Relative host-pathogen diversity

Ideas around the effect of pathogen diversity on epidemiology and host-pathogen coevolution, specifically in the context of variation in host resistance

**Related topics:**

* Coinfection
* Sexual reproduction
* Coevolution

Note that these three threads shouldn’t be pulled individually, but are knotted at the base

# Coinfection

Coinfection is often considered in two ways, with different outcomes:

1. A host is sequentially infected by different pathogen genotypes/species
   1. The host clears the first pathogen prior to subsequent infection(s) and recovers, such that fitness doesn’t change
   2. The host clears the first pathogen prior to subsequent infection(s), but experiences reduced fitness due to reduced host condition
   3. The host clears the first pathogen prior to subsequent infection(s), but has increased fitness due to adaptive immunity
2. A host is simultaneously infected by different pathogen genotypes/species
   1. Direct competition between coinfecting pathogens over host resources
   2. Direct interference between coinfecting pathogens
   3. Apparent competition between coinfecting pathogens due to stimulation of host immunity

Coinfection tends to be thought about at the level of the individual host – a single infected individual is the stage on which between-pathogen interactions occur. This might be in multicellular eukaryote, or within single-cells, either free-living or as part of a multicellular organism.

What I’m interested in is how pathogen diversity influences disease dynamics and host-pathogen coevolution when a pathogen population and a host population encounter each other. Instead of asking questions about the role of pathogen diversity once infection has occurred, I want to explore the role of pathogen diversity before the epidemic begins.

What are the consequences of relative host-pathogen diversity at the population, rather than individual, level?

I think that there’ll be a lot of useful parallels between the within-host coinfection literature and thinking about relative diversity at the population level.

# Coevolution

Diversity is necessary for coevolution to take place. In turn, coevolutionary processes are expected to influence the degree of diversity within and between populations (Agrawal & Lively 2002; Salathe et al 2008). Coevolution does generate diversity in the CRISPR-phage system (lots of refs).

Already know that *S. thermophilus* coevolves according to an arms race (Common et al 2019), and my own data has shown a similar but more rapid arms race occurs in *P. aeruginosa*. Further, this arms race weakens (in favour of the host, and also a tonne of variation in infectivity of ‘future’ phage) with slight increases in diversity. Maybe this data could be included in any paper on this idk?

Diverse phage populations are what we tend to find in natural communities (maybe some Banfield lab refs? And perhaps also the Paez-Espino papers). While lab studies suggest that the CRISPR-phage interaction will eventually wipe out phage, this clearly isn’t what we see. Phage diversity is coming from somewhere (migration and/or coevolution), and its consequences need to be explored.

So what could happen when phage diversity is considered experimentally?

* Increased transmission could cause a shift to SM
* Protective effects of diversity might disappear
* Transmission/force of infection might not change at the population, among-host level, which might lead to more CRISPR than might be expected
* Lead to more spacer acquisition and diversity in the hosts
* Or the degree of diversity in the phage population might select against increased spacer acquisition
* Could lead to a ‘kill the winner’ dynamic, similar to Red Queen, and cause fluctuations in genotype frequency and stable coexistence between phage and a predominantly CRISPR population
* Might affect the evolution of virulence: the start of the epidemic could favour more virulent phage as new hosts are exploited and between-phage competition occurs, but might stabilise to less virulent phage later in the epidemic. Berngruber et al 2013 saw this happen with *E. coli* infected with temperate (less virulent) and lytic (more virulent) phage.

A few old-ish papers that talk about pathogen diversity that would be worth reading:

* Arista S, Giammanco GM, De Grazia S, Ramirez S, Lo Biundo C, et al. (2006) Heterogeneity and temporal dynamics of evolution of G1 human rotaviruses in a settled population. J Virol 80: 10724–10733.
* Gallimore CI, Iturriza-Gomara M, Xerry J, Adigwe J, Gray JJ (2007) Inter-seasonal diversity of norovirus genotypes: Emergence and selection of virus variants. Arch Virol 152: 1295–1303.
* Ojosnegros S, Beerenwinkel N, Antal T, Nowak MA, Escarmis C, et al. (2010) Competition-colonization dynamics in an RNA virus. Proc Natl Acad Sci USA 107: 2108–2112.
* Wright CF, Morelli MJ, Thébaud G, Knowles NJ, Herzyk P, et al. (2011) Beyond the consensus: Dissecting within-host viral population diversity of foot-and-mouth disease virus by using next-generation genome sequencing. J Virol 85: 2266–2275.
* Vijaykrishna D, Smith GJ, Pybus OG, Zhu H, Bhatt S, et al. (2011) Long-term evolution and transmission dynamics of swine influenza A virus. Nature 473: 519–522.

