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Review

Host–parasite coevolution: why changing population size matters☆

Andrei Papkou[a], Chaitanya S. Gokhale[b], Arne Traulsen[c], Hinrich Schulenburg[a,*]

[a] Department of Evolutionary Ecology and Genetics, Christian-Albrechts-University of Kiel, 24098, Kiel, Germany
[b] New Zealand Institute for Advanced Study, Massey University, Private Bag 102904, Auckland 0745, New Zealand
[c] Department of Evolutionary Theory, Max Planck Institute for Evolutionary Biology, August-Thienemann-Straße 2, 24306 Plön, Germany

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ABSTRACT

Host–parasite coevolution is widely assumed to have a major influence on biological evolution, especially as these interactions impose high selective pressure on the reciprocally interacting antagonists. The exact nature of the underlying dynamics is yet under debate and may be determined by recurrent selective sweeps (i.e., arms race dynamics), negative frequency-dependent selection (i.e., Red Queen dynamics), or a combination thereof. These interactions are often associated with reciprocally induced changes in population size, which, in turn, should have a strong impact on co-adaptation processes, yet are neglected in most current work on the topic. Here, we discuss potential consequences of temporal variations in population size on host–parasite coevolution. The limited empirical data available and the current theoretical literature in this field highlight that the consideration of such interaction-dependent population size changes is likely key for the full understanding of the coevolutionary dynamics, and, thus, a more realistic view on the complex nature of species interactions.

Contents

1. Introduction

Over the past decades host–parasite coevolution has received particular scientific interest because it is associated with very high selective constraints, resulting in fast and complex evolutionary dynamics that affect a large variety of trait functions (Woolhouse et al., 2002). On the one hand, parasite-induced reduction in host fitness enhances selection for host resistance mechanisms. On the other hand, novel host defences increase selection on the parasite. Genetic variants (alleles) conferring an advantage in the antagonistic interaction can rapidly spread through the population and go to fixation (Buckling and Rainey, 2002). Ultimately, this can lead to so-called recurrent selective sweeps (RSS) or arms race dynamics, consisting of a series of fixation events occurring sequentially or even in parallel in host and parasite (Fig. 1A). Alternatively, an allele may only provide an advantage when rare and would be disfavoured as it increases in frequency in the population (e.g., because parasites have a resource advantage when targeting the common host genotypes). Allele frequency changes in the host population would then cause a corresponding allele frequency change in the parasite population and vice versa, leading to continuous

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* Corresponding author. Tel.: +49-4318804143; fax: +49-4318802403.
E-mail address: hschulenburg@zoologie.uni-kiel.de (H. Schulenburg).

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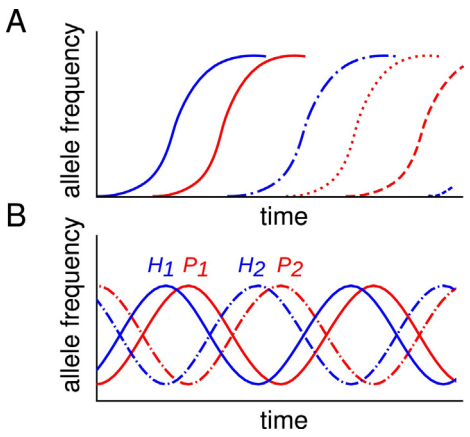

Fig. 1. Allele frequency dynamics during host–parasite coevolution. (A) Recurrent selective sweeps (RSS) and (B) negative frequency-dependent selection (NFDS).

negative frequency-dependent allele oscillations (i.e, negative frequency-dependent selection, NFDS), which are often referred to as Red Queen dynamics (Decaestecker et al., 2007). NFDS can favour the coexistence of several alleles over long time periods (Fig. 1B).

