

# Pathogen Interactions, Population Cycles, and Phase Shifts

Joanne Lello,<sup>1,\*</sup> Rachel A. Norman,<sup>2,†</sup> Brian Boag,<sup>3,‡</sup> Peter J. Hudson,<sup>4,§</sup> and Andrew Fenton<sup>5,||</sup>

1. School of Biosciences, Cardiff University, Cardiff CF10 3TL, Wales, United Kingdom;

2. Department of Computer Science and Mathematics, University of Stirling, Stirling FK9 4LA, Scotland, United Kingdom;

3. Birch Brae, Knapp, Perth and Kinross PH14 9SW, Scotland, United Kingdom;

4. Department of Biology, Pennsylvania State University, University Park, Pennsylvania 16802;

5. School of Biological Sciences, Biosciences Building, Crown Street, University of Liverpool, Liverpool L69 7ZB, United Kingdom

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**ABSTRACT:** Interspecific pathogen interactions can profoundly affect pathogen population dynamics and the efficacy of control strategies. However, many pathogens exhibit cyclic abundance patterns (e.g., seasonality), and temporal asynchrony between interacting pathogens could reduce the impact of those interactions. Here we use an extension of our previously published model to investigate the effects of cycles on pathogen interaction. We demonstrate that host immune memory can maintain the impact of an interaction, even when the effector pathogen abundance is low or the pathogen is absent. Paradoxically, immune memory can result in pathogens interacting more strongly when temporally out of phase. We find that interactions between species can result in changes to the temporal pattern of the affected species. We further demonstrate that this may be observed in a natural host-pathogen system. Given the continuing debate regarding the relevance of pathogen interactions in natural systems and increasing concern about treatment strategies for coinfections, both the discovery of a shift in cycle in empirical data and the mechanism by which we identified it are important. Finally, because the model structure used here is analogous to models of a simple predator-prey system, we also consider the consequences of these findings in the context of that system.

Interspecific interactions of all forms (e.g., predator-prey relationships [Murrell 2005], host-pathogen relationships [Hudson et al. 1998], resource competition [Carney 1987]) have the capacity to alter the population dynamics of the interacting species. Further, there is growing interest in the dynamical consequences that coinfecting pathogen species have on each other (Lello et al. 2004). Such interspecific pathogen interactions can crucially alter pathogen dynamics, host health, and the success of control strategies (Pedersen and Fenton 2007). Nevertheless, while most forms of interspecific interaction are well documented, unequivocal evidence of the existence of interspecific pathogen interactions under field conditions is rare. This has led to suggestions that interspecific interactions are of little importance in shaping pathogen communities under natural conditions (Dash 1981; Bush and Holmes 1986; Lotz and Font 1991; Haukisalmi and Henttonen 1993; Holmes and Bartoli 1993; Forbes et al. 1994, 1999; Nilssen et al. 1998; Behnke et al. 2001; Poulin 2001; Dezfuli et al. 2002). This debate continues despite the fact that the importance of pathogen interactions is becoming increasingly obvious in clinical settings (Wanji et al. 2003; Verhoeven et al. 2004; Kyriacou et al. 2006; Lyke et al. 2006; Thio et al. 2007). One possible explanation for the apparent lack of interactions between pathogen species in wild host systems is that the pathogens may be temporally asynchronous within their hosts, resulting in a form of niche segregation and reducing the likelihood of direct interaction (Christensen et al. 1987; Haukisalmi and Henttonen 1993).

In earlier work, we were able to detect evidence of a network of interspecific parasite interactions among the gut helminth community of the wild rabbit (*Oryctolagus cuniculus*; Lello et al. 2004). However, in all the statistical analyses of these helminths, month emerged as a strongly significant term (Lello et al. 2004). Therefore, the interplay between seasonal dynamics and the interspecific pathogen interactions may be important. If two pathogen species are temporally separated because of differing cyclic (e.g., seasonal) abundance, it is feasible that any potential in-

\* Corresponding author; e-mail: [lelloj@cardiff.ac.uk](mailto:lelloj@cardiff.ac.uk).

† E-mail: [ran@cs.stir.ac.uk](mailto:ran@cs.stir.ac.uk).

‡ E-mail: [bboag@scri.ac.uk](mailto:bboag@scri.ac.uk).

