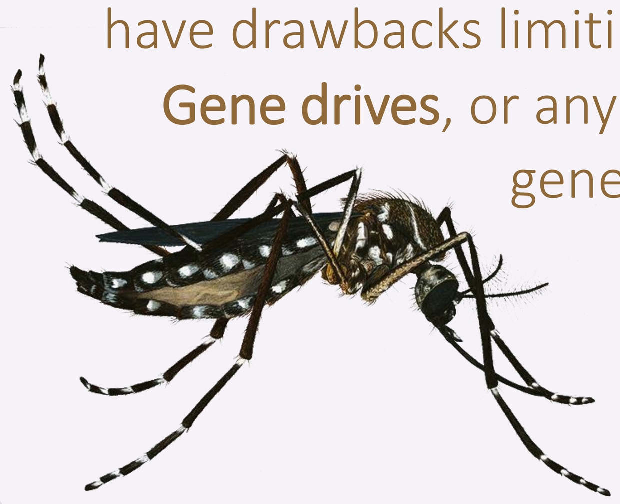
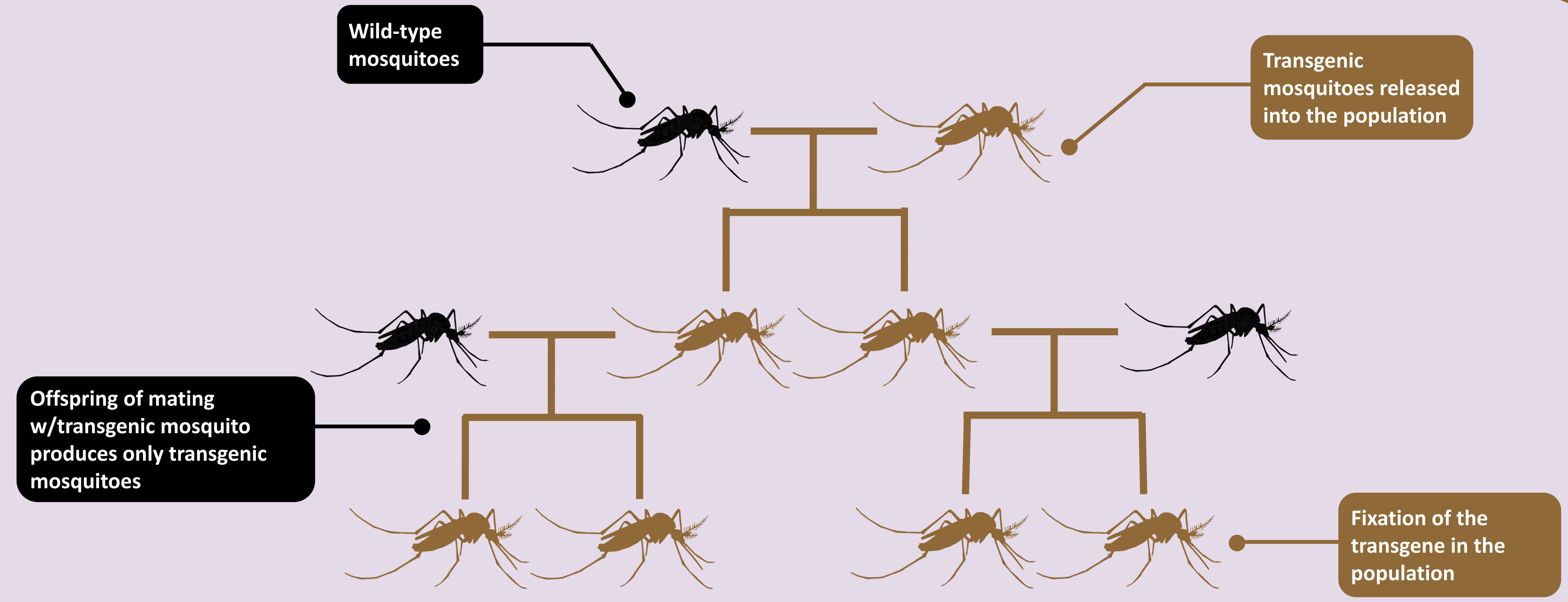
Gene drive in mosquito populations: How the consequences of genetic load are modulated by density dependence

Gene drive technology offers a promising approach to curb the morbidity and mortality caused by mosquito-borne disease. This is accomplished by reducing natural mosquito populations and therefore mitigating the potential of disease transmission to humans. The extent of population suppression is influenced by many natural dynamics, such as density dependence. We explore the nature of this reliance and find that ecological factors can significantly alter gene drive effectiveness.

