. [3] in this issue of Current Biology, demonstrate that pupil-indexed brain state already shapes processing in the retinal axonal inputs to the brain, in thalamus [3] and superior colliculus [4]. Both studies used a recently developed technique to study retinal axonal boutons by injecting, into the contralateral eye, an adeno-associated virus that expresses a sensing protein (GCaMP6f) in the boutons. Then, while the head-fixed mice stood still or walked on a running wheel or treadmill, both studies used two-photon microscopy to image GCaMP6f activity in the retinal synaptic boutons in the awake brain. In both target structures (thalamus and superior colliculus), the groups found that larger pupil diameter was associated with diverse effects across boutons. The main effect was an average reduction in response to drifting grating stimuli without changing their preferred orientations.

Pupil Size and Visual Processing: Modulations from Top to Bottom
Both studies [3,4] used pupil size as their primary state metric. What does pupil size indicate about brain arousal state? The pupil constricts in response to light. But since at least Renaissance Italy, with the cosmetic use of the muscarinic antagonist Atropa belladonna to dilate the eye’s pupil, and the 16th century French poet Guillaume de Salluste Du Bartas who described pupils as “these lovely lamps, these windows of the soul”, it has been known that the pupil signals much more than just light levels. In the scientific domain, the foundational work of Hess and Pott and Kahneman and Beatty in the 1960s established that the pupil robustly dilates in association with the interest value or emotional salience of sensory stimuli and with mental load during diverse behavioral tasks [5]. Anatomically, the pupil is under sympathetic and parasympathetic control, via the dilator and constrictor muscles, respectively. Thus, outside