



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Within-Host Dynamics of Multi-Species Infections

Citation for published version:

Eswarappa, SM, Estrela, S & Brown, SP 2012, 'Within-Host Dynamics of Multi-Species Infections: Facilitation, Competition and Virulence', *PLoS ONE*, vol. 7, no. 6, e38730.
<https://doi.org/10.1371/journal.pone.0038730>

Digital Object Identifier (DOI):

[10.1371/journal.pone.0038730](https://doi.org/10.1371/journal.pone.0038730)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

Published In:

PLoS ONE

Publisher Rights Statement:

This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



Within-Host Dynamics of Multi-Species Infections: Facilitation, Competition and Virulence

Sandeepa M. Eswarappa^{1*}, Sylvie Estrela^{2,3}, Sam P. Brown^{2,3,4*}

1 Department of Cell Biology, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, United States of America, **2** Centre for Immunity, Infection and Evolution, University of Edinburgh, Edinburgh, United Kingdom, **3** Institute of Evolutionary Biology, School of Biological Sciences, University of Edinburgh, Edinburgh, United Kingdom, **4** Department of Zoology, University of Oxford, Oxford, United Kingdom

Abstract

Host individuals are often infected with more than one parasite species (parasites defined broadly, to include viruses and bacteria). Yet, research in infection biology is dominated by studies on single-parasite infections. A focus on single-parasite infections is justified if the interactions among parasites are additive, however increasing evidence points to non-additive interactions being the norm. Here we review this evidence and theoretically explore the implications of non-additive interactions between co-infecting parasites. We use classic Lotka-Volterra two-species competition equations to investigate the within-host dynamical consequences of various mixes of competition and facilitation between a pair of co-infecting species. We then consider the implications of these dynamics for the virulence (damage to host) of co-infections and consequent evolution of parasite strategies of exploitation. We find that whereas one-way facilitation poses some increased virulence risk, reciprocal facilitation presents a qualitatively distinct destabilization of within-host dynamics and the greatest risk of severe disease.

Citation: Eswarappa SM, Estrela S, Brown SP (2012) Within-Host Dynamics of Multi-Species Infections: Facilitation, Competition and Virulence. PLoS ONE 7(6): e38730. doi:10.1371/journal.pone.0038730

Editor: Martin Heil, Centro de Investigación y de Estudios Avanzados, Mexico

Received: November 28, 2011; **Accepted:** May 10, 2012; **Published:** June 21, 2012

Copyright: © 2012 Eswarappa et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: The research was supported by Wellcome Trust Grant 082273/Z/07/Z (to S.P.B.), American Heart Association's postdoctoral fellowship (to S.M.E.), and Fundação para a Ciência e Tecnologia, Portugal, SFRH/BD/33856/2009 (to S.E.). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: eswaras@ccf.org (SME); sam.brown@ed.ac.uk (SPB)

Introduction

Parasitism is ubiquitous – all cellular organisms are potential hosts to damaging infectious agents, from viruses to worms. Parasites (organisms that live on or in a host and get their food from or at the expense of its host) are now recognized as dominant components of diverse biological communities, both in terms of diversity and even in terms of total biomass [1]. Given the incredible prevalence and diversity of parasites within host populations, it is unsurprising that host individuals are often found to be co-infected with multiple parasite species [2]. However, research into host-parasite interactions remains dominated by the study of single infections in isolation, with only occasional consideration for the mechanistic interactions between parasites and their ecological and evolutionary implications [3,4,5,6,7,8]. Pedersen and Fenton categorized a range of mechanisms that can cause parasite interactions, ranging from reciprocal competition (e.g. species A and species B compete for a shared resource, thus A inhibits the growth of B and vice-versa) to reciprocal facilitation (e.g. species A and species B cross-feed on the byproducts of their partner, thus A enhances the growth of B and vice-versa) [3].

Studying multi-species infections is of particular biomedical importance as several infectious diseases are complicated by secondary or opportunistic infections, for example, HIV and associated infections (such as tuberculosis) [9,10], and Lyme disease and its associated tick-borne infections [11]. Besides impeding host

recovery [12], co-infections can create confusion and delay in diagnosis and treatment.

