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► **To cite this version:**

Samuel Alizon. Modelling parasitoid virulence evolution with seasonality. 2021, pp.100129. <10.24072/pci.evolbiol.100129>. <hal-03289840>

HAL Id: hal-03289840

<https://hal.science/hal-03289840v1>

Submitted on 19 Jul 2021

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Modelling parasitoid virulence evolution with seasonality

Samuel Alizon based on reviews by Alex Best and 2 anonymous reviewers

A recommendation of:

Host phenology can drive the evolution of intermediate virulence strategies in some obligate-killer parasites

Hannelore MacDonald, Erol Akçay, Dustin Brisson(2021), *bioRxiv*, 2021.03.13.435259, ver. 8 peer-reviewed and recommended by Peer Community in Evolutionary Biology [10.1101/2021.03.13.435259](https://doi.org/10.1101/2021.03.13.435259)

Open Access

Submitted: 14 March 2021, Recommended: 16 July 2021

Published: 19 July 2021

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Recommendation

The harm most parasites cause to their host, i.e. the virulence, is a mystery because host death often means the end of the infectious period. For obligate killer parasites, or “parasitoids”, that need to kill their host to transmit to other hosts the question is reversed. Indeed, more rapid host death means shorter generation intervals between two infections and mathematical models show that, in the simplest settings, natural selection should always favour more virulent strains (Levin and Lenski, 1983). Adding biological details to the model modifies this conclusion and, for instance, if the relationship between the infection duration and the number of parasites transmission stages produced in a host is non-linear, strains with intermediate levels of virulence can be favoured (Ebert and Weisser 1997). Other effects, such as spatial structure, could yield similar effects (Lion and van Baalen, 2007).

In their study, MacDonald *et al.* (2021) explore another type of constraint, which is seasonality. Earlier studies, such as that by Donnelly *et al.* (2013) showed that this constraint can affect virulence evolution but they had focused on directly transmitted parasites. Using a mathematical model capturing the dynamics of a parasitoid, MacDonald *et al.* (2021) show if two main assumptions are met, namely that at the end of the season only transmission stages (or “propagules”) survive and that there is a constant decay of these propagules with time, then strains with intermediate levels of virulence are favoured.

Practically, the authors use delay differential equations and an adaptive dynamics approach to identify evolutionary stable strategies. As expected, the

longer the shorter the season length, the higher the virulence (because propagule decay matters less). The authors also identify a non-linear relationship between the variation in host development time and virulence. Generally, the larger the variation, the higher the virulence because the parasitoid has to kill its host before the end of the season. However, if the variation is too wide, some hosts become physically impossible to use for the parasite, whence a decrease in virulence.

Finally, MacDonald *et al.* (2021) show that the consequence of adding trade-offs between infection duration and the number of propagules produced is in line with earlier studies (Ebert and Weisser 1997). These mathematical modelling results provide testable predictions for using well-described systems in evolutionary ecology such as daphnia parasitoids, baculoviruses, or lytic phages.

Reference

Donnelly R, Best A, White A, Boots M (2013) Seasonality selects for more acutely virulent parasites when virulence is density dependent. *Proc R Soc B*, 280, 20122464. <https://doi.org/10.1098/rspb.2012.2464>

Ebert D, Weisser WW (1997) Optimal killing for obligate killers: the evolution of life histories and virulence of semelparous parasites. *Proc R Soc B*, 264, 985–991. <https://doi.org/10.1098/rspb.1997.0136>

Levin BR, Lenski RE (1983) Coevolution in bacteria and their viruses and plasmids. In: Futuyma DJ, Slatkin M eds. *Coevolution*. Sunderland, MA, USA: Sinauer Associates, Inc., 99–127.