§ E-mail: [pjh18@psu.edu](mailto:pjh18@psu.edu).

|| E-mail: [a.fenton@liv.ac.uk](mailto:a.fenton@liv.ac.uk).

teraction between them might be nullified. However, we hypothesize that if an interspecific pathogen interaction is mediated by the host's immune system, via some level of cross-immunity between the pathogens, interaction may still occur because of the "ghost of infection past" acting through immune memory. Under such conditions, the longevity of the immune memory mediating the interaction will be critical in determining the overall net strength of the interaction and its impact on the dynamics of the component species.

Using a theoretical framework (see "Methods"), we examine the relationship between immune-mediated interspecific interactions and seasonal patterns of pathogen abundance. Specifically, we address four key questions: (1) Does seasonality alter host immune-mediated interactions between pathogens? (2) How does temporal asynchrony between pathogens affect the impact of their interaction? (3) How does immune memory alter the interaction between species? (4) Can immune-mediated interactions alter the cyclic dynamics of a pathogen? We then analyze a natural pathogen system and ask whether such shifts in dynamics may be observed in the seasonal abundance patterns of a pathogen species for which interaction has already been suggested by other evidence.

It is worth noting that, because of the simplicity of its construction, the model framework used here is extremely flexible. In addition to pathogen interactions, the model may simulate many systems where interaction is indirect. For example, the model could also represent apparent competition in certain predator-prey systems with specialist and generalist predators.

## Methods

The basic model is an adaptation of that published in Lello et al. (2004), with the exception that, for simplicity, the pathogen uptake term is altered to be a constant uptake rate,

$$\frac{dP_i}{dt} = \Lambda_i e^{-c_i t} - d_i P_i, \quad (1)$$

where  $P_i$  is abundance of pathogen species  $i$ ,  $t$  is time,  $\Lambda_i$  is the constant uptake rate of pathogen species  $i$ ,  $c_i$  is a constant that moderates the immune response against the pathogen,  $I_i$  is the immune response created against pathogen  $i$ , and  $d_i$  is the death rate of pathogen  $i$ . Broadly speaking, the immune response against pathogen infection can act in two ways, either to reduce the establishment of incoming pathogen stages or to kill pathogens already established within the host. In this model, we mimic the former case, where immune action acts on pathogen establishment (incorporated in the uptake term). However,

in many pathogen systems, the immune response acts to both prevent pathogen establishment and increase pathogen mortality. While, for simplicity, we did not incorporate immune action on death rate in this article, we repeated our analyses with the immune response activity split between a reduction in uptake and an increase in death rate. In these analyses (not presented), the results were qualitatively the same as those where immune activity is modeled as acting on uptake rate alone.

We assume that seasonal variation in pathogen abundance is driven by seasonal variations in parasite transmission between hosts (which may incorporate seasonality in, for instance, contact rates between hosts or mortality rates of free-living infective stages on pasture). We therefore modified the parasite uptake term by a sine function,

$$\frac{dP_i}{dt} = \Lambda_i \left[ 1 + \lambda_i \sin \frac{2\pi(t + g_i)}{\tau} \right] e^{-c_i t} - d_i P_i, \quad (2)$$

where  $\lambda_i$  determines the amplitude of the seasonal wave and lies between 0 and 1,  $t$  is time,  $g_i$  is a phase shift and determines when the seasonal abundance peak for species  $i$  occurs, and  $\tau$  is the period.

An immune response is created against each pathogen and may be moderated (increased or decreased) by a second species,

$$\frac{dI_i}{dt} = \alpha_i P_i + \gamma_{ji} P_j - \delta_i I_i, \quad (3)$$

where  $I_i$  is the immunity produced against pathogen  $i$ ,  $\alpha_i$  is the rate of production of immunity stimulated by pathogen  $i$ ,  $\gamma_{ji}$  is the rate of production of immunity by pathogen  $j$  against pathogen  $i$ ,  $P_j$  is the abundance of pathogen species  $j$ , and  $\delta_i$  is the rate of immunity decay. Interactions between pathogens are therefore incorporated by increasing or decreasing the production of immunity against one species due to the presence of a second species (i.e., varying the  $\gamma_{ji}$  values). Unless otherwise stated in the text,  $\Lambda_i = 1,000$ ,  $c_i = 0.05$ ,  $\lambda_i = 1$ ,  $d_i = 1.5$ ,  $g_i = 0$ ,  $\tau = 12$ ,  $\alpha_i = 1$ ,  $\gamma_{12} = 0.5$ , and  $\delta_i = 4.6$  for all model runs. In all sections below, results are reported from the models after they have settled to stable dynamics.