Over the past few years there has been an increasing interest in studying multispecies co-infections [13,14]. A recent study in wild-rodent populations demonstrated that host susceptibility to a microparasite infection was significantly affected by secondary infections [14]. Their results also highlighted the possibility of different types of microparasite species associations leading to different types of interactions (one way/reciprocal positive/negative association). For example, while infection with the bacterium *Anaplasma phagocytophilum* decreased the host susceptibility to *Bartonella* spp. infection, *Anaplasma phagocytophilum* increased susceptibility to cowpox virus. According to another study, host susceptibility to *Streptococcus pneumoniae* transmission and disease are increased if previously infected with influenza [15]. The negative influence of co-infection on mortality was highlighted in a study on rainbow trout showing that fish co-infection with an ectoparasite and a bacterial pathogen significantly decreased the fish survival. Although mono-infections with the ectoparasite did not affect fish survival, it enhanced the susceptibility to the bacterial pathogen [16].

Here we use basic ecological theory to investigate the within-host dynamical consequences of various mixes of competition and facilitation between a pair of co-infecting species. We then consider the implications of these dynamics for the virulence of co-infections and consequent evolution of parasite strategies of exploitation. We find that whereas one-way facilitation poses some increased virulence risk, reciprocal facilitation presents a

qualitatively distinct destabilization of within-host dynamics and the greatest risk of severe disease.

Materials and Methods

To describe the growth of two parasite species (A and B) within a single host, we begin with the classic Lotka-Volterra two species competition equations [17].

$$dA/dt = A(1 - A - xB) \quad (1a)$$

$$dB/dt = B(1 - yA - zB) \quad (1b)$$

Here, A and B represent densities of A and B, respectively, scaled to the carrying capacity of A (for details on the rescaling of model 1, see [17] and Text S1). x and y are interspecific competition coefficients, measuring the relative competitive (inhibitory) weight of an interspecific individual, relative to a conspecific individual. Finally, z is a measure of intraspecific competition within the B population (implying that the carrying capacity of B is $1/z$ times that of A, where $z > 0$). These assumptions imply that single species infections will tend to stable equilibrium densities ($A^* = 1$ for species A, $B^* = 1/z$ for species B), i.e., we describe the dynamics of chronic infections [18]. This assumption of single species chronicity can be viewed as a statement that on the timescale of superinfection (expected time from 1st to 2nd infection), the initial infection dynamics are relatively stable. As infection dynamics become more acute, then the incidence of superinfection will correspondingly decrease (in other words, the multiple-infection issues addressed in this paper are generally a property of parasites that are relatively chronic).

In the classic implementation of Model 1, all parameters are constrained to be positive (i.e., we have both intraspecific and interspecific competition). However, if we allow x and/or y to turn negative, we can consider the potential for reciprocal or one-way facilitation [17]. Specifically, if $x < 0$, parasite B will facilitate the growth of A, and if $y < 0$, parasite A will facilitate the growth of B.

To link the within host dynamics of A and B to virulence (additional mortality and/or morbidity), we assume that virulence $V(t)$ is proportional to the densities of the two parasites [19], hence $V(t) = aA(t) + bB(t)$.

Results and Discussion

To characterize the dynamics of Model 1, we first note that the system has 3 non-zero equilibria – either we find A alone (at $A^* = 1$), B alone (at $B^* = 1/z$) or A plus B coexistence (at $A^* = (z-x)/(z-xy)$ and $B^* = (1-y)/(z-xy)$). A stability analysis of these equilibria [17,20] reveals that when $y > 1$ (i.e., if A is strongly inhibitory to B) then A alone is stable. Similarly, if $x > z$ (i.e., if B is strongly inhibitory to A), then B alone is stable. If both of these inequalities hold (and therefore interspecific competition dominates) then both A alone and B alone are locally stable (bistable dynamics), with A dominating whenever the proportion of A exceeds $(z-x)/(z-x-y+1)$ (i.e., $A^*/(A^*+B^*)$). Bistable dynamics describe a simple resident advantage – whichever parasite establishes first is likely to resist colonization and replacement by a novel intruder (Figure S1).

In the absence of strong interspecific competition (i.e., when $x < z$ and $y < 1$), neither species can exclude the other, and so we observe coexistence. In addition, in the absence of facilitation (such that $0 < x < z$ and $0 < y < 1$) we find that the coexistence

equilibrium is stable. Figure 1 illustrates the behaviour of the coexistence equilibrium over the range of parameter values where coexistence is guaranteed. This coexistence remains stable if we introduce one-way facilitation (either x or y turning negative) and even for weak reciprocal facilitation. However, for sufficiently strong reciprocal facilitation ($x < 0, y < 0$ and $xy > z$) all equilibria are destabilized and the within-host dynamics enter into a runaway process, characterized by uncontrolled growth of both parasite lineages (Red region in Figure 1).