Lion S, van Baalen M (2008) Self-structuring in spatial evolutionary ecology. *Ecol. Lett.*, 11, 277–295. <https://doi.org/10.1111/j.1461-0248.2007.01132.x>

MacDonald H, Akçay E, Brisson D (2021) Host phenology can drive the evolution of intermediate virulence strategies in some obligate-killer parasites. *bioRxiv*, 2021.03.13.435259, ver. 8 peer-reviewed and recommended by Peer Community in Evolutionary Biology. <https://doi.org/10.1101/2021.03.13.435259>

Cite this recommendation as:

Samuel Alizon (2021) Modelling parasitoid virulence evolution with seasonality. *Peer Community in Evolutionary Biology*, 100129. [10.24072/pci.evolbiol.100129](https://doi.org/10.24072/pci.evolbiol.100129)

Revision round #3

2021-06-22

Author's Reply

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Decision round #3

The reviewers all think that the manuscript has improved but they raise several concerns, with which I agree.

First, there seem to be at least typos in some equations. As stressed by one of the reviewers, since these are delay-differential equations, notations are paramount so please double (triple) check the mathematical notations.

Second, I agree with another reviewer that the manuscript would probably benefit from a tuning down of the novelty claims (e.g. no model has shown that, or there is no trade-off) to instead better describe the originality of the model, i.e. adding seasonality for an obligate-killer parasite.

These are only minor revisions but I believe they are necessary, especially for the accuracy of the notations and formulations.

Preprint DOI: [10.1101/2021.03.13.435259](https://doi.org/10.1101/2021.03.13.435259)

Reviewed by anonymous reviewer, 2021-06-15 15:50

The authors made minor changes to the manuscript, primarily by adding a helpful discussion comparing their study to past obligate killer models.

Unfortunately, however, my main concern from the previous round remains unaddressed. As I previously stated, I disagree with the assertion made by the authors that they investigate virulence evolution “in the absence of any explicit mechanistic trade-off,” (L37). In my view, this claim is grossly overstated. The fact that the parasite needs to kill the host to complete transmission is a form of trade-off – not unlike the classic virulence-transmission trade-off. I recommended the authors refrain from generalising the manuscript as a model “in the absence of traditional mechanistic trade-offs” (in abstract). I notice that neither “obligator killer” or “parasitoid” appears in the title or abstract. I believe that the readers will benefit from more explicit reframing as a system specific model.

Reviewed by Alex Best, 2021-06-10 10:33

I enjoyed reading this manuscript last time, and it still seems very interesting and well conducted to me. The authors have engaged with my comments constructively. I just have one remaining comment, which is that the function g is still stated to be a probability density function in the text, which I still think can't be the correct definition (as you state in your response and the 2nd half of that sentence, I think it is just a rate). Otherwise I think you've done a great job.

Reviewed by anonymous reviewer, 2021-06-17 16:05

The authors addressed all my comments but those concerning the mathematical rigor one would expect from such a theoretical paper.

Specifically, concerning item #4.9 of the “Response to reviewers”, the authors only fixed some “typos” while I was requesting much more rigor and detail in the appendices. For instance, in the current version of the preprint, $v_2(t)$ is expressed for $\tau < t < t_I$ (implying $\tau < t_I$), while

τ can clearly be greater than t_I (see e.g. Fig. 1). I realize that my previous review suggested the authors to make this correction although what I meant is that v_2 should be defined from $t=\tau$ (as opposed to $t=0$). There is still an issue with the handling of the delay. In addition, some key steps are missing to convince the reader that the expression of $v_2(t)$ is correct. The notations are confusing (e.g. d , both a parameter and a mathematical notation, and s , both a state variable and a dummy variable). After having struggled with the equations, I reached the conclusion that the authors simply attempted to copy the equations from their Mathematica notebook (more or less carefully, assuming it does the right thing anyway). However, since these are delay differential equations coupled with several discontinuities in time (at times $t=T$ and $t=t_I$), I would have expected the authors to be much more careful in writing their mathematical derivations. If this is properly done in the Mathematica notebook, and if the case $\tau < t_I$ is just shown as an example in appendix, then this should be explicitly stated. Moreover, an additional Mathematica notebook in pdf version focusing on these derivations should be provided as supplementary material. (I am not a Mathematica user so I had to use Wolfram player to open the current notebook, in which I noticed that the case $\tau < T - t_I$ is treated separately, but not the case $\tau < t_I$ as far as I could see.)