## Results

### *Does Seasonality Alter Host Immune-Mediated Interactions between Pathogens?*

Using the model described above, we examined whether seasonality per se could alter host immune-mediated interaction between pathogens. A simple two-pathogen sim-

ulation was undertaken where pathogen 1 ( $P_1$ ) was allowed to have either a positive or a negative effect on pathogen 2 ( $P_2$ ) by varying the strength of the interaction, ( $\gamma_{12}$ ) between  $-2$  and  $2$ , while pathogen 2 had no effect on pathogen 1 ( $\gamma_{21} = 0$ ). The immune decay rate ( $\delta$ ) was set to  $4.6$ , which reduced the value of the immune response at time step  $t$  to  $1\%$  by time step  $t + 1$  (1 month later), assuming that no further increase in immunity had occurred. The simulations were conducted both with and without seasonality, and the mean pathogen values of  $P_2$  after the initial transient period were compared.

The addition of seasonality changed the mean pathogen abundances, even in the absence of interspecific pathogen interactions ( $\gamma_{12} = 0$ ). However, the percentage change in the average  $P_2$  numbers at different levels of  $\gamma_{12}$ , compared to the average at  $\gamma_{12} = 0$  for the same model, were similar for the seasonal and nonseasonal models (the largest difference in the percentage change in  $P_2$  between the two models was  $2.0\%$ ). Therefore, assuming that the sine function is a reasonable representation of natural seasonality, we may conclude that seasonality per se has a negligible effect on the impact of interspecific pathogen interactions when the seasonal abundance changes are synchronous.

#### *How Does Temporal Asynchrony between Pathogens Affect the Impact of Their Interaction?*

While seasonality per se may be of little consequence to interspecific pathogen interactions, differences in the timing of seasonal abundance between pathogen species may play a greater role. For instance, when the two pathogens are completely out of phase with each other, we might expect there to be a much-reduced interaction between them. We therefore assessed the influence of such temporal differences in seasonal abundance on the interaction by varying the timing of the peak in uptake of  $P_2$  ( $g_2$  in eq. [3]) from  $0$  (complete synchrony in uptake between the parasites) up to an 11-month lag between the species' peaks.

As might be expected, when the immune response was very short-lived (e.g.,  $\delta = 4.6$ ), such that immunity decays by  $99\%$  in one time step, the least effect of  $P_2$  on  $P_1$  occurred at approximately the point when the two pathogens were most out of phase (around 5.5 months; fig. 1a), and the strongest interaction (the greatest suppression of  $P_2$ ) occurred when the two species were perfectly in phase ( $g_2 = 0$ ; fig. 1a). Under these conditions, the immune-mediated impact of  $P_1$  on  $P_2$  is instantaneous and transient, so the strength of the interaction at any point in time is completely determined by current parasite levels.

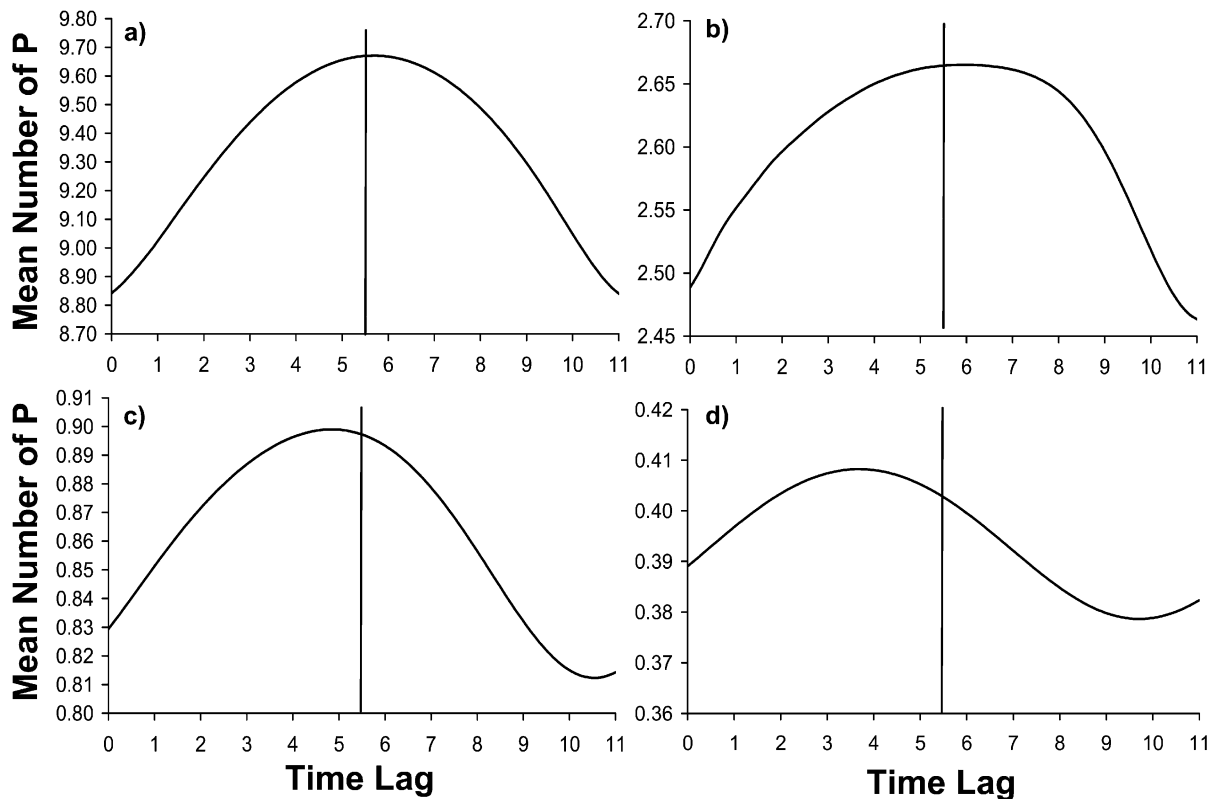
#### *How Does Immune Memory Alter the Interaction between Species?*

