any clear ambitions, other than not to starve or become homeless. I take up a problem, work on it until I either solve it or abandon it and then go on to the next one. I like to understand things by either finding them out for myself or studying what others (mostly much more gifted than myself) have discovered. I find the question that often gets asked at job interviews "where do you see yourself in X years' time" quite annoying; the whole point of research is that you don't know what (if anything) you are going to discover in a year or so's time.

Do you feel a push towards more applied science? I think that funding agencies are under a lot of pressure from governments and businesses to push people towards doing more applied work. This is misguided because good scientists are primarily motivated by curiosity about how the world works; a lot of applied science research is quite dull and leads nowhere. In addition, advances in pure science have unpredictable applications. For instance, genetic counselling and the identification of human disease genes by GWAS would not be possible without the basic understanding of genetics that originated with Mendel and Morgan, who worked on model organisms rather than humans. Scientists usually have better ideas about what's important than ministers, civil servants and businesspeople. Business in the UK is notorious for its emphasis on short-term profits and failure to follow up on scientific innovations.

Which aspect of science, your field or in general, do you wish the general public knew more about? I think that the general ignorance about basic probability and statistics has been vividly brought out by the current coronavirus epidemic. A major issue is that people in government and media are nearly all devoid of any scientific education and often seem actively proud of their inability to understand quantitative data and the associated uncertainties. We need to do far more to inform school students about these matters. Unfortunately, the government seems to want schools to drill, rather than educate, children.

Institute of Evolutionary Biology, University of Edinburgh, Charlotte Auerbach Road, Edinburgh EH9 3FL, UK.
E-mail: brian.charlesworth@ed.ac.uk

Quick guide

Balanced lethal systems

Ben Wielstra[1,2]

What are balanced lethal systems? Balanced lethal systems pose an evolutionary mystery. Although natural selection should keep lethal alleles (dysfunctional versions of essential genes) in check, the frequency of lethal alleles in a balanced lethal system is highly inflated. Here is how it works: in a balanced lethal system, two homologous chromosomes each carry private, recessive lethal alleles, each of which is reciprocally compensated for by a functional gene copy on the other homologue. Therefore, an individual needs both chromosome forms — and in effect their linked lethal alleles — to survive. Yet, parents randomly transmit only one of the two forms via each gamete. As a consequence, progeny may receive two copies of the same chromosome form and miss the essential other one. In accordance with the rules of Mendelian inheritance, half of the offspring will be homozygous for either of the chromosomes and hence genetically pre-determined to die (Figure 1). Such a high mortality rate, recurring every single generation, appears to defy the basic tenets of evolutionary theory.

How could such a wasteful system evolve? Balanced lethal systems have been described in plants (the genera *Isotoma*, *Oenothera*, *Rhoeo* and *Gaphytum*) and insects (*Drosophila tropicalis* and *Tribolium castaneum*), but the best-known case is observed in vertebrates, in newts of the genus *Triturus* (Figure 2). This broad taxonomic spread suggests that a general evolutionary principle is at work. Yet, considering the incredible genetic load associated with balanced lethal systems, this seems counterintuitive. Natural selection is expected to: prevent a balanced lethal system from becoming established, because conspecifics that do not suffer from a balanced lethal system enjoy a considerable fitness advantage over, and should outcompete, carriers; and counter a balanced lethal system that is in place, because

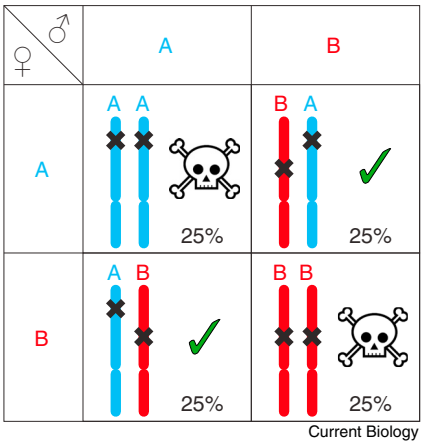

Figure 1. Punnett square explaining how a balanced lethal system operates.
Adults possess two forms of a particular chromosome, A and B. Form A compensates a lethal allele (cross) on form B and vice versa. Parents transmit either A or B in each gamete at equal frequency and, accordingly, offspring receive A or B at random from their father and mother. Four genotypes are generated, each with a 25% chance: AA, AB, BA and BB. The two heterozygous genotypes (AB and BA), representing half of the total number of offspring, are fine. However, the two homozygous genotypes (AA and BB), the other half of the offspring, are not viable because the recessive lethal allele is expressed.

recombination should detach lethal alleles from a particular chromosome form, creating conspecifics liberated from the burden of the balanced lethal system. Explaining the evolution of balanced lethal systems requires a scenario in which short-term benefits 'fool' natural selection into opting for an arrangement that is actually detrimental in the long run, and in which two chromosome forms that amass private lethal alleles are involved. Sex chromosomes and supergenes could be implicated.