Then, the criterion for the parasite-free equilibrium to be unstable should be $f(0) > 1$, with $v_2(T) = f(v_1(0))$. Instead the authors heuristically assume $v_1(0) = 1$ and consider $v_2(T) > 1$ as a stability criterion. However, it is unclear whether this heuristic assumption is mathematically valid. I would have expected a more rigorous derivation in appendix.

The same concerns apply to the derivation of the mutant invasion criterion. Since invasion fitness is expressed relatively implicitly (with integral terms) and numerically computed with Mathematica, wouldn't it be possible to numerically evaluate $f_m'(0)$ with Mathematica instead of making use of a heuristic argument?

To sum up, and as already indicated in my previous review, the appendices mostly repeat the text. Their usefulness is therefore limited. I would have expected more detailed and rigorous mathematics in the appendices, or alternatively supplementary Mathematica notebook in pdf version dedicated to explaining the mathematical derivations. To be recommendable, a preprint must be technically sound. I am not yet convinced this is the case.

Other remarks:

- In the para preceding eq. 1: τ is introduced without having been defined.
- In the eq. preceding line 74: there is a +- typo in the exponential term.
- Lines 89-90: that sentence does not make sense to me.
- Line 136: replace high with low.
- Line 220: regarding the consequences for population dynamics, you might consider citing Hilker, F. M., Sun, T. A., Allen, L. J. S., & Hamelin, F. M. (2020). Separate seasons of infection and reproduction can lead to multi-year population cycles. *Journal of theoretical biology*, 489, 110158.
- Line 247: you might add "monocyclic plant parasites" and consider citing (again)

Hamelin, F. M., Castel, M., Poggi, S., Andrivon, D., & Mailleret, L. (2011). Seasonality and the evolutionary divergence of plant parasites. *Ecology*, 92(12), 2159-2166.

Revision round #2

2021-05-25

Author's Reply

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Decision round #2

Dear authors,

I have read with interest the detailed revisions of your manuscript and I think it is worth sending back to the reviewers. However, I noticed that the discussion of earlier results on modelling the evolution of virulence in host-parasitoid interactions (or "obligate killers") is still lacking. I believe this is an important issue since in simple parasitoid model will always select for higher virulences.

For instance, consider the following system of ODEs:

$$dS/dt = -\beta SV$$

$$dI/dt = \beta SV - (\mu + \alpha + \gamma)I$$

$$dV/dt = \sigma \alpha I - \delta V$$

where S are susceptible hosts, I are infected hosts, and V are free parasites (or viruses). β is the transmission rate, α is the virulence (disease-induced host mortality), μ is the natural mortality, γ is the recovery rate, δ is the clearance rate of free parasitoids, and σ is the number of parasitoids produced upon host death.

Following the next generation theory (Diekmann et al 1990), the invasion fitness of a mutant parasitoid in the system is given by

$$R(\alpha_m, \alpha) = \beta \sigma S(\alpha) \delta \alpha_m \mu + \gamma + \alpha_m$$

If we try to find the virulence that maximises this infection fitness, we get

$$\partial R(\alpha_m, \alpha) / \partial \alpha_m = \beta \sigma S(\alpha) \delta \mu + \gamma + (\mu + \gamma + \alpha_m)^2$$

This partial derivative is always greater or equal than 0, meaning that in this simple model only parasitoids with greater virulence can invade.

In terms of references to mention but also, more importantly, to discuss and acknowledge, I can suggest the seminal article by Ebert & Weisser (1997, *Proc B*), the model by Sasaki & Godfray (1999) which includes coevolution, the study by Caraco & Wang (2006, *JTB*) more focused on phages, and potentially Sofonea et al (2018) for an ebola model.

These are mainly suggestions and it is very possible I missed some relevant model so feel free to further investigate the literature.

Best regards,
- Samuel Alizon

Preprint DOI: [10.1101/2021.03.13.435259](https://doi.org/10.1101/2021.03.13.435259)

Revision round #1

2021-04-06

Author's Reply

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Decision round #1

The authors investigate the evolution of parasite life-history trait in the context of a specific kind of host-parasite interactions. The originality of the study is that they include seasonal host activities to determine optimal parasite strategies.

The recommendations from the reviewers are balanced but I think they agree on several points.

