Engineered Translocation-based Underdominance Gene Drive

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A recent paper by Buchman et al. in A***CS Synthetic Biology*** details the development of an underdominance effect through engineered chromosomal translocations in *Drosophila melanogaster*.

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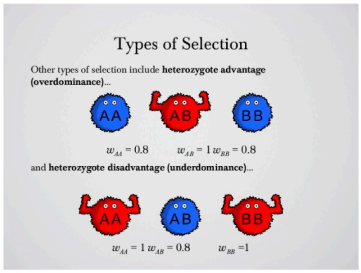
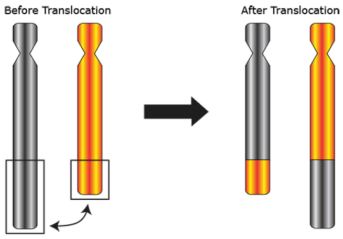
The principle of using underdominance as a mechanism for driving desirable genes into populations has been around in principle for several decades, with few practical successes. Underdominance is defined classically as the condition where the fitness of heterozygotes is lower than the fitness of either corresponding homozygote, and at the population level it can be used to produce a frequency dependent gene drive, replacing wildtype individuals with engineered homozygotes (carrying a desirable genetic cargo), in a stable and geographically localised manner.



COMPARISON OF UNDERDOMINANCE AND OVERDOMINANCE. NOTE THAT STRONG UNDERDOMINANCE WOULD OCCUR WHEN THE RELATIVE FITNESS OF HETEROZYGOTES IS ZERO.

Buchman et al. generated homozygous chromosomal translocations between chromosomes 2 and 3 in *D. melanogaster* using two previously inserted transgenes carrying rare base cutters inserted at different loci. Simultaneous cutting and homologous recombination of these two transgenes generates *de novo* chromosome arrangements Individuals bearing the homozygous reciprocal chromosomal translocations are fertile at meiosis as the modified chromosomes can pair with their modified homologs; however in translocation heterozygotes modified chromosomes do not match their homolog across the entire length – and thus attempt to pair with multiple chromosomes at once.



The resultant aneuploidy (non-balanced chromosomes) causes death in 50% of gametes; with the other 50% comprised of balanced chromosomes, half wildtype, half reciprocal translocations.

This system is designed to generate a high fitness cost to hybridisation between translocation individuals and wt – and Buchman et al carried out caged population trials to investigate this as a drive system. With trials demonstrating that this system spread to fixation at introduction frequencies >50% (60%, 70% and 80% tested), and drop to extinction at frequencies <50% (20%, 30%, 40% tested). Rates of spread to fixation and elimination were respectively slower and faster than predicted indicating fitness costs associated with the chromosome translocations that were higher than expected.

Modelling of spatial limitations for this system shows that the continued introduction of wildtypes into an established replaced population would keep the equilibrium frequency below 100% and above zero in neighbouring populations, the authors therefore suggest that target areas would require barriers to migration in order to maintain a truly spatial limitation to introductions.

This report demonstrates an impressive technical accomplishment in establishing a viable underdominance system with comprehensive testing and modelling. Development of this system in target pest species will necessitate trial and error in developing several concurrent novel recombinant chromosomes, as fitness costs from each new recombinant event will be unpredictable.

Buchman AB, Ivy T, Marshall JM, Akbari OS, Hay BA. 2018. Engineered Reciprocal Chromosome Translocations Drive High Threshold, Reversible Population Replacement in Drosophila. *ACS Synthetic Biology* **7**: 1359-1370.