Peer Community In Evolutionary Biology

Modelling the evolution of how vector-borne parasites manipulate the vector's host choice

Samuel Alizon *based on peer reviews by* ***Nicole Mideo*** *and* ***Samuel Alizon***

Sylvain Gandon (2017) Evolution and manipulation of vector host choice. Missing preprint_server, ver. Missing article_version, peer-reviewed and recommended by Peer Community in Evolutionary Biology. 10.1101/110577

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Published: 12 June 2017

Many parasites can manipulate their hosts, thus increasing their transmission to new hosts [1]. This is particularly the case for vector-borne parasites, which can alter the feeding behaviour of their hosts. However, predicting the optimal strategy is not straightforward because three actors are involved and the interests of the parasite may conflict with that of the vector. There are few models that consider the evolution of host manipulation by parasites [but see 2-4], but there are virtually none that investigated how parasites can manipulate the host choice of vectors. Even on the empirical side, many aspects of this choice remain unknown. Gandon [5] develops a simple evolutionary epidemiology model that allows him to formulate clear and testable predictions. These depend on which actor controls the trait (the vector or the parasite) and, when there is manipulation, whether it is realised via infected hosts (to attract vectors) or infected vectors (to change host choice). In addition to clarifying the big picture, Gandon [5] identifies some nice properties of the model, for instance an independence of the density/frequency-dependent transmission assumption or a backward bifurcation at R0=1, which suggests that parasites could persist even if their R0 is driven below unity. Overall, this study calls for further investigation of the different scenarios with more detailed models and experimental validation of general predictions.

References:

[1] Hughes D, Brodeur J, Thomas F. 2012. Host manipulation by parasites. Oxford University Press.

[2] Brown SP. 1999. Cooperation and conflict in host-manipulating parasites. Proceedings of the Royal Society of London B: Biological Sciences 266: 1899–1904. doi: [10.1098/rspb.1999.0864](https://doi.org/10.1098/rspb.1999.0864)

[3] Lion S, van Baalen M, Wilson WG. 2006. The evolution of parasite manipulation of host dispersal. Proceedings of the Royal Society of London B: Biological Sciences. 273: 1063–1071. doi: [10.1098/rspb.2005.3412](https://doi.org/10.1098/rspb.2005.3412)

[4] Vickery WL, Poulin R. 2010. The evolution of host manipulation by parasites: a game theory analysis. Evolutionary Ecology 24: 773–788. doi: [10.1007/s10682-009-9334-0](https://doi.org/10.1007/s10682-009-9334-0)

[5] Gandon S. 2017. Evolution and manipulation of vector host choice. bioRxiv 110577, ver. 3 of 7th June 2017. doi: [10.1101/110577](https://doi.org/10.1101/110577)

Reviews

Evaluation round #2

DOI or URL of the preprint: **10.1101/110577**
Version of the preprint: 2

Authors' reply, 07 June 2017

Review by Nicole Mideo:

I appreciate the author's responses to my previous comments. I think the edits to the model presentation do help with understanding.

A have a few additional minor comments. 1. I still think Figure 1's caption needs more detail, e.g., "shades of gray indicate different values of R0 from 1 to 6 (darkest to lightest)". Additionally, saying somewhere that 1 = complete preference for infected host would be helpful (or at a minimum, adding the p and pi to the axes, like in Figure 3? I note too that Fig 2 has a different label ("preference" rather than "choice"). Is this intentional?)

I modified the legend of figure 1.

1. l. 354. "indicates" feels a bit strong here. Perhaps "suggests"?

   Done

   l. 355-358. I wonder if the ordering of these sentences should be swapped? E.g., some viruses seem to induce these conditional strategies...malaria parasites do not...extending the model to allow the incubation period could lead to new insights on additional constraints at play.

2. I modified the text around this part.

3. Related to 3, the note about handling time being a reasonable approximation for an incubation period is interesting. I wonder if it's worth throwing in a line in the main text around here too, though noting that it would (presumably?) require a handling time specific for infected hosts.

   I am not sure how to add this comment. My feeling is that the end of the discussion is alredy full of possible extensions of the model.

More editorial things. - l. 51 the references are messed up • l. 114 were instead of "where"

Done

• l. 255 attractive instead of "attracted"

Done

• l. 284 their propensity instead of “its propensity”

Done

• l. 305 and 306. Should this be viruliferous (as in l. 274, instead of viruleferous?)

Done

• Appendix, pg 3. First sentence: “density OF uninfected vectorS in a searching state”. Also first sentence of section 2: “...number of vectorS...”