First, it is important to clarify the terminology. Indeed, the parasite is here assumed to only be transmitted after killing the host. Such a life cycle is often referred to as that of an "obligate killer" and is known to greatly affect the constraints on virulence. This should be stressed very clearly (ideally in the title) and I think it also calls for strong rewriting of the Introduction. Furthermore, I found the model notations difficult to follow, probably because many are missing in Table 1 (adding units in the table would also be a plus). Finally, as pointed out by one of the reviewers, the definition of fitness is central and perhaps deserves a more careful justification.

Second, the biological relevance could be improved. One of the reviewers suggested mentioning specific host-parasite systems or which this model could apply (especially with regards to some of the strong assumptions it makes). Discussing the parasitoid literature also seems important given the key assumption of the model (parasites do not transmit unless they kill their host).

Third, related to the previous point, many important references from the literature seem to be missing. The reviewers mentioned relevant articles on parasitoids and on seasonality. I would also add the study by King et al (2009, Am Nat, DOI: [10.1086/597217](https://doi.org/10.1086/597217)) about persistence constraint.

Preprint DOI: [10.1101/2021.03.13.435259](https://doi.org/10.1101/2021.03.13.435259)

Reviewed by anonymous reviewer, 2021-03-30 15:20

The study investigates the impact of host phenology on the evolution of virulence using the evolutionary invasion analysis. The study finds that the duration of the host activity period and synchronicity of the host emergence timing influences virulence. The authors present a mathematical model that is biologically interesting while being mathematically tractable. The

manuscript is concise and very well written. Below I outline my comments regarding the interpretation of modelling assumptions and provide minor suggestions.

I appreciate that the introduction provides a thorough general context to the virulence evolution. Having said that, the modelled system is a fairly specific one: a plant virus that is environmentally transmitted. The readers may benefit from a further background of the modelled system as the majority of the literature on evolutionary epidemiology employs rather generic direct transmission models. For example, it might be useful for the readers to know that environmental transmission lowers the cost of host exploitation in comparison to direct transmission.

More importantly, the parasite considered in this manuscript is, in an ecological sense, a parasitoid. I believe that the fact that the parasite needs to kill the host to complete transmission is a form of trade-off – not unlike the classic virulence-transmission trade-off – that selects against avirulence. As such, I tend not to agree with the assertion made by the authors that they investigate virulence evolution “in the absence of any explicit mechanistic trade-off,” (L38). If this claim is crucial to the main thesis of this manuscript, I recommend the authors provide further clarifications as to how the “kill-to-transmit” does not qualify as an evolutionary trade-off. Specifically, the readers may benefit from discussions on whether the key findings are applicable outside “parasitoid” systems.

In the paragraph starting at L111, the readers may benefit from explanations with more specific references to different parts of the figures (e.g. Figure 3A,ii).

I appreciate the authors’ intent for transparency, but I noticed that the Github link is not working as of March 30th 2021.

Reviewed by anonymous reviewer, 2021-04-05 19:40

This preprint addresses the evolution of the latent period of monocyclic parasites in a seasonal environment. Hosts have non-overlapping generations and are alive for one season. The latent period is defined as the time between host infection and the release of free-living forms that may survive and infect hosts of the next season/generation. Monocyclic parasites can perform only one round of infection per season. That is, there are no secondary infections (host-to-host contaminations) within a season/generation. The authors show that if hosts emerge synchronously at the beginning of the season, then the optimal latent period is roughly equal to the length of the season. This is because survival as a free-living form is less likely than within-host survival. However, if the host emergence time is spread over a time interval, the optimal latent period is shorter. It is roughly equal to the mean time between host emergence and the end of the season.

I have several concerns with this preprint:

1. The authors interpret their results in terms of virulence rather than latent period. I realize that for obligate killers the latent period is the same as the time to host death (the inverse of virulence), but obligate killers are a very specific case. The authors should not draw general conclusions from such a very specific case. Moreover, the authors do not provide a single

example of an obligate killer parasite which would be monocyclic, and that would infect a host with non-overlapping generations. Furthermore, the authors argue that there is no trade-off (unlike previous studies on the evolution of virulence) while there is by essence a trade-off in obligate-killers, since they cannot transmit without killing their host. The sooner they kill their host, the sooner they can infect new hosts in principle. Unfortunately, obligate killers are one of the few examples clearly supporting a trade-off between transmission and virulence. The authors may argue that this trade-off does not hold for monocyclic obligate-killer parasites, which leads me to my second point.