Broadly, virulence will tend to increase as x and y decrease and become negative (as facilitation dominates) (Figure 1C and Table S1). However, if virulence is determined primarily by one or the other of the species (and the other is relatively cryptic with respect to the host) then increasing one-way facilitation can in some cases decrease virulence (Figure 2). For example, if virulence is largely defined by A ($a >> b$) and B inhibits A ($x > 0$), then increasing facilitation of B (increasing $-y$) can reduce virulence (see dashed white line on Figure 2G for an example). Figure 2 illustrates that virulence may decrease under one of the following scenarios: a) Increasing reciprocal competition, if virulence of the two parasites is symmetric ($a = b$, see Figure 2A, E, I); b) Increasing competition imposed by the less virulent species on the more virulent species, if there is reciprocal competition ($x > 0$ and $y > 0$, see Figure 2C, G); c) Increasing facilitation by the more virulent species on the less virulent strain when one-way facilitation (either x or y negative, e.g. on Figure 2C, G). These results follow from the simple effect that giving aid to (or harming) a competitor acts to increase (or decrease) competitive costs. For illustrative purpose we used a linear mapping between virulence and parasite densities in Figure 1C and 2 (i.e. $V = aA^* + bB^*$). Relaxing this assumption will change the contour spacings represented in these figures, however the primary prediction of a qualitative shift in virulence given reciprocal facilitation holds for any case where V is a monotonically increasing function of A and of B . Under this more general condition, any run-away in A and B densities will translate to an unbounded increase in virulence.

The various mixes of net facilitation and competition outlined in Figures 1 and 2 provide a simple sketch of more complex within-host interactions, including indirect interactions via inducible (immune-mediated) defences [21] or shared phages [22]. For example, if parasite A suppresses host immunity, that may favour infection by parasite B resulting in a net indirect facilitation of B by A. Similarly, a parasite which induces a host generalised immune response can result in indirect harm to other co-infecting parasites. Note that a more mechanistic predator-prey model has been applied to understand immune-mediated within-host interspecies parasite interactions [21]. While this model focuses explicitly on parasite interactions that are mediated by the host's immune response (an indirect interaction), our model is more general by assuming both direct and indirect interactions of any net sign.

Reciprocal competition ($x > 0$ and $y > 0$) can be considered the default net interaction – co-infecting parasites are competing for the limited resource of one single host. However many examples of facilitation can be found in the literature. HIV and oral candidiasis is potentially a good example of one-way facilitation [23]. *Candida albicans*, the fungus that causes oral candidiasis, is a commensal in the normal human oral mucosa. During HIV infection, immunosuppression promotes the proliferation of this fungus beyond normal limits leading to oral candidiasis, thus HIV facilitates the growth of the fungus (if HIV = parasite A, then $y < 0$). In return, there is no evidence that the enhanced proliferation of *C. albicans* has any marked impact on HIV proliferation, indicating that *C. albicans* remains a commensal towards HIV (x close to zero), even as it turns pathogenic towards the shared host (increasing B).