Done

Review by Samuel Alizon:

My main comment still has to do with section 4, which I find too independent from the rest of the text. Unless I missed it, the only reference to the results in section 4 is in line 246. I think there are two ways to improve this: either have more references to the results in section 4, or present section 4 before the model and more or less reformulate the abstract to say that the model is developed to try and make sense observed data.

I agree. I modified the end of the abstract and I am more explicit in my references to the theoretical predictions in section 4.

Detailed comments l.16-17: In general, I tend to be frustrated when the conclusion is that things are very ”complex”... Furthermore, using models to ”confirm” that patterns are complex seems trivial. As suggested above, I find it more constructive to say that we use models to try and make sense of this complexity.

I modified the end of the abstract

l.114: were assumed (no h)

Done

l.145: delete ”analysis of the”

Done

Decision by Samuel Alizon, posted 07 June 2017

Decision and reviews

The two reviewers only suggested marginal revisions before the manuscript can be formally recommended.

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A have a few additional minor comments.

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l.145: delete "analysis of the"

Evaluation round #1

DOI or URL of the preprint: **10.1101/110577**
Version of the preprint: 1

Authors' reply, 03 May 2017

REVIEWER #1 (Samuel Alizon) This model provides clear biology insights because it manages to reach some general conclusions with a minimal number of assumptions. However, I also think some aspects could be simplified. I also think that giving an intuitive prediction in the Introduction (vectors should avoid infected hosts, parasites should try to get infected vectors to bite uninfected hosts and uninfected vectors to bite infected hosts) would help the reader to grasp when the intuition fails. I also have several concerns. 1) I did not fully understand the difference between the handling time and the incubation period that is often present in many models vector-borne transmission models. Are the two equivalent?

> Biologically these two things are very different but in the model they both describe a state where the vector is not yet infectious after biting an infected host. In the appendix I explicitly model the handling time where I track the densities of vectors which are still busy feeding on their hosts. One may argue that this model could adequately account for the time required by the parasite to develop in the vector before being ready to infect a new host (e.g. the time required for malaria parasites to develop into sporozoites and reach the salivary glands of the mosquitoes). Note, however, that in my model the distribution of this time is exponential. Usually, however, the

incubation period is modeled as a fixed period of time. I have added a sentence in the appendix to discuss that briefly.

2) I appreciated the fact that the conclusions are obtained almost without trade-offs. Unless I am mistaken, the only assumption of this kind has to do with the idea that maximum fecundities increase with host density. I think more details would help here, e.g. explain why the function has the same shape as the one involved in parasite transmission. Does this mean that the underlying assumption is that blood meals are the limiting factor on vector fecundity?

I agree that I need to be more explicit about the underlying assumptions regarding the fecundity of the vector (reviewer #2 had a very similar comment on this part). I want to show two different epidemiological scenarios in figure 1. In figure1A the maximal fecundity of the vector is a fixed quantity and in figure 1B I allow this fecundity to be limited by the availability and/or the quality of the host. In the revised version of the manuscript these two scenarios are presented in the epidemiological model (section 2).

3) I found the section on the vector evolution in absence of pathogen a bit misleading (lines 125-131). Indeed, this study is about the evolution of feeding on infected or uninfected host but this part of the study is about the evolution of another trait. Furthermore, it involves a specific (and arbitrary) trade-off to capture the fecundity cost associated with investment in higher searching efficiency. Overall, I think this bit could be removed without great loss from the article.

I want to keep this in because the aim of this work is to present a theoretical framework to study the evolution and the manipulation of vector behavior. I agree that this is not directly relevant for the evolution of host preference but it does help to see how the model can be used to study the evolution of other traits.

4) I find the superinfection hypothesis quite strong. From a biological standpoint I am not sure I know examples of such dynamics in vectors. From a mathematical standpoint, the superinfection terms do not depend on i and j (the host and vector strains). Does this mean that the nature of the strain does not affect the outcome of the multiple infection? In other words, what governs the success is where the strain is (in the host or in the vector). Overall, although this 'superinfection' is handy to introduce epidemiological feedbacks, I find it a bit far from the biology. To be convinced about the importance of superinfection here I think either more biology or a simple within-host model would be helpful.

One always has to make approximations to model multiple infections. The superinfection model does capture the essence of what is at stake here: within-host evolution. Of course I could develop that further (e.g. allow the ability to oust the resident strain to depend on each pathogen strategies) but this would drag me too far from to the main topic of this work. I've added a sentence to recall that this model is a crude approximation and a couple of references showing that, in malaria, multiple infections do occur in both the host and in the vector.

5) Section 4 regroups some very valuable information and helps illustrate the model but I find that it also breaks the continuity of the article. My suggestion would be to try and turn it into a Table (and perhaps keep the text as an Appendix) to make the whole article easier to read.