Although, for very short-lived immune responses (i.e., at high immune decay rates), the relationship between the two interacting pathogens appears simple (i.e., seasonal asynchrony reduces the effect of the interaction), in reality, immune responses are typically much longer-lived because of the creation of immune memory. Reducing the immune decay rate (i.e.,  $\delta = 0.76, 0.18,$  and  $0.07$ , reducing immunity by  $99\%$  after 6, 24, and 60 months, respectively) substantially increased the overall effect of  $P_1$  on  $P_2$  (note the different Y-axis scales in fig. 1), because lower immune decay rates result in immune response levels at any point in time being made up of current immunity plus the integral of prior immunity over time. However, an additional and unexpected consequence of this reduction in immune decay was that the point of least effect for  $P_1$  on  $P_2$  (i.e., the lag at which the peak of the mean  $P_2$  value occurs) was not at 5.5 months (as for  $\delta = 4.6$ ) when the two pathogens were most out of phase (fig. 1b–1d). When immunity was long-lived, both the shape of the effect curve and the points of least and greatest interaction between the two pathogens changed. The least effect of  $P_1$  on  $P_2$  occurred at approximately 6 months for  $\delta = 0.76$ , at 4.75 months for  $\delta = 0.18$ , and at 4 months for  $\delta = 0.07$ , with the point of greatest interaction occurring 6 months later (fig. 1b–1d). Therefore, when immunity is long-lived, pathogens may interact most strongly when they are seasonally out of phase with each other.

In order to understand this apparently counterintuitive relationship (i.e., that  $P_1$  can have a greater effect on  $P_2$  when the two parasites are out of phase than when they are in phase), we must examine the relationship between the effector species ( $P_1$ ) and its immunity ( $I_1$ ). At high immune decay rates ( $\delta = 4.6$ ),  $P_1$  cycles almost synchronously with  $I_1$  (fig. 2a). However, when immune decay rates are low ( $\delta = 0.07$ ), there is a phase shift, and  $I_1$  cycles asynchronously with  $P_1$  (fig. 2b). At low immune decay rates, there is always a relatively high value for  $I_1$ , and this keeps both  $P_1$  and  $P_2$  at low values. Since the "growth rate" of  $I_1$  is dependent on the value of  $P_1$ , low  $P_1$  values result in a slow  $I_1$  growth rate, thereby pushing the immunity out of phase with the pathogen.