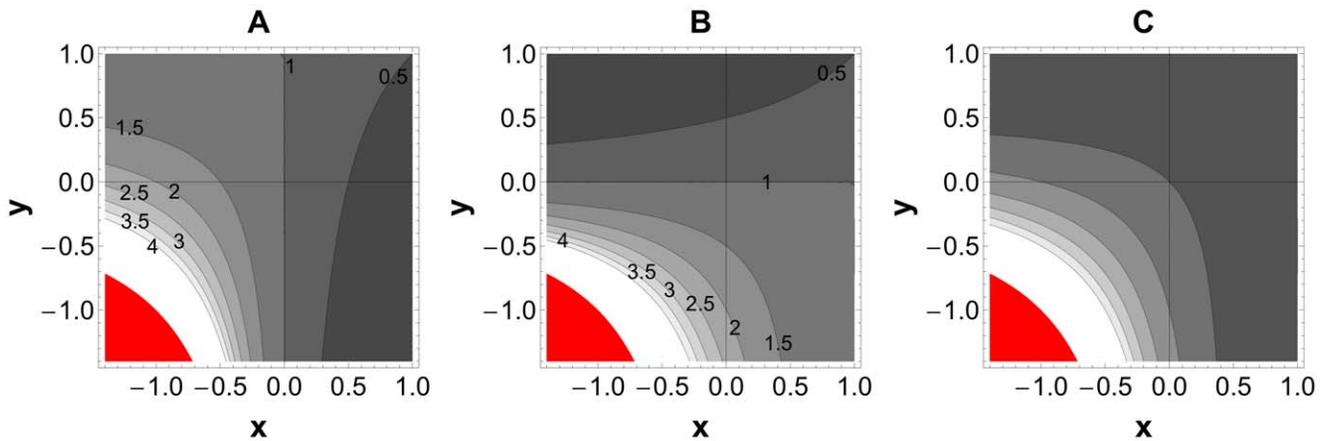


Figure 1. Effect of various mixes of facilitation and competition on the within-host dynamics of coinfecting species. **A**, Equilibrium densities of parasite A (A^*). **B**, Equilibrium densities of parasite B (B^*). **C**, Virulence such that $V = aA^* + bB^*$. The red region represents the region where all equilibria are destabilized (i.e. $xy > z$, $x < 0$ and $y < 0$). Darker regions indicate lower values. The values on the contour lines indicate the relative densities of parasite at equilibrium. The line $x=0$ defines the density of parasite A alone, and $y=0$ defines the density of parasite B alone. The parameter values used are $a=b=z=1$. doi:10.1371/journal.pone.0038730.g001

On the other hand, if the facilitation is two-sided (i.e., $x < 0$ and $y < 0$) the equilibrium densities of both parasites will be higher given co-infection (Figure 1A and B). Of particular concern is the case where the reciprocal facilitation is sufficiently strong to destabilize the coexistence state (i.e., $xy > z$, red region in Figure 1). When this condition is met, the infection is predicted to grow without bounds demanding immediate and rigorous management. Coinfection of HIV and *Mycobacterium tuberculosis* is a potential example for such a dangerous collaboration. HIV not only helps reactivation of dormant *Mycobacterium* bacilli, but also promotes fresh infection and reinfection [24]. Specifically, HIV aids the survival and proliferation of *Mycobacterium* by decreasing the number of CD4 T cells, inactivating macrophage functions and affecting *Mycobacterium*-specific T cell response [25]. *Mycobacterium* on the other hand boosts the replication of HIV by some unclear mechanism [26]. It has been demonstrated that *Mycobacterium* can increase HIV transcription in transiently transfected T and monocytic cell lines and that *Mycobacterium* increases HIV production in chronically infected or acutely infected monocytic cell lines. A correlation between *Mycobacterium*-induced HIV production and secretion of certain inflammatory cytokines has also been observed [27,28,29].

Facilitatory interactions involving HIV are relatively well documented due to the immuno-suppressive impact of HIV and the extent of research effort into this disease. However other examples exist, for instance co-infections of *Salmonella* and *Plasmodium* are suggestive of reciprocal facilitation. Leucopenia during typhoid fever [30] caused by *Salmonella* can facilitate the entry and survival of *Plasmodium* in blood. On the other hand, iron released during RBC lysis in malaria caused by *Plasmodium* can boost the growth of intracellular *Salmonella* [31,32,33]. Thus, the combination of typhoid fever and malaria in the same host is a dangerous condition demanding rigorous management. In fact, coinfection of *Salmonella* and *Plasmodium* has been reported in several places across the globe [34,35,36,37,38]. It is likely that an increasing knowledge of the pathobiology of combination infections will lead to the discovery of many more potentially dangerous collaborations among pathogenic microbes.

Our dynamical analysis of two-species interaction highlights that the dynamics of a focal species can be significantly modulated as a result of mechanistic interactions with a second, co-infecting

species (Figure 1 and 2): the equilibrium density of the focal species can be increased, decreased or entirely destabilised as a result of the interaction. These effects raise an important evolutionary question – does selection favour facilitatory or inhibitory (competitive) interactions with co-infecting species (i.e., changes in parasite traits underlying the interspecific interaction parameters x and y)? An important ingredient in any answer to this question is an understanding of the frequency of coinfection between focal and partner species. If coinfection (with any partner) is a relatively rare occurrence, then standard virulence evolution theory predicts selection will favour intermediate levels of ‘prudent’ exploitation that efficiently balance the advantages of exploitation (transmission) with the costs (host death) [18,39,40,41]. The addition of a second partner co-infection would then induce a non-adaptive perturbation, no matter whether the direction of the effect was towards higher or lower rates of within-host growth (facilitation or competition).