2. The authors assume that there are no secondary infections without any justification (not even a single example clearly checking all model assumptions). The naïve reader may believe that the focus on monocyclic parasites was made for simplicity only. However, this assumption is all but unimportant. If parasites can perform secondary infections, then parasites that infect early hosts can also infect later hosts and preempt infections from a parasite that would be more prudent and would keep alive its host longer. This would select for increased virulence despite the fact that this strategy does not maximize survival at the end of the season (sort of tragedy of the commons).

3. The authors do not cite previous studies on the topic (van den Berg et al 2011; Hamelin et al 2011), which take into account secondary infections, and different trade-offs between transmission and virulence, and transmission and survival. Some of the results are reminiscent of these studies.

4. The mathematics are unclear:

4.1. The initial conditions are never specified. Around equation (1), it should be specified $s(0)=0$, $v_1(0^+)=v_2(0^-)$ (or any other notation dealing with the discontinuity), $v_2(\tau)=0$.

4.2. In equation (2), γ has never been defined.

4.3. In equation (3), if $\alpha=0$, one should recover the equation expressing $v_2(T)$ on page 3, right? That does not seem to be the case.

4.4. In equation (3), s_1 and v^* have never been defined.

4.5. It is unclear whether evolution maximizes (3) (see Lion and Metz 2018 for a review). For an optimization principle to hold, one must show that the invasion criterion of the mutant depends in a one-dimensional way of the resident, which is all but obvious from equation (3) (in which there are several implicit functions). However, I guess this is true when τ is the only trait that differs between the resident and the mutant.

4.6. Where is the difference between equation (3) and equation (5)? When β_m differs from β , there is likely no optimization principle although an ESS indeed satisfies (4) (if correct). I assume that the authors performed correct computations, but they should be much more careful and explicit in describing what they did (at least in appendix).

4.7. In appendix A, the first row of equation v_2 should be defined for $\tau < t < t_l$ (not $0 < t < t_l$). This would have been clearer if you had specified initial conditions, i.e. $v_2(\tau)=0$.

4.8. In appendix A, there is a mistake in the second row of equation v_2 , which is defined for $t=t_l$ and depends on the future ($v_2(t_l+\tau)$). I think there is a mess with the handling of the delay

(tau), which is the trait under consideration. Consequently, I cannot be confident in the central equation (3).

4.9. Appendix B does not bring much compared to the text (and contains the same typos or mistakes). One would expect much more rigor and details in the appendices.

While I do not think the above possible mistakes would qualitatively change the results (which are expected), I am not 100% confident that the mathematics are correct.

Other remarks:

- Page 7, line 107: By contrast?
- Page 10, lines 160-161: I do not agree with "this phenomenon could occur more broadly than the specific system investigated here"
- Page 10, lines 167-168: "avirulence is maladaptive as..." is simply an assumption of the model (obligate-killer parasite)
- Fig. 3, panel B: one of the ii's should be replaced with iii
- Page 12, line 191: the reference to *T. parva* comes out of nowhere

Overall, although I have been quite critical in my review, it might be that the authors could revise their manuscript to make it recommendable. I would recommend tuning down the results and even changing the focus of the manuscript. If the host-parasite species the authors have in mind are e.g. baculoviruses of forest Lepidoptera, they should clearly describe how their mathematical model fits these species, and introduce the research question with respect to these species only. The results would be much less general, but much more convincing, especially if they challenge previous ideas concerning these species (which remains to be shown, as the results are quite intuitive thus far).

References:

- van den Berg, F., Bacaer, N., Metz, J. A., Lannou, C., & van den Bosch, F. (2011). Periodic host absence can select for higher or lower parasite transmission rates. *Evolutionary Ecology*, 25(1), 121-137.
- Hamelin, F. M., Castel, M., Poggi, S., Andrivon, D., & Mailleret, L. (2011). Seasonality and the evolutionary divergence of plant parasites. *Ecology*, 92(12), 2159-2166.
- Lion, S., & Metz, J. A. (2018). Beyond R_0 maximisation: on pathogen evolution and environmental dimensions. *Trends in ecology & evolution*, 33(6), 458-473.