#### *Can Immune-Mediated Interactions Alter the Cyclic Dynamics of a Pathogen?*

The model reveals that the interplay between seasonality and immune memory can alter the timing of the peak effect of an immune-mediated interspecific pathogen interaction. Further, slow immune decay rates have the effect of shifting the immune response such that it is out of



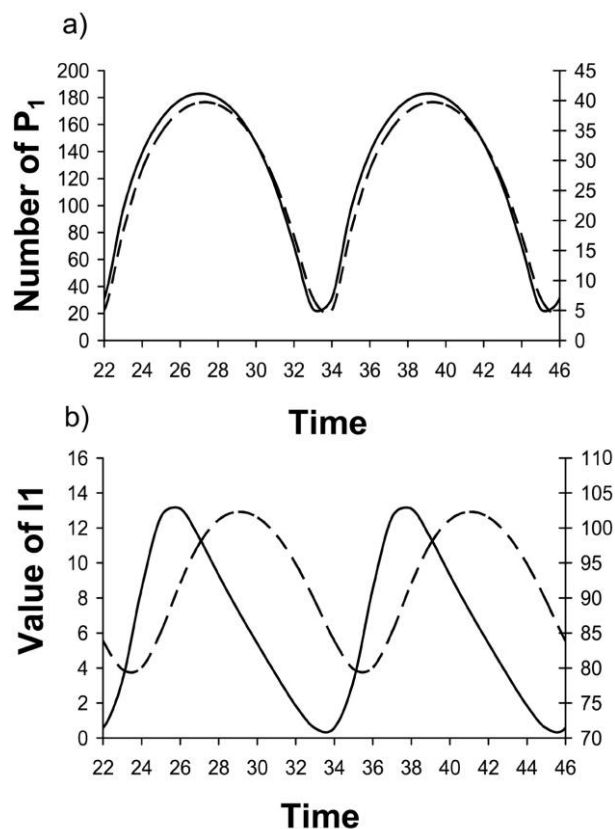
**Figure 1:** Effect of changing the rate of immune decay ( $\delta$ ) and the time lag between pathogen seasonal peaks on the interaction between pathogen species 1 and 2 ( $P_1$  and  $P_2$ ). As immune longevity increases,  $\delta = 4.6$  (a), 0.76 (b), 0.18 (c), and 0.07 (d), and the point of least interaction (i.e., when  $P_2$  is at its highest average value) shifts away from the midpoint of the time lags. In addition, the shape of the curve also changes.

phase with the pathogen against which it is produced. Therefore, another question arises as to whether these effects can change the seasonal dynamics of the affected species. To test this, we again varied the seasonal lag in uptake between the two pathogen species, but this time we allowed the seasonal dynamics of the effector species  $P_1$  to vary (i.e., by changing  $g_1$  while keeping  $g_2$  fixed) and observed the impact on the temporal dynamics of  $P_2$ . Both the timing of the seasonal peak of  $P_2$  and the shape of the seasonal abundance curve can be markedly altered by changing the seasonal peak of  $P_1$  (fig. 3). Therefore, peak shifts resulting from pathogen interactions could potentially force pathogens that would normally cycle in phase to be pushed apart, effectively producing completely different seasonal patterns for each pathogen.

#### *Can Changes in Seasonal Abundance due to Interspecific Interaction Be Observed in a Natural Pathogen System?*

The model clearly predicts that a sufficiently strong immune-mediated interspecific pathogen interaction should

be detectable as a shift in the seasonal abundance pattern of an affected species. In earlier work, we presented evidence of interaction between the gut helminths of the adult wild rabbit (*Oryctolagus cuniculus*; Lello et al. 2004). In particular, we demonstrated that *Graphidium strigosum* showed a substantial reduction in intensity ( $-29\%$ ) when *Trichostrongylus retortaeformis* was present. Further, we hypothesized that the relationship between *T. retortaeformis* and *G. strigosum* must be indirect, as the latter is upstream (in the gut) from the former and thus direct interaction is not feasible. The most likely mechanism for this interaction was therefore mediation through host immunity. These two species also show clear seasonal abundance patterns, which may be approximated by a fitted sine wave function. In order to assess whether we could detect the interaction between these two species as a shift in the seasonal abundance of *G. strigosum*, we divided the adult rabbit data (myxomatosis negative only) into *T. retortaeformis*-infected ( $n = 1,423$ ) and uninfected ( $n = 313$ ) rabbits. Using the nonlinear least squares regression in the S-PLUS statistical package, we fitted a sine wave to the *G.*



**Figure 2:** Abundance, after initial transient period, of pathogen species 1 ( $P_1$ ; solid line) and level of the immunity produced against it (dashed line) through time with (a) relatively rapid ( $\delta = 4.6$ ) and (b) slow ( $\delta = 0.07$ ) immune decay rates.