If, in contrast, co-infection is a common and predictable occurrence, then selection could act to modify the single species exploitation strategy given the expected sign of interaction with the partner species. The impact of within-host competition (positive x and y) on the evolution of virulence has been the subject of a diverse range of models and empirical tests, offering contrasting explanations for either an increase or a decrease in virulence as within-host diversity increases [42]. The different virulence outcomes result from selection of different mechanisms of winning a greater share of the limited host resource – increased within-host replication [39,43]; decreased contribution to collective exploitation [44,45]; increased investment in interference competition [22,46,47].

The literature on virulence evolution in mixed infections has focused almost entirely on single species interactions among strains that compete largely symmetrically for shared limited resources. What happens when we move away from this single species paradigm? A few studies have considered multi-species competitive interactions and the greater competitive asymmetries that result [48,49,50] however to our knowledge there has been no consideration of virulence evolution given facilitatory within-host interactions despite the existence of numerous empirical examples, as detailed above. We propose that repeated facilitatory interactions will select for strategies that maximize a focal species yield in the context of the predictable facilitatory perturbation from the partner species. Specifically, this may take the form of a reduced

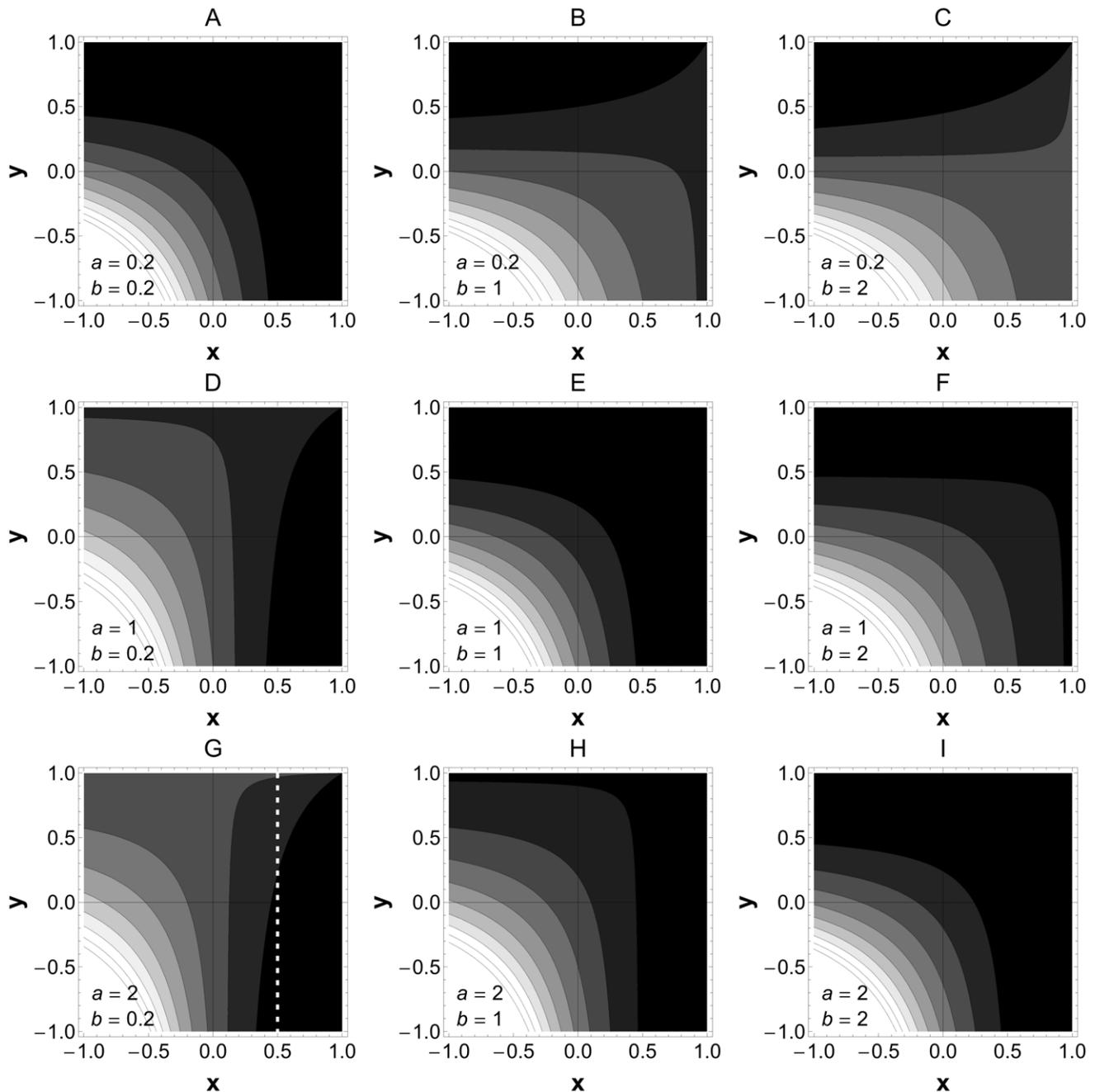


Figure 2. Effect of asymmetric ($a \neq b$) and symmetric ($a = b$) parasites' contribution to total virulence (V). Given a pair of values (a, b) the contour lines in each figure represent the total virulence on the host ($V = aA^* + bB^*$) for different values of x (parasite B competition/facilitation of parasite A) and y (parasite A competition/facilitation of parasite B). Lighter the region higher the virulence. $z=1$ (i.e., symmetric intraspecific competition). The dashed white line exemplifies a situation where virulence is largely defined by parasite A ($a \gg b$) and parasite B inhibits parasite A ($x > 0$). Moving along this line by increasing $-y$ (i.e. increasing facilitation to B) may decrease the overall virulence. doi:10.1371/journal.pone.0038730.g002

growth rate, given the expectation of facilitation restoring growth towards the prudent optimum. Under this scenario, facilitatory interactions could form part of a truly mutualistic partnership, in so far as they restored the partner dynamics towards their optima. However, a dependence on a corrective input from a partner species would leave open the possibility of even greater perturbations in the event of the establishment of an inappropriate partnership. For species facing significant uncertainty over the sign of interaction with partner species, a possible solution is to adapt

plastic responses, modulating behaviours in response to changes in co-infection status [51,52].

In addition to the evolutionary context, a further and marked simplification of our model is our limitation to a two-species context. In practice, within-host parasite community structure can be vastly more complex and multi-dimensional, featuring networks of facilitatory and inhibitory interactions. The exploration of appropriately multi-dimensional community models represents an important challenge for future research. Our results hint that networks

characterized by reciprocal facilitation will be significantly more prone to extinction (via host death), therefore biasing observed networks towards more robust inhibitory interactions, where the sum of parasite effects is significantly less than their effects alone.

Supporting Information

Figure S1 Bistable dynamics of the co-infection (either parasite A alone or parasite B alone at equilibrium). **A**, Temporal dynamics of the proportion of parasite A ($p = A/(A + B)$) for different initial p values ranging from 0.1 to 0.9. $y = 1.2$, $x = 0.9$, and $z = 0.7$. The repeller value is at $p^* = A^*/(A^* + B^*) = (z - x)/(z - x - y + 1) = 0.5$ (dashed line). **B**, The threshold of invasion by parasite A (i.e. minimum p value for which A invades) increases with x and decreases with y ($z = 1$). **C**, The threshold of invasion by parasite A (i.e. minimum p value for which A invades) increases with x and decreases with z ($y = 1.2$). (EPS)