I want to keep this in the main text because the biology is fascinating. Besides, it shows that many important things are missing in the current model. There is already a table (table S1) that sums up key informations on these different biological systems but it is impossible to give enough details in this table. Detailed comments

l.55: The intro is very well written and focused but I think that adding a 'Darwinian demon' prediction (see above) could help.

I already mention in the introduction that conditional modifications of vector behavior seem very adaptive but I don't want to go too far into verbal arguments. The whole point of this analysis is to provide a rational evaluation of what is adaptive and what is not.

l.73: How realistic is the assumption of density-dependent fecundity? Especially since the maximum fecundity is also density-dependent.

Note that there are two densities here (vector density and host density). The first density-dependence has to do with the density of vectors (for instance the competition taking place in water between mosquito larvae). The second density-dependence has to do with the availability of the host. This is now much more explicit in section 2.

l.108-109: About the extinction, I think it would be fair to mention that this only occurs if the vectors behaviours are maladaptive for the parasite, i.e. infected vectors bit infected hosts and uninfected vectors bite uninfected hosts.

At this stage of the paper it is not yet very clear what is adaptive and what is not. As we will see later in the paper the adaptive nature depends a lot on the details of the control of the trait. Besides natural selection can favor preference strategies that may lead towards extinction.

l.125-131: I would remove this paragraph and the corresponding Appendix.

As explained above I want to keep this in.

l.151: This is the R0 of the resident correct?

Yes. At this stage there is no mutant in the model.

Also, perhaps here you could cite epidemiological models that have found such a bifurcation, e.g. van den Driessche & Watmough (2002).

I refer to other papers in the discussion that are even more relevant because they focus on vector-borne diseases.

l.160-162: This sentence is perhaps strong given that here the virulence of the infection to the vector is assumed to be 0 (it is only the ”quality” of the infected vector that matters) and given the renewed interest in the literature on the pleiotropic effects of parasites (e.g. Michalakis et al. 1992).

The virulence of the infection is not assumed to be zero. The infection can act on both the survival and the fecundity of the vector.

l. 164: Just to clarify, in Figure 2, when all hosts have the same quality for the vector, the latter prefers to bite infected hosts because there are more infected than uninfected hosts? If so, this sounds like a strong assumption on parasite prevalence.

Indeed, when phi=1 vector prefer towards infected hosts is driven by the prevalence of the infection for these parameter values. Remember that the prevalence is a dynamical variable in this model. I don't think it is a very strong assumption if the prevalence of the infection is higher than 50%. Many diseases like malaria have a very high prevalence.

l.178-182: See also Sofonea et al. (2017) on the problems of assuming a superinfection framework (in short, when the trait evolves you might be switching from superinfection to coinfection)

Again, the superinfection model I am using is an attempt to do ”as simple as possible”.

l.193: rephrase ”selection selects”

Done

l.331: replace ”and leads” by ”, which leads”?

Done

l.334-335: suggestion ”from observed preference patterns”.

Done

l.338-339: suggestion ”selection favours”

Done

Figure 3: Would it be possible to have all four patterns on the same figure? Otherwise add some more information to distinguish all 4?

Difficult to put all 4 patterns in a single figure (too many arrows). I tried to improve the readability of this figure in the revised version.

REVIEWER #2 (Nicole Mideo) This is a well-written paper on the evolution of vector feeding behaviour when preferences for feeding on infected versus uninfected hosts are governed by vectors, pathogens, or both. The author presents a simple model for vector-borne disease dynamics, first explores the effects of feeding behaviour on epidemiological outcomes, and then extends the model to predict the evolution of feeding preferences under a number of different scenarios. There are some really interesting inferences in this paper including (1) vector control may not be as effective as predicted due to subtleties of vector foraging behaviour (2) it would be hard to disentangle whether vector feeding preferences are controlled by vector genetics or pathogen genetics when the pathogen only ‘controls’ feeding of infected vectors (i.e., does not alter the ‘attractiveness’ of infected hosts). A further really nice element of this paper is the comparison with available empirical data. As the author points out, there is a dearth of studies looking at feeding preferences of BOTH infected and uninfected vectors, but the few studies available suggest that only rarely, and apparently only for viral infections, are uninfected vectors disproportionately attracted to infected hosts. It would certainly be nice for this paper to motivate further empirical work. I have two major comments / suggested changes for this manuscript. First, I wish a bit more of the math was in the main text. In section 3.1, for example, I think it will be hard for folks to intuit how to go from equation 1 to a prediction for the evolution of searching efficiency on its own in the absence of infection. Obviously this depends on the audience, but I am assuming that the target is not an explicitly theoretical crowd. I think moving the 3.1 section from the SM to the main text could help generally: we see how the costs are incorporated and the F_s is defined (it is currently undefined in the main text, I believe). That on its own might be enough additional math in the main text – for me, that seemed like the biggest missing logical link – but again, depending on the target journal it might be reasonable to shift more of the SM over.