# Key questions & predictions

1. The effect of relative diversity on resistance evolution
2. The role of frequency-dependence on coexistence:
   1. Dilution effect
   2. Genotypic stability of host population
3. The potential for the evolution of generalist phage

As relative diversity increases, does selection for resistance decrease?

* When a monoclonal host is challenged by a polyclonal pathogen, there will be a strong selective pressure for hosts to increase their spacer repertoire
* When a polyclonal host is challenged by a polyclonal pathogen, there will be weaker selection for enhanced resistance, and potentially an invasion of sensitives as phage are driven extinct

What degree, if any, of relative diversity promotes coexistence?

* Expect that intermediate relative diversity will promote frequency-dependent/kill-the-winner coexistence, due to a balance between epidemic size and host dilution
* Genotypic composition (in terms of CRISPR clones) might be most stable at intermediate relative diversity

How does dilution of susceptible hosts impact phage population size?

* In diverse host populations, any given susceptible host is still less frequent
* Hence, the dilution effect may still protect hosts even when phage diversity is high
* The effect of intermediate diversity that promotes evolutionary emergence might be negated when the phage population is diverse: the whole host population is potentially infected, so selection/opportunity to escape might be weakened

What is the potential for the evolution of generalist phage?

* Recombination between different phages may be selected for under conditions of high relative diversity
* This could lead to the evolution of generalist phage genotypes that can infect multiple hosts

## More reading notes – 13/9/2019

Basically trawling through the references for pathogen diversity that are cited in the introduction of Betts, Gray [1].

*“The early phase of novel interactions associated with host shifts is thus likely to be dominated by episodes of directional selection, rather than cycling of existing allelic variants”* [2]

So host shift is expected to be an important part of RQ dynamics. Suppose that precisely what defines a host shift/novel interaction is determined by the nature of the host-pathogen interaction network (e.g. immune system, targets of selection, etc).

*Notes from Telfer, Lambin [3]*

Most of the time, most hosts are infected with multiple parasite species [4]. Parasites may interact directly via competition for host resources or indirectly via the host immune system [5].

*“Interactions may be antagonistic to at least one of the parasites, either as a result of resource shortage or where there are cross-effective immune responses, or they may be beneficial to one or both parasites, as a result of parasite-induced immunosuppression or down-regulation of all or part of the immune system [they cite Pedersen and Fenton [6]]”*

I think this has relevance to my idea that intermediate relative diversity between CRISPR and phage could limit evolutionary emergence. Basically an ecological effect that relaxes selection for evolutionary emergence. Whether or not this is a “beneficial” interaction depends on what happens next in terms of phage survival (and could have different implications e.g. avoids pathogen niche overlap in multi-species communities?).

Rest of this paper is about coinfection, rather than diversity at an explicitly community level

Betts *et al*. (2018) used entirely susceptible populations of *P. aeruginosa* infected with communities of one to five lytic phages (PEV2, LUZ19, LUZ7, 14-1, and LMA2). My approach differs in that a) diversity is intra-specific and b) diversity in host resistance is included.

*Apparent competition can act through parasitism when levels of infection depend primarily on the rate at which the parasites flow from a tolerant species to a sensitive species, rather than on the density of the sensitive species. Detailed studies of the shared parasite* Heterakis gallinarum *in pheasants and partridges show that the fitness of a single infective stage entering a pheasant is 100 times greater than a similar stage entering a partridge [7] because the parasite is more likely to establish, grow bigger and produce more infective stages in pheasants. Given that the partridges suffer reduced fitness from parasites, the presence of pheasants could increase infection in partridges and lead indirectly to their localized extirpation [7]* – from Hudson, Dobson [8]

Really interesting example of how differences in host susceptibility in a community context can influence competition among host species. It’s also basically superspreaders right?

Hudson, Dobson [8] make the point that the diversity-disease effect and/or the density-dependent transmission effect have a lot of relevance to the Janzen-Connell hypothesis (JCH) [9, 10]. Even though the JCH is about how tropical tree diversity is promoted by strong positive frequency-dependent seed predation, it has more general application to pathogens and non-tropical ecosystems [11]. For example, fungal pathogens influence species composition in tropical tree communities [12-14], temperate forests [15], and temperate grassland [16].