Reviewed by Alex Best, 2021-03-25 16:19

The manuscript examines a model of host-parasite interactions where hosts have non-overlapping generations and a fixed 'emergence period' each generation. Parasites must infect hosts and have produced progeny before the end of the season for those progeny to be carried forward to the next generation. The focus of the study is on how the parasite might evolve the duration of infection to maximise its fitness. The key result is that even without any trade-off, an intermediate infective duration - linked to virulence - is selected for.

The manuscript is really nicely written and the results presented pretty clearly. The code is made available, which is great (I don't know how many people use Mathematica, but still, it's there). The existing literature is mostly well covered, but there are a few papers I think should be added. I've enjoyed reading the preprint and it got me thinking, which is perhaps the biggest compliment I can give.

Below are some mostly minor comments.

P2 L16 - The main empirical example in the cited paper, that of myxomatosis, actually considers a recovery-virulence trade-off. I wonder if it is worth tweaking this sentence to stress that.

P3 below L54 - This is the first time you have referred to 'the resistant life stage'. Please could you expand on what you mean.

P3 above L55 - I'm trying to decompose the parasite progeny production term. Am I right that it is the product of:

- * the density of newly infected hosts at (t-tau) [the $\alpha(s(t\text{-tau}) * v_1(t\text{-tau}))$ term],
- * the density (number?) of parasites produced upon *parasite-induced* death [beta],
- * the number of hosts that survive infection between t-tau and t [the $\exp(-d * \text{tau})$]?

If this is correct, I have a couple of questions:

(a) Why do infected hosts who died from background mortality not release parasites into the environment?

(b) Does this imply that there is a sort of 'programmed death' type situation, where once beta parasite progeny are ready, the parasite kills its host? This value (beta) is fixed for most of your study, so in effect it is parasite growth rate that evolves - how slow or fast does the parasite reach this magic number of beta. In that sense I see the link with more classic definitions of virulence as simply mortality rate, where faster growth leads to higher mortality. But it is still a bit different.

P3 L61 - Does it make sense for $g(t, t_1)$ to be a PDF in terms of units? Assuming \hat{s} is a density doesn't $g(t, t_1)$ need to be a per-capita rate for the units to balance?

P5 L77 - Gamma has appeared in the equations which wasn't there before. Please add a definition.

P5 L87 - Since fitness is a function of both resident and mutant traits, it is usual to denote the fitness derivatives as partial derivatives.

P7 L95 - 'The duration of host activity can select against....' is a bit vague. I guess you mean 'Longer durations of host activity can select against...'?

P7 L110 - This linear relationship is interesting. Does it imply that the parasite's best strategy is just to ensure (mean) death at a fixed time before the season ends?

P7 L111 - Is t_1 really the 'time at which each host first becomes active'? In what sense does it become active then? Is it not simply the length of the emergence season? Similarly, in figure 3 the x-axis label of 'host emergence concentration' isn't right I think - it is the *inverse* of this isn't it? Again, in my head it makes more sense to think of it as the duration of emergence.

P12 L202 - In terms of discussion points, I find myself mulling over how much of your results rest on the model assumptions. I think the non-overlapping generations in particular has quite

a big impact, as well as the nature of quite what virulence is in your model (effectively growth rate). As you describe, your key result stems from the combination of factors that parasites have to ensure they have produced progeny before the end of the season, and that they can only release those progeny all in one go. It seems likely that under different set-ups - fully continuous-time with overlapping generations, for example - this results might disappear? I wonder if you might comment on other models of parasite evolution in seasonal environments where generations are overlapping. I'm particularly thinking of Koelle et al. (2005), Sorrel et al. (2009) and Donnelly et al. (2013) [all in Proc Roy Soc B]. My reading of these is that you wouldn't get intermediate virulence without a further trade-off, though I'm not sure any specifically say it.