I think this comment is related to the point made by the first reviewer regarding density dependence. I reshuffled a bit the presentation of the model in the revised version and I am now much more explicit about the assumptions of the model on fecundity. In contrast to review#1, this reviewer would like more details about the evolution of searching efficiency in the main text (section 3.1). I agree that this part might be a bit difficult to grasp but I don’t want to develop it too much in the main text. I prefer to stick to my original plan to mention this scenario in the main text and put all the details of the derivation in the sup info.

Second, the observation that conditional preference strategies only occur for vector-borne viral infections and there is no evidence of conditional strategies for things like malaria is interesting. It is entirely possible that malaria parasites are one of scenarios 3a-c. where preferences are the same, but I wonder if development time in the vector would alter evolutionary predictions. I’m quite happy with the model being formulated as it is,

but for many vector-borne diseases, a period of maturation within the vector is required before transmission is possible. (I'm assuming that this isn't true for many of the viral pathogens of plants described, but I may be wrong.)

There is a wide diversity of transmission modes in viruses. Some viruses can be transmitted immediately (for instance CMV) but other viruses need to replicate in the vector before reaching a sufficient viral load to allow transmission.

Given that this period can be quite long relative to the lifespan of the vector, feeding preferences during this phase could be important too. I could imagine a 3-phase conditional strategy or one where "exposed" vectors are constrained to act either like uninfected or infected vectors. I'm not suggesting the model be extended to explore this, but I wonder if (hope?) the author could speculate on how this might alter evolutionary trajectories. I could imagine that, if the pathogen controls vector behaviour, but there isn't a separate "exposed" feeding preference, the cost of getting the vector feeding preference wrong during that development phase could be quite high.

Interesting suggestion. The manipulation of the biting rate of exposed-but-not-yet-infectious vectors has been studied contrasted to the biting rate of infectious vectors in previous experiments. But I am not aware of similar experiments on host preference. One difficulty, here is to capture the consequences of this behavior in terms of within-host competition in the vector.

Minor comments. - l. 82-84. Should this say it varies with the number of infected hosts? (We're talking about the Vs and Vi equations, right?)

The time between two bites varies with the nb of hosts but the handling time is assumed to be a fixed parameter. I reformulated a bit this sentence.

- l. 160-162. I feel like this statement needs a reference. I'm wildly out of touch with this literature, but the last thing I read about it suggested the data was equivocal, at least for malaria parasites (Ferguson & Read 2002). Plus, at least some folks seem to have the notion that vectors are, by definition, rather unaffected by parasites (e.g., the "morbidity" definition described in Wilson et al. 2017 Phil Trans 372:20160085).

Yes, I know this is a controversial and interesting issue. The model allows to consider very different scenarios. In malaria, for instance, the effect of the infection on mosquito survival is not clear but infection does reduce fecundity. I developed a bit this issue (in the context of malaria) in the revised version of the paper.

- l. 281 it's not immediately clear to me how increasing dispersal is necessarily the same as increasing searching efficiency. - I feel like I need a little more detail in the Figure 1 caption. Maybe adding "with the white region the highest" after "R0 from 1 to 6" in the second sentence? - last line of SM p6. I'm not clear on how Figure 2 shows this (as in, I don't know what prevalence is across this figure).

I agree that it is not obvious and I dropped the reference to the parameter alpha in my model. Figure 1 will not really help because it does not illustrate the effects of searching efficiency but host preference (host preference is a ratio of searching efficiency, see table 1). When I review these biological cases we are necessarily reaching the limits of the current model. I think it is quite useful to see that the biology is much more complex that what I model.

Editorial things. - l.80 "uninfected anD infected hosts"

Done

- l. 102 do you specifically mean mosquitoes here, or should this say "vectors"?

Done

- l. 157, one of these (ii)s should be (iii)

  Done

- l. 253 chabaudi has one i.

  Done

- l. 260 study -> studies?

  Done

- l. 270 I don't know what "viruliferous" means. Is it simply "infected"? Infected and infectious - Equation references in the SM seem to be off. E.g., p5 reference to equation 6 should be eq.3; p7 a reference to eq.8 should be 5.

  Done

- l. 284-286. Something is wrong with this sentence, but I don't know how to fix it!