In terms of community processes:

*When species biodiversity falls but total plant abundance is held constant, specialist pathogens have a bigger effect because the higher host density of remaining species increases the transmission of the specialized rust between individuals [17]* – Hudson *et al.* (2006)

This is a nice example of a dilution effect in action, but what is even more interesting is that in this grassland system reduced biodiversity can lead to reduced productivity [18] due to damage to photosynthetic ability and root production [19].

### More reading notes – 03/10/19

This paper [20] by Alice Ekroth is very interesting. Basically a meta-analysis of the diversity-disease effect. Importantly for the relative diversity question, they did not detect a significant interaction between parasite and host diversity from 13 studies. I’ve followed up these 13 studies as I think they’re going to be the main points of reference, and I sum them up below.

*Altermatt & Ebert 2008 Ecol Lett* [21]

Two host (*Daphnia magna*) diversity treatments: Hlow = 1 genotype, Hhigh = 10 genotypes. Three parasite (microsporidium *Octosporea bayeri*): no parasite, Plow = 1 isolate, Phigh = 10 isolates. Parasite diversity is explicit here.

*Calleri et al 2006 Proc R Soc B [22]*

Termite host (*Zootermopsis angusticollis*) with inbred and outbred colonies as diversity treatments. Fungal pathogen (*Metarhizium anisopliae*) with three treatments: no conidia, low dose, and high dose. Pathogen diversity is assumed to be >1 genotype here simply because it wasn’t controlled.

*Manlik et al 2017* *Infect Genet Evol {Manlik, 2017 #1753}*

Bumblebee host (*Bombus terrestris*) and microsporidium *Nosema bombi*. Host diversity was between two haplotypes, one in Gotland and the other in Switzerland. Parasite diversity is assumed to be >1 here because it wasn’t controlled.

*Pearman & Garner 2005 Ecol Lett {Pearman, 2005 #341}*

Frog host (*Rana latastei*) and *Ranavirus* pathogen. Host diversity measured across a cline in 6 wild populations from N Italy. Pathogen diversity in three treatments: no virus control, low exposure, and high exposure. Again, pathogen diversity is assumed to be >1 because it wasn’t controlled.

*Schmidt* *et al 2011 Ecol Entomol {Schmidt, 2011 #1754}*

Pharoah ant host (*Monomorium pharaonis*) and entomopathogenic fungal (*Beauveria bassiana*) pathogen. Host diversity treatments as high or low within- or betwee-individual variation, after crossing etc. Pathogen diversity wasn’t controlled so assumed to be >1.

*Seeley & Tarpy 2006 Proc R Soc B {Seeley, 2006 #1755}*

*Apis mellifera* host and bacterial (*Paenibacillus larvae*) pathogen. Host diversity treatment was low and high, established by heading colonies with queens inseminated with sperm from 1 or 10 drones. Exposed to *P. larvae* by spraying a 1x107 spores ml-1solution over the hive. Pathogen diversity wasn’t controlled for so assumed to be >1.

*Shykov & Schmid-Hempel 1991 Proc R Soc B {Shykoff, 1991 #1756}*

Bumblebee (*B. terrestris*) and trypanosome (*Crithidia bombi*) pathogen. Host diversity measured as the degree of relatedness within groups. Parasite diversity not measured, assumed to be >1.

*Strauss et al Proc 2017 Proc R Soc B*

*Daphnia dentifera* host and fungal pathogen *Metschnikowia bicuspidata*. Host diversity in two treatments, ‘constrained’ and ‘variable’ (but they note that they didn’t manipulate host genotypic diversity *per se*). Parasite diversity not diversity not measured, so assumed to be >1.

*Smallbone, van Oosterhout, & Cable 2016 Exp Parasitol*

Guppy *(Poecilia reticulata*) host and monogenian *Gyrodactylus turnbulli* parasite. Host diversity manipulated with three breeding regimes: control, inbred, and outbred. Parasite diversity not measured, assumed to be >1.

So in summary, only 1 of the studies that Ekroth *et al*. included for their analysis of an interaction between parasite and host diversity on parasite success actually make parasite diversity explicit and tested it experimentally. Strange also that they didn’t include Ganz & Ebert 2010 Ecol.

**References**

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