*strigosum* abundance by month for both data sets. The sine wave had the form

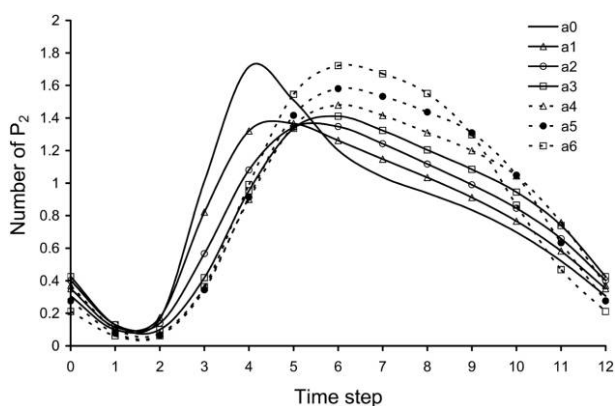
$$y = c + a \times \sin \frac{x + g}{h}, \tag{4}$$

where  $y$  represents the raw data for *G. strigosum* (with or without *T. retortaeformis*) in each month,  $x$  is month (where January = 0 and December = 11), and  $h = 11/(2\pi)$ , which constrains the sine wave to a complete single cycle of exactly 12 months in length. The parameter  $c$  is the constant, or center point, of the sine wave, and parameter  $a$  determines the amplitude of the wave. Parameter  $g$  determines the wave's position along the  $X$ -axis, and as such, it determines the timing of the seasonal peak of *G. strigosum*. The fitted sine waves (fig. 4) reveal that the seasonal peak for *G. strigosum* in the presence of *T. retortaeformis* occurs 2 weeks later than that for *G. strigosum* alone. To determine the statistical significance of this shift, we created, in the Mathematica computing pack-

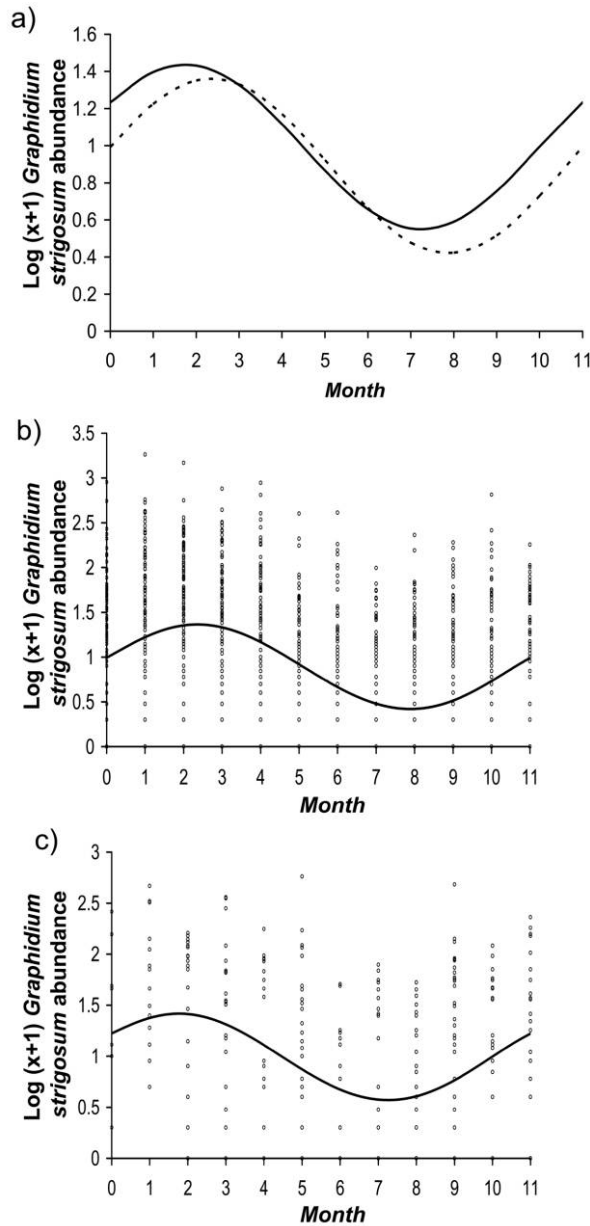
age, a bootstrapping procedure that generated 1,000 values of  $g$  at random from normal distributions based on the estimates of  $g$  obtained from the S-PLUS analyses for *G. strigosum* with and without *T. retortaeformis* coinfection. For each of these bootstrapped values of  $g$ , the timing of the peak in abundance was calculated by differentiating equation 1 with respect to  $x$  (month), setting the equation equal to zero, and solving for  $x$ . An ANOVA then compared the 1,000 peak time values for each data subset, revealing a highly significant difference between the peaks ( $F$  ratio = 2,819.11,  $df = 1, 1,000$ ,  $P < .0001$ ) of the two data subsets, such that the presence of *T. retortaeformis* induces a significant delay in the peak timing of *G. strigosum* abundance. This analysis demonstrates that a shift in pathogen seasonal abundance induced by an interspecific pathogen interaction is detectable in natural data, as the model predicts.