  Done

- l. 305-306. Remove comma after "Unlike" and end parenthesis after "[17]".

  Done

- l. 367 "multiples" -> "multiple" - is "attractivity" a word? Could go with "attractiveness"?

  Done

- totally nit-picky, personal preference thing: I noted the switch from "we" to "I" in the manuscript. I would go with "I" throughout.

  Done

Decision by Samuel Alizon, posted 03 May 2017

Revision needed

This evolutionary epidemiology model nicely formalises several intuitions on vector manipulation by parasites but it also provides us with new original insights. However, before recommending this article, another reviewer and myself suggested some modifications. Some of the concerns revolved around avoid loosing the reader, either due to a lack of mathematical details, or to a profusion of biological examples. The reviewer and I also pointed out that some assumptions should be discussed a bit more thoroughly (e.g. handling time vs. incubation period or 'superinfection').

Reviewed by Samuel Alizon, 01 June 2017

Summary

The author studies the epidemiology and evolution of the manipulation of vector biting behaviour by the parasite. This manipulation can occur when the parasite is infecting the host, intuitively by making the host more attractive to uninfected vectors, and/or when the parasite is infecting the vector, intuitively by making it bite more and/or be more attracted by uninfected hosts. Using adaptive dynamics theory, the author shows that these intuitions might not always apply, for instance due to multiple infections.

Concerns

This model provides clear biology insights because it manages to reach some general conclusions with a minimal number of assumptions. However, I also think some aspects could be simplified. I also think that giving an intuitive prediction in the Introduction (vectors should avoid infected hosts, parasites should try to get infected vectors to bite uninfected hosts and uninfected vectors to bite infected hosts) would help the reader to grasp when the intuition fails. I also have several concerns.

1) I did not fully understand the difference between the handling time and the incubation period that is often present in many models vector-borne transmission models. Are the two equivalent?

2) I appreciated the fact that the conclusions are obtained almost without trade-offs. Unless I am mistaken, the only assumption of this kind has to do with the idea that maximum fecundities increase with host density. I think more details would help here, e.g. explain why the function has the same shape as the one involved in parasite transmission. Does this mean that the underlying assumption is that blood meals are the limiting factor on vector fecundity?

3) I found the section on the vector evolution in absence of pathogen a bit misleading (lines 125-131). Indeed, this study is about the evolution of feeding on infected or uninfected host but this part of the study is about the evolution of another trait. Furthermore, it involves a specific (and arbitrary) trade-off to capture the fecundity cost associated with investment in higher searching efficiency. Overall, I think this bit could be removed without great loss from the article.

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Detailed comments

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References

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Sofonea M, Alizon S, Michalakis Y 2015 From within-host interactions to epidemiological competition: a general model for multiple infections. Philos Trans R Soc Lond B 370:20140303

van den Driessche P, Watmough J 2002 Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math. Biosci. 180:29-48

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Minor comments. - l. 82-84. Should this say it varies with the number of infected hosts? (We're talking about the Vs and Vi equations, right?) - l. 160-162. I feel like this statement needs a reference. I'm wildly out of touch with this literature, but the last thing I read about it suggested the data was equivocal, at least for malaria parasites (Ferguson & Read 2002). Plus, at least some folks seem to have the notion that vectors are, by definition, rather unaffected by parasites (e.g., the "morbidity" definition described in Wilson et al. 2017 Phil Trans 372:20160085).

- l. 281 it's not immediately clear to me how increasing dispersal is necessarily the same as increasing searching efficiency. - I feel like I need a little more detail in the Figure 1 caption. Maybe adding "with the white region the highest" after "R0 from 1 to 6" in the second sentence? - last line of SM p6. I'm not clear on how Figure 2 shows this (as in, I don't know what prevalence is across this figure).

Editorial things. - l.80 "uninfected anD infected hosts" - l. 102 do you specifically mean mosquitoes here, or should this say "vectors"? - l. 157, one of these (ii)s should be (iii) - l. 253 chabaudi has one i. - l. 260 study -> studies? - l. 270 I don't know what "viruliferous" means. Is it simply "infected"? - Equation references in the SM seem to be off. E.g., p5 reference to equation 6 should be eq.3; p7 a reference to eq.8 should be 5. - l. 284-286. Something is wrong with this sentence, but I don't know how to fix it! - l. 305-306. Remove comma after "Unlike" and end parenthesis after "[17]". - l. 367 "multiples" -> "multiple" - is "attractivity" a word? Could go with "attractiveness"? - totally nit-picky, personal preference thing: I noted the switch from "we" to "I" in the manuscript. I would go with "I" throughout.