1 What is a gene drive and why does it matter?

Hundreds of millions of people fall ill with a mosquito-borne illness each year, and hundreds of thousands of these people will succumb to their disease. Conventional methods of control have drawbacks limiting their effectiveness, such as insecticide resistance in mosquitoes. **Gene drives**, or any natural or artificial (engineered) mechanism that propagates genetic elements throughout a population, circumvent many of these drawbacks and have shown promise *in vitro* in their capability to substantially reduce mosquito populations. Our potential use of gene drive technology in the wild relies on a thorough understanding of the population dynamics of the target organism.





2 Density dependence in mosquito populations

Density dependence (DD) affects mosquito larval survival and the time it takes for juveniles to emerge as adults [1,2]. Regarding the former, larval competition makes it so that survival is more likely when larvae are fewer. Much of the literature on gene drive in mosquito populations neglects this important ecological factor. For those studies that do not, however, they vary greatly in their approaches to incorporating DD in mathematical models. One way of unifying these dissimilar approaches is discussing DD in terms of its strength. A mosquito population with **strong** DD will better resist fluctuations than a population with **weak** DD. In the context of gene drive, stronger DD can severely limit the ability of the drive to crash the mosquito population. In the reverse scenario, in a system in which DD is weak, the population is less resistant to fluctuations, indirectly boosting drive effectiveness.

3

Theoretical drive performance can be qualitatively understood using a **genetic load**, or a constant culling of mosquito juveniles. A genetic load of 0.5, for example, corresponds to 50% juvenile mortality. Fig. 1 shows the dramatic effect different strengths of DD can have on the capability of genetic load to reduce a mosquito population. This finding can be extended to any gene drive that kills mosquitoes during their juvenile stages. To test this, we study how a two-locus engineered underdominance (EU, Fig. 3) drive performed in a system with varying DD strength (Fig. 2). The differences between systems are striking: at certain points, the EU drive kills four times as many mosquitoes in the system with weak DD than in the system with strong DD.

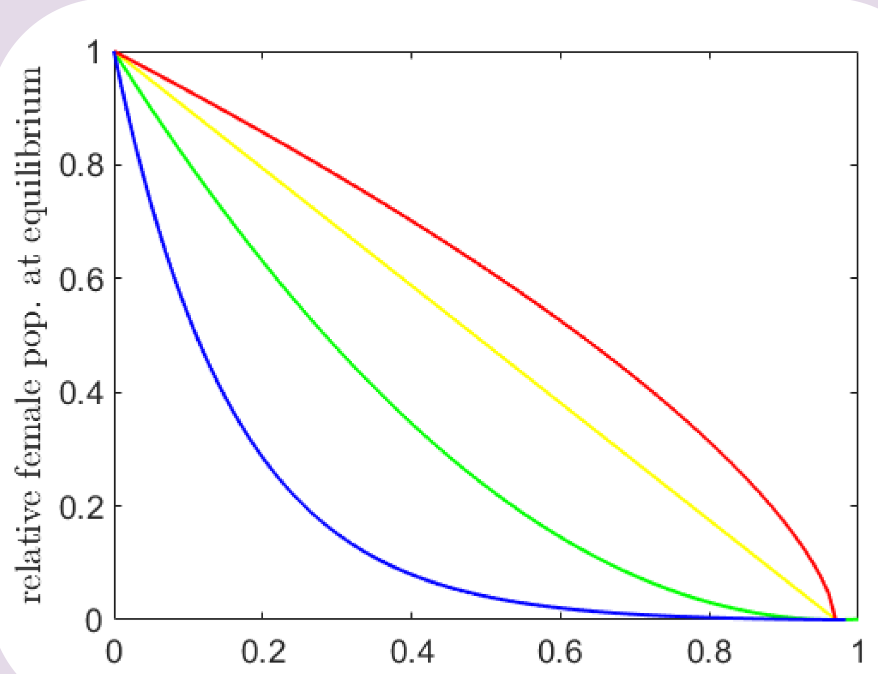


Fig. 1. Extent of female mosquito population reduction versus genetic load as DD strength is increased (warmer colors correspond to stronger DD).

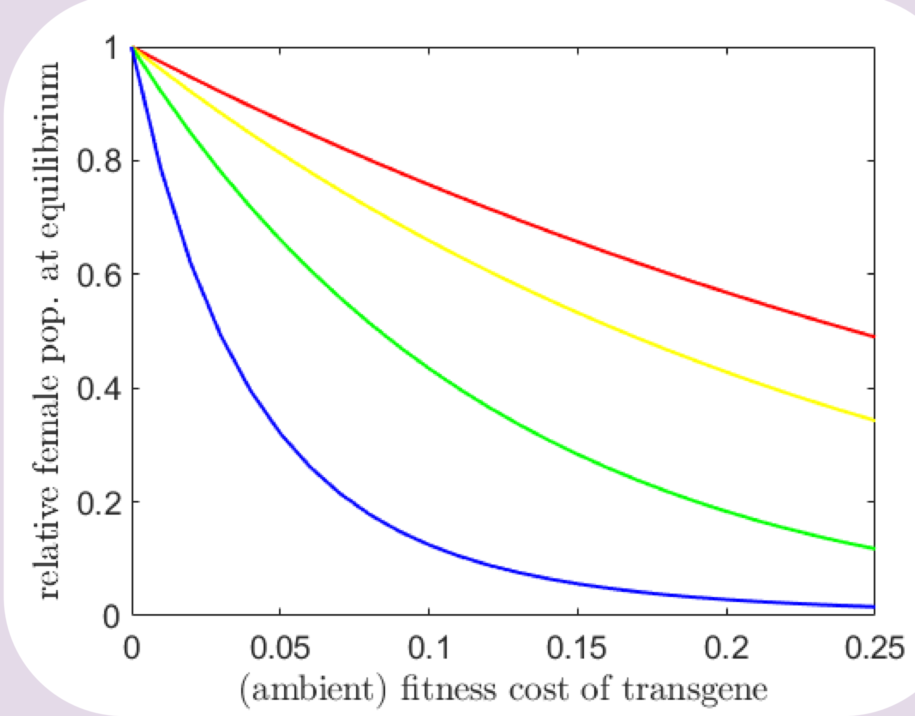


Fig. 2. Extent of female mosquito population reduction versus fitness cost imposed by an engineered underdominance drive.

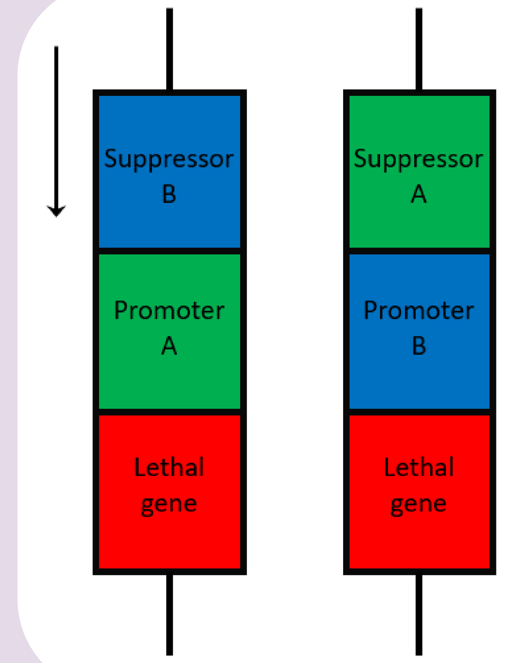


Fig. 3. A schematic of the construct used in an engineered underdominance drive.

4 Conclusion

Gene drive technology can greatly reduce the burden of mosquito-borne illness. Before we get to the point of wild releases, however, it is essential that we account for the factors most influential to drive outcomes. As we have shown, ecological factors such as density-dependent dynamics have heavy consequences on drive performance. These findings underline the importance of continued research into this area for not just mosquitoes, but any pest for which this technology might be useful in controlling.

References

[1] Alto, B. W., Lounibos, L. P., Higgs, S., & Juliano, S. A. (2005). Larval competition differentially affects arbovirus infection in *Aedes* mosquitoes. *Ecology*, 86(12), 3279–3288.
[2] Hancock, P. A., White, V. L., Callahan, A. G., Godfray, C. H. J., Hoffmann, A. A., & Ritchie, S.A. (2016). Density-dependent population dynamics in *Aedes aegypti* slow the spread of wMel Wolbachia. *Journal of Applied Ecology*, 53(3), 785–793.

NC STATE UNIVERSITY
GENETICS & GENOMICS INITIATIVE