### Discussion

Our work suggests that the interplay between seasonality and immune function can have substantial effects on both the strength and the timing of interaction between species and potentially on the seasonal abundance pattern of the affected species. In practical terms, this suggests that when there is immune memory, pathogens may interact with one another even if they have entirely different seasonal abundance patterns. Further, when immune memory is long-lived, pathogens may interact more strongly when they display different seasonal abundance patterns than when they cycle synchronously. Finally, pathogens interacting via host immunity may shift one another's seasonal



**Figure 3:** Changes in pathogen 2 ( $P_2$ ) abundance dynamics obtained when the seasonality parameter ( $g_1$ ) of pathogen 1 is altered. All values of  $g_1 > 0$  result in a shift in the seasonal pattern of abundance for  $P_2$ , with the greatest effect being a 2-month shift in the peak abundance of  $P_2$ . This indicates that pathogen interactions could act to alter not only the numbers but also the seasonal patterns of an interacting species.



**Figure 4:** a, Fitted sine waves for the monthly abundance of the nematode *Graphidium strigosum* calculated from hosts without (solid line) and co-infected with (dashed line) the nematode *Trichostrongylus retortaeformis*, revealing the 2-week seasonal shift between the two subgroups. Plots b and c show the same fitted lines for rabbits uninfected with *T. retortaeformis* and coinfected rabbits, respectively, along with the raw *G. strigosum* abundance data for each group. For all plots, month 0 is January and month 11 is December.

abundance patterns. This model prediction is upheld by examination of the interaction between *Trichostrongylus retortaeformis* and *Graphidium strigosum* in a natural wild rabbit data set. By examining these data, we found a sig-

nificant shift in the seasonal abundance of *G. strigosum* in the presence of *T. retortaeformis*. This not only confirms the relevance of the model predictions but also provides another method for seeking evidence for interactions in real data. Evidence for the presence and/or effects of interspecific pathogen interactions in natural systems is very rare. The provision of any novel methodology for identifying interaction from wild host data is therefore a very useful step forward.

The simplicity of the chosen model format should make it applicable to a wide range of pathogen systems because few assumptions regarding the type of system are made. The sine function chosen to model seasonality is also applicable to other simple forms of temporal cycle. In addition, it is the immune decay rate that causes the temporal shifts, and this is merely made visible by the cyclic function; therefore, any function that extrinsically forces cycles, as does the sine wave, should allow the phase shifts to occur. The immunity in our model acts in a manner similar to a predator's, and immune decay rate is therefore analogous to a predator death rate. As stated above, the model could therefore be viewed as a two prey–two predator system, with one generalist and one specialist predator (i.e.,  $I_1$  and  $I_2$ , respectively). In this case, the model indicates that apparent competition between two prey species, mediated via a generalist predator, can have effects over and above a simple reduction in prey numbers. Relatively long-lived predators could act similarly to the long-lived immunity, and thus two prey species might be pushed out of temporal synchrony via predation. Alternatively, two prey species may have evolved to cycle out of phase in order to avoid competition for a particular resource. If predation were to push such species into phase, then the apparent competition due to the predator could potentially be exacerbated by increasing direct competition for a particular resource.

The concept of shifting temporal behavior, in either a pathogen or a prey population, caused through apparent competition with a second species could profoundly affect the way interactions between species are examined. We conclude that pathogen interactions will not normally be prevented by cyclic pathogen dynamics. Indeed, it is clear that cyclic dynamics may themselves be altered by interaction and that host immunity and immune memory will play a complex and dynamic role in this process.