References

- Kuris AM, Hechinger RF, Shaw JC, Whitney KL, Aguirre-Macedo L, et al. (2008) Ecosystem energetic implications of parasite and free-living biomass in three estuaries. *Nature* 454: 515–518.
- Petney TN, Andrews RH (1998) Multiparasite communities in animals and humans: frequency, structure and pathogenic significance. *International Journal for Parasitology* 28: 377–393.
- Pedersen AB, Fenton A (2007) Emphasizing the ecology in parasite community ecology. *Trends Ecol Evol* 22: 133–139.
- Cox FE (2001) Concomitant infections, parasites and immune responses. *Parasitology* 122 Suppl: S23–38.
- Fenton A, Viney ME, Lello J (2010) Detecting interspecific macroparasite interactions from ecological data: patterns and process. *Ecol Lett* 13: 606–615.
- Lello J, Hussell T (2008) Functional group/guild modelling of inter-specific pathogen interactions: a potential tool for predicting the consequences of co-infection. *Parasitology* 135: 825–839.
- Lello J, Norman RA, Boag B, Hudson PJ, Fenton A (2008) Pathogen interactions, population cycles, and phase shifts. *Am Nat* 171: 176–182.
- Lello J, Boag B, Fenton A, Stevenson IR, Hudson PJ (2004) Competition and mutualism among the gut helminths of a mammalian host. *Nature* 428: 840–844.
- Kaplan JE, Hu DJ, Holmes KK, Jaffe HW, Masur H, et al. (1996) Preventing opportunistic infections in human immunodeficiency virus-infected persons: implications for the developing world. *Am J Trop Med Hyg* 55: 1–11.
- Harries AD, Zachariah R, Corbett EL, Lawn SD, Santos-Filho ET, et al. (2010) The HIV-associated tuberculosis epidemic—when will we act? *Lancet* 375: 1906–1919.
- Swanson SJ, Neitzel D, Reed KD, Belongia EA (2006) Coinfections acquired from ixodes ticks. *Clin Microbiol Rev* 19: 708–727.
- Griffiths EC, Pedersen AB, Fenton A, Petchey OL (2011) The nature and consequences of coinfection in humans. *J Infect* 63: 200–206.
- Graham AL (2008) Ecological rules governing helminth-microparasite coinfection. *Proc Natl Acad Sci U S A* 105: 566–570.
- Teller S, Lambin X, Birtles R, Beldomenico P, Burthe S, et al. (2010) Species interactions in a parasite community drive infection risk in a wildlife population. *Science* 330: 243–246.
- McCullers JA, McAuley JL, Browall S, Iverson AR, Boyd KL, et al. (2010) Influenza enhances susceptibility to natural acquisition of and disease due to *Streptococcus pneumoniae* in ferrets. *J Infect Dis* 202: 1287–1295.
- Bandilla M, Valtonen ET, Suomalainen LR, Aphalo PJ, Hakalahti T (2006) A link between ectoparasite infection and susceptibility to bacterial disease in rainbow trout. *Int J Parasitol* 36: 987–991.
- Murray JD (2002) *Mathematical biology*. New York: Springer. v. p.
- Alizon S, van Baalen M (2008) Acute or chronic? Within-host models with immune dynamics, infection outcome, and parasite evolution. *Am Nat* 172: E244–256.
- Alizon S, van Baalen M (2005) Emergence of a convex trade-off between transmission and virulence. *Am Nat* 165: E155–167.
- Otto SP, Day T (2007) *A Biologist's Guide to Mathematical Modeling in Ecology and Evolution*: Association of American Publishers.
- Fenton A, Perkins SE (2010) Applying predator-prey theory to modelling immune-mediated, within-host interspecific parasite interactions. *Parasitology* 137: 1027–1038.
- Brown SP, Fredrik Inglis R, Taddei F (2009) SYNTHESIS: Evolutionary ecology of microbial wars: within-host competition and (incidental) virulence. *Evolutionary Applications* 2: 32–39.
- Egusa H, Soysa NS, Ellepola AN, Yatani H, Samaranyake LP (2008) Oral candidosis in HIV-infected patients. *Curr HIV Res* 6: 485–499.