What could lead to fixation of the lethal alleles? Repressed recombination plays a fundamental part in balanced lethal systems. This explains why private lethal alleles cannot be purged from the two distinct chromosome forms. The acquisition of deleterious mutations is a well-known side effect of suppressed recombination, through a process known as Muller's ratchet. Without recombination, purifying selection is less efficient in ridding an evolutionary lineage of deleterious mutations. Because genetic drift will eventually result in the

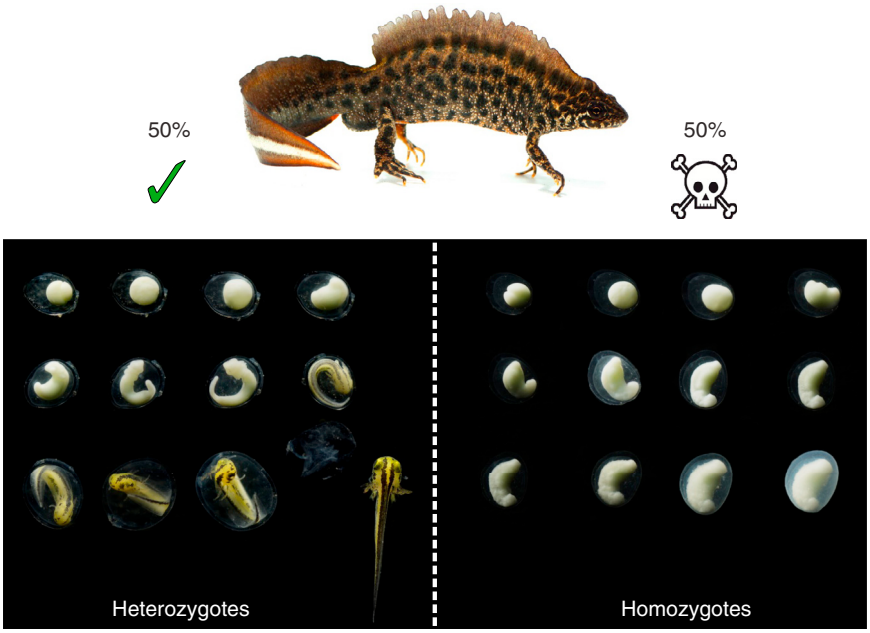

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Figure 2. A balanced lethal system in action.
Chromosome 1 syndrome, so called because two forms of chromosome 1 are involved in this balanced lethal system, is observed in all newts of the genus *Triturus*, such as this Balkan crested newt *T. ivanbureschi.* Heterozygous offspring experience normal embryonic development, while homozygous offspring experience developmental arrest and die halfway through normal embryogenesis. Hence, chromosome 1 syndrome is responsible for half of eggs laid never hatching. (Photos: Michael Fahrbach; taken from: Fahrbach, M., and Gerlach, U. (2018). The genus *Triturus:* History, Biology, Systematics, Captive Breeding. (Edition Chimaira, Frankfurt am Main, Germany).)

loss of those genomes with the lowest number of deleterious mutations, the average number of deleterious mutations per genome in the population can only increase over time. Therefore, lethal alleles would accumulate as unidirectional clicks of a ratchet.

Are balanced lethal systems ancient sex chromosomes? The hypothesis that balanced lethal systems are 'ghosts of sex chromosomes past' rests on a number of assumptions. Y chromosomes typically possess non-recombining regions. Two distinct Y chromosomes that differ in their chromosomal arrangement and that have accumulated unique lethals via Muller's ratchet may co-segregate in a population. As in some species sex is not purely genetically determined, but also influenced by temperature, a shift in temperature, causing a switch from genetic to temperature-dependent sex determination, could lead to female-biased sex-reversal and the loss of the X chromosome altogether. Subsequent development of a masculinizing mutation on another chromosome could give rise to a new male-heterogametic system and allow for an even sex ratio to be restored. At this point, the two ancestral Y chromosomes, incapable of recombining and each possessing private lethals, could take up the part of a balanced lethal system. While modelling suggests that all this could, under very strict conditions, occur via natural selection, a serious restriction is that it could only ever apply to taxa for which temperature-dependent sex-reversal is a possibility. Hence, this hypothesis does not provide a general explanation for balanced lethal system evolution.

Are balanced lethal systems collapsed supergenes? Supergenes are batteries of physically linked genes that are inherited as a single unit, because recombination between alternative genomic arrangements of these alleles (i.e. different supergene alleles) is suppressed. If two supergene alleles each have a unique advantage, balancing selection would favour possession of both. However, repressed recombination also makes supergenes susceptible to Muller's Ratchet. This could generate a feedback loop: heterozygote advantage means relatively few homozygotes reproduce, leading to less recombination and the accumulation of private deleterious alleles, which in turn reinforces heterozygote advantage. If unique recessive lethals eventually become fixed on each supergene allele, homozygotes are no longer viable, and a balanced lethal system is born. This 'decay of supergenes in a balanced polymorphism' hypothesis would provide a broadly applicable explanation for the origin of balanced lethal systems and needs further testing.

Could genomics provide the answer? While the rarity of examples suggests that balanced lethal systems could be evolutionary oddities, they might be overlooked. The associated die-off occurs early on in life and consistently heterozygous sites in the genomes of survivors may be too easily dismissed as paralogs. All we currently know empirically derives from studies that did not look deeper than embryo morphology and karyotypes. However, recent sequencing developments make it possible to unravel the genomic architecture of chromosome re-arrangements responsible for the repressed recombination in balanced lethal systems. Comparative genomics with related but unaffected species would provide further insight into the (former) function of the genomic region involved. We are on the verge of finally understanding this evolutionary enigma.

Where can I find out more?

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[1]Institute of Biology Leiden, Leiden University, 2300 RA Leiden, The Netherlands. [2]Naturalis Biodiversity Center, 2300 RA Leiden, The Netherlands.
E-mail: b.m.wielstra@biology.leidenuniv.nl