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### Literature Cited

- Behnke, J. M., A. Bajer, E. Sinski, and D. Wakelin. 2001. Interactions involving intestinal nematodes of rodents: experimental and field studies. *Parasitology* 122:S39–S49.
- Bush, A. O., and J. C. Holmes. 1986. Intestinal helminths of lesser scaup ducks: an interactive community. *Canadian Journal of Zoology* 64:142–152.
- Carney, H. J. 1987. Field tests of interspecific resource-based competition among phytoplankton. *Proceedings of the National Academy of Sciences of the USA* 84:4148–4150.
- Christensen, N. Ø., P. Nansen, B. O. Fagbemi, and J. Monrad. 1987. Heterologous antagonistic and synergistic interactions between helminths and between helminths and protozoans in concurrent experimental infection of mammalian hosts. *Parasitology Research* 73:387–410.
- Dash, K. M. 1981. Interaction between *Oesophagostomum columbianum* and *Oesophagostomum venulosum* in sheep. *International Journal for Parasitology* 11:201–207.
- Dezfuli, B. S., S. Volponi, I. Beltrami, and R. Poulin. 2002. Intra- and interspecific density-dependent effects on growth in helminth parasites of the cormorant, *Phalacrocorax carbo sinensis*. *Parasitology* 124:537–544.
- Forbes, M., P. J. Weatherhead, and G. F. Bennett. 1994. Blood parasites of blue grouse: variation in prevalence and patterns of interspecific association. *Oecologia (Berlin)* 97:520–525.
- Forbes, M. R., R. T. Alisauskas, J. D. McLaughlin, and K. M. Cuddington. 1999. Explaining co-occurrence among helminth species of lesser snow geese (*Chen caerulescens*) during their winter and spring migration. *Oecologia (Berlin)* 120:613–620.
- Haukisalmi, V., and H. Henttonen. 1993. Coexistence in helminths of the bank vole *Clethrionomys glareolus*. 1. Patterns of co-occurrence. *Journal of Animal Ecology* 62:221–229.
- Holmes, J., and P. Bartoli. 1993. Spatiotemporal structure of the communities of helminths in the digestive tract of *Sciaena umbra* L. 1758 (Teleostei). *Parasitology* 106:519–525.
- Hudson, P. J., A. P. Dobson, and D. Newborn. 1998. Prevention of population cycles by parasite removal. *Science* 282:2256–2258.
- Kyriacou, A., M. A. Kingston, and S. P. Higgins. 2006. The effect of concomitant HIV infection on the clinical manifestations of syphilis. *Sexually Transmitted Infections* 82(suppl. 2):A3.
- Lello, J., B. Boag, A. Fenton, I. R. Stevenson, and P. J. Hudson. 2004. Competition and mutualism among the gut helminths of a mammalian host. *Nature* 428:840–844.
- Lotz, J. M., and W. F. Font. 1991. The role of positive and negative interspecific associations in the organization of communities of intestinal helminths of bats. *Parasitology* 103:127–138.
- Lyke, K. E., A. Dabo, L. Sangare, C. Arama, M. Daou, I. Diarra, C. V. Plowe, O. K. Doumbo, and M. B. Szein. 2006. Effects of concomitant *Schistosoma haematobium* infection on the serum cytokine levels elicited by acute *Plasmodium falciparum* malaria infection in Malian children. *Infection and Immunity* 74:5718–5724.
- Murrell, D. J. 2005. Local spatial structure and predator-prey dynamics: counterintuitive effects of prey enrichment. *American Naturalist* 166:354–367.
- Nilssen, A. C., R. E. Haugerud, and I. Folstad. 1998. No interspecific covariation in intensities of macroparasites of reindeer, *Rangifer tarandus* (L.). *Parasitology* 117:273–281.
- Pedersen, A. B., and A. Fenton. 2007. Emphasising the ecology in parasite community ecology. *Trends in Ecology & Evolution* 22:133–139.
- Poulin, R. 2001. Interactions between species and the structure of helminth communities. *Parasitology* 122:S3–S11.
- Thio, C. L., J. Astemborski, A. Bashirova, T. Mosbrugger, S. Greer, M. D. Witt, J. J. Goedert, et al. 2007. Genetic protection against hepatitis B virus conferred by *CCR5Δ32*: evidence that *CCR5* contributes to viral persistence. *Journal of Virology* 81:441–445.
- Verhoeven, V., M. Baay, J. Weyler, D. Avonts, F. Lardon, P. Van Royen, and J. B. Vermorken. 2004. Concomitant *Chlamydia trachomatis* and human papilloma virus infection cannot be attributed solely to sexual behaviour. *European Journal of Clinical Microbiology and Infectious Diseases* 23:735–737.
- Wanji, S., N. Tendongfor, M. Esum, S. Ndindeng, and P. Enyong. 2003. Epidemiology of concomitant infections due to *Loa loa*, *Mansonella perstans*, and *Onchocerca volvulus* in rain forest villages of Cameroon. *Medical Microbiology and Immunology* 192:15–21.

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