- Small PM, Shafer RW, Hopewell PC, Singh SP, Murphy MJ, et al. (1993) Exogenous reinfection with multidrug-resistant *Mycobacterium tuberculosis* in patients with advanced HIV infection. *N Engl J Med* 328: 1137–1144.
- Diedrich CR, Flynn JL (2011) HIV-1/*mycobacterium tuberculosis* coinfection immunology: how does HIV-1 exacerbate tuberculosis? *Infect Immun* 79: 1407–1417.
- Goletti D, Weissman D, Jackson RW, Graham NM, Vlahov D, et al. (1996) Effect of *Mycobacterium tuberculosis* on HIV replication. Role of immune activation. *J Immunol* 157: 1271–1278.
- Shattock RJ, Friedland JS, Griffin GE (1993) Modulation of HIV transcription in and release from human monocytic cells following phagocytosis of *Mycobacterium tuberculosis*. *Res Virol* 144: 7–12.
- Zhang Y, Nakata K, Weiden M, Rom WN (1995) *Mycobacterium tuberculosis* enhances human immunodeficiency virus-1 replication by transcriptional activation at the long terminal repeat. *J Clin Invest* 95: 2324–2331.
- Lederman MM, Georges DL, Kusner DJ, Mudido P, Giam CZ, et al. (1994) *Mycobacterium tuberculosis* and its purified protein derivative activate expression of the human immunodeficiency virus. *J Acquir Immune Defic Syndr* 7: 727–733.
- Cunha BA (2006) Typhoid fever: the temporal relations of key clinical diagnostic points. *Lancet Infect Dis* 6: 318–320; author reply 320–311.
- Kaye D, Merselis JG Jr, Hook EW (1965) Influence of *Plasmodium berghei* infection on susceptibility to salmonella infection. *Proc Soc Exp Biol Med* 120: 810–813.
- Kaye D, Hook EW (1963) The Influence of Hemolysis on Susceptibility to Salmonella Infection: Additional Observations. *J Immunol* 91: 518–527.
- Collins HL (2003) The role of iron in infections with intracellular bacteria. *Immunol Lett* 85: 193–195.
- Akinyemi KO, Bamiro BS, Coker AO (2007) Salmonellosis in Lagos, Nigeria: incidence of *Plasmodium falciparum*-associated co-infection, patterns of antimicrobial resistance, and emergence of reduced susceptibility to fluoroquinolones. *J Health Popul Nutr* 25: 351–358.
- Mabey DC, Brown A, Greenwood BM (1987) *Plasmodium falciparum* malaria and *Salmonella* infections in Gambian children. *J Infect Dis* 155: 1319–1321.
- Uneke CJ (2008) Concurrent malaria and typhoid fever in the tropics: the diagnostic challenges and public health implications. *J Vector Borne Dis* 45: 133–142.
- Chowdhury F, Chisti MJ, Khan AH, Chowdhury MA, Pietroni MA (2010) *Salmonella typhi* and *Plasmodium falciparum* co-infection in a 12-year old girl with haemoglobin E trait from a non-malarious area in Bangladesh. *J Health Popul Nutr* 28: 529–531.
- Ammah A, Nkuo-Akenji T, Ndi R, Deas JE (1999) An update on concurrent malaria and typhoid fever in Cameroon. *Trans R Soc Trop Med Hyg* 93: 127–129.
- Frank SA (1996) Models of parasite virulence. *Q Rev Biol* 71: 37–78.
- Levin BR (1996) The evolution and maintenance of virulence in microparasites. *Emerg Infect Dis* 2: 93–102.
- Anderson RM, May RM (1982) Coevolution of hosts and parasites. *Parasitology* 85 (Pt 2): 411–426.
- Buckling A, Brockhurst MA (2008) Kin selection and the evolution of virulence. *Heredity* 100: 484–488.
- de Roode JC, Pansini R, Cheesman SJ, Helinski ME, Huijben S, et al. (2005) Virulence and competitive ability in genetically diverse malaria infections. *Proc Natl Acad Sci U S A* 102: 7624–7628.
- Brown SP, Hochberg ME, Grenfell BT (2002) Does multiple infection select for raised virulence? *Trends Microbiol* 10: 401–405.