Both types of selection dynamics, RSS and NFDS, are supported by experimental studies (Buckling and Rainey, 2002; Decaestecker et al., 2007; Betts et al., 2014; Gómez et al., 2015), but their exact role in natural host–parasite interactions is not fully understood. As highlighted in different articles of the current issue and also additional studies, various factors are likely to shape the coevolutionary dynamics. These include, for example, genetic diversity (Lively and Apanius, 1995), the genetic system of the interaction (Agrawal and Lively, 2002), different aspects of life history (Barrett et al., 2008; see also an article in the current issue by Strauss et al., 2016), epidemiological characteristics (Tellier and Brown, 2007; see also an article in the current issue by González-Tortuero et al., 2016), metapopulation structure (Gandon and Michalakis, 2002; Thrall and Burdon, 2002), fluctuating environmental changes (Wolinska and King, 2009), phenotypic plasticity, epigenetics, and tolerance (reviewed in the current issue by Kutzer and Armitage, 2016; Milutinović et al., 2016; Vilcinskas, 2016), social interactions within the host taxon (reviewed in the current issue by Kurze et al., 2016; Joop and Vilcinskas, 2016), and the presence of multiple parasites (reviewed in the current issue by Bose et al., 2016). Paradoxically, one important outcome of the host–parasite interaction, namely population size changes, is usually not taken into account. In fact, the influence of population size is excluded from many theoretical models of coevolution (for some exceptions see May and Anderson, 1983; Frank, 1991, 1993; Gandon et al., 1996; Quigley et al., 2012; Gokhale et al., 2013; Ashby and Gupta , 2014; Song et al., 2015) and kept constant, where possible, in experimental systems (Bérénos et al., 2009; Greeff and Schmid-Hempel, 2010; Schulte et al., 2010). This is surprising, because host–parasite interactions are often associated with dramatic changes in population size (Section 2), and such changes are usually an integral part of epidemiological processes (e.g., transmission bottleneck, Section 3). Therefore, it is pivotal to elucidate their role in reciprocal adaptations between host and parasite.

In the present paper, we review the evidence for temporal changes in population size induced by host–parasite interactions and discuss their consequences for coevolution (Section 4). As population size has a central influence on the process of adaptation and as enormous demographic changes can occur during host–parasite interactions, further empirical and theoretical studies are required to systematically assess the role of such temporal population size variations in shaping coevolutionary dynamics (Section 5).

2. Population size changes are a common consequence of host–parasite interactions

By definition, a parasite reduces host fitness through its negative effect on host survival and reproduction. Such host exploitation at the individual level can decrease overall host population size, especially if a large number of hosts is infected (e.g., the most frequent host genotype(s)), as assumed under both RSS and NFDS. At the same time, a reduction in host abundance automatically decreases niche size (resources) for the parasite. This ultimately leads to reciprocally induced changes in the population size of both host and parasite. The principle of mutual dependence of population sizes among antagonistically interacting species was already formalized by Lotka and Volterra almost 90 years ago as a set of differential equations (i.e., the Lotka–Volterra model) (Volterra, 1928; Lotka, 1932). The Lotka–Volterra model produces periodic cycles in host (prey) population size tracked by cycles in parasite (predator) abundance (Fig. 2A). In accordance with the theoretical predictions, numerous field studies obtained evidence for demographic variations in interacting host and parasite populations. Some examples are listed in Table 1 and more can be found elsewhere (Anderson and May, 1980; Dobson and Hudson, 1992).

The parasites' influence on host population dynamics was additionally tested directly through controlled experiments (see Table 1). In an early experiment by Utida (1957), the host azuki bean weevil and its parasitoid wasp were propagated under laboratory conditions for many generations, resulting in characteristic cyclic oscillations in population size (Fig. 2B). Another type of experiment was performed in wild populations of red grouse; anthelmintic treatment succeeded in removing the population cycles, which are otherwise induced by parasitic nematodes (Fig. 2C) (Hudson et al., 1998). These experimental findings demonstrate that host population size can be directly regulated by parasites, although generalizations to a broader context are still under discussion (Tompkins and Begon, 1999; Redpath et al., 2006). We would like to point out that, even if the measurable effect of an infection on host survival and reproduction is low, in a realistic situation parasites are still very likely to play an important role by additionally interacting with other factors. For example, an infected host may be less successful in competing for food or mates, more prone to predation, less likely to survive a cold winter or starvation period (Savage et al., 2011; Hayward et al., 2014). Thus, the presence of a complex set of factors does not preclude a central contribution of parasites, but rather suggests that there are potentially numerous ways in which parasites can exert their influence on host abundance (Holmes, 1982).

The above examples of coupled oscillations in population size are limited to an endemic situation, where a parasite is permanently present with substantial prevalence. In reality, contacts among host and parasite species are often discontinuous in time and space. Accordingly, population dynamics are then rather shaped by epidemics, i.e. the episodic presence of a parasite that spreads within a host population (Anderson and May, 1992). The predicted consequences of epidemics for population dynamics range from complete parasite elimination to local host extinction or from regular to chaotic epidemic cycles (Frank, 1991; Anderson and May, 1992; Heesterbeek and Roberts, 1995), and, hence, epidemics commonly affect