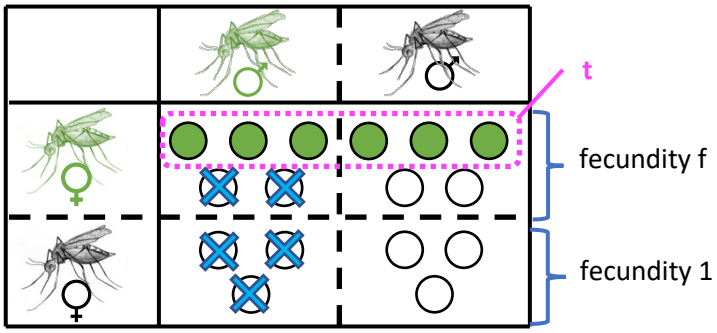
Report on the manuscript
"Positive fitness effects help explain the broad range of Wolbachia prevalences in natural populations"
by Karisto et al.

Karisto et al. revisit models of propagation of a Wolbachia endosymbiont within a host population. They consider a pleiotropic effect of the symbiont on the host fitness, namely a direct fitness effect manifested in a relative fecundity rate f of females carrying the symbiont, and a cytoplasmic incompatibility that results in either a reduced survival or a masculinization of uninfected eggs fertilized by infected males. Classical models have focused on deleterious direct fitness effects ($f < 1$), that necessarily result in either extinction of the symbiont from the host population, or an equilibrium frequency of symbiont-carrying host close to fixation. In contrast, Karisto et al. propose to focus on beneficial direct fitness effect. They study the fixed points (values and stability) of three different models (diplo-diploid, haplo-diploid with female killing and haplo-diploid with masculinization) and robustly conclude that a beneficial direct fitness effect ($f > 1$) provides a plausible and potentially testable explanation for the low frequencies of symbiont-carrying hosts sometimes observed in nature. I find the manuscript very interesting and well written, and have no scientific concern to raise. In the following, I only ask a few minor remaining questions and provide a few suggestions to streamline the manuscript, which could gain in conciseness in order to be more easily accessible to a broader audience.

General comments & broader questions

a. I would strongly advise to add a figure with drawings recapitulating the key parameters of the model, for example in the line of this:



b. I understand that this goes beyond the scope of this paper, but for my own curiosity: what about the evolution of the total size of the host population, not only of the frequency of symbiont-carrying hosts? I was wondering if you could comment on that, as I am assuming that this is a key parameter in using *Wolbachia* CI as a potential way to control mosquito populations?

c. In the paper you are focusing on the fixed points and their stability. But what about the dynamics to approach the fixed points? Do we know anything about the time to fixation? If dampening oscillations are to be expected? This is also probably going beyond the scope of the paper, but I am also expecting this to be of importance, again, if CI is to be used as a controlling tool.

d. From what I understand, Wolbachia has the ability to "jump" from one host species to another quite easily. In these conditions, the initial symbiont-carrying host frequency will always be low. Are there mechanisms other than stochastic fluctuations that are being proposed to explain how the invasion threshold can be overcome?

Abstract

1. I think the use of the term "pleiotropy" in the abstract is unnecessarily complicated for non-specialists and would rather suggest something in the line of "additional direct fitness effect", as is otherwise used in different sections of the manuscript

2. L34: I think the use of "infection rates" here is not exactly correct, because it suggests an evolution in time. I think just removing "rates" restores what I think you mean.

Introduction

3. L64: the spread of the *Wolbachia* → the spread of *Wolbachia*

4. L74-76: At first read, the meaning of this sentence was unclear (in particular, do they also consider CI in the mentioned paper?)

Models and analysis

5. L130: I think it should be the contrary ($t \leq 1, L > 0$) to prove the point that $f \geq 1$ (even though both are true).

6. Pages 7-8-9-10 in particular would benefit from being more concise. What could help is to follow more closely the order of the panels of the figures in their textual description (or alternatively, reorder the panels). More particularly, L142-148 and L164-181 could be shortened, I think.

7. L209-210: I did not understand *"this case is fully captured by the analogy to the asexual lineages A and B above"*, could you please clarify?

8. L227: Why only 2c? From my understanding I would have said that the whole of figure 2 is relevant here?

9. L283: I would suggest to make the change (many eggs → many fertilized eggs) for clarity.

10. L297 and following: here I would suggest to make it clearer that you speak only of the masculinization version of the haplodiploid model. In general, I think the manuscript might gain in clarity if these two cases are more clearly separated.

Discussion

11. L 339-345: here it is not clear to me how would a model with two different *Wolbachia* strains, one with $f_1 = 1$, the other with $f_2 \neq f_1$ would be any different from the current model with infection vs. no infection. Could you maybe comment on this?

12. L361-363 I would suggest to move this sentence by one paragraph, to keep all the comments on empirical data together (this sentence looks more specifically linked to L377-378 in my opinion).

13. L390-392: Could you please elaborate on mtDNA genotype diversity? I am not familiar with how this could help elucidate temporal evolutions in the context of endosymbionts. Is that because the host's cells are expected to lose redundant genes in streamlining coevolution?

14. L394-396: I am assuming that the studies mentioned here refer to dengue-carrying mosquitoes' populations monitoring. I would explicitly mention the host species to make it immediately crystal clear.

Figures

15. Figure 1: On panel 1b, it could be useful to have a zoom insert of what happens close to zero. I would add on the figures 1b and c $ft > 1$ and $ft < 1$, respectively, to make the comparison easier without refering to the text of the caption.

16. Figure 4: In the caption, I don't think "FK" and "MD" have been defined before, and I am still unsure what the D stands for. I think it should be capital M and F in the equilibria notations (but this also occurs in the caption of figure 5, and I might have missed other occurrences – be sure to make the notation uniform). I would recommend to write the f values on top of the columns to ease comparison of the panels (and since most parameters are conserved). Would it be possible to also take L=0.65 in d) for consistency?

17. Figure 5: as before, I think it should be capital M and F in the equilibria notations. In addition, I think it might be nice to have the shades of grey also directly explained on the figures, without having to refer to the caption text (this is also valid for figure 3).

Annexes

18. L422: "the real part" here is not clear (only if the determinant is negative are the solutions complex conjugates).

19. L432: I think there lacks one final parenthesis in the denominator of $\widehat{p_F}$ (which is correctly written in r_F a few lines down the page). Maybe the expression for $\widehat{p_F}$ and $\widehat{p_M}$ could also be squeezed into a single line to not have to repeat the same denominator twice.

20. Page 27 might benefit from a couple of drawings to follow the reasoning more easily. Also on this page, "when $f \leq 1$" L 442 should be made clearer from the beginning of the argument and be stated explicitly that it is a proof by contradiction.

21. L536: I think there is a parenthesis error (it should be after the first $p_M L$, not the second, like in B9).

22. L544: I think there is a sign error (it should be a + instead of the first -, as in L546).

23. L554: notations should be standardized ("x" or ","), also with the following section.