45. Harrison F, Browning LE, Vos M, Buckling A (2006) Cooperation and virulence in acute *Pseudomonas aeruginosa* infections. *BMC Biol* 4: 21.
46. Gardner A, West SA, Buckling A (2004) Bacteriocins, spite and virulence. *Proc Biol Sci* 271: 1529–1535.
47. Inglis RF, Gardner A, Cornelis P, Buckling A (2009) Spite and virulence in the bacterium *Pseudomonas aeruginosa*. *Proc Natl Acad Sci U S A* 106: 5703–5707.
48. Brown SP, Le Chat L, Taddei F (2008) Evolution of virulence: triggering host inflammation allows invading pathogens to exclude competitors. *Ecol Lett* 11: 44–51.
49. Lysenko ES, Lijek RS, Brown SP, Weiser JN (2010) Within-host competition drives selection for the capsule virulence determinant of *Streptococcus pneumoniae*. *Curr Biol* 20: 1222–1226.
50. Staves PA, Knell RJ (2010) Virulence and competitiveness: testing the relationship during inter- and intraspecific mixed infections. *Evolution* 64: 2643–2652.
51. Thomas F, Brown SP, Sukhdeo M, Renaud F (2002) Understanding parasite strategies: a state-dependent approach? *Trends Parasitol* 18: 387–390.
52. Reece SE, Ramiro RS, Nussey DH (2009) Plastic parasites: sophisticated strategies for survival and reproduction? *Evol Appl* 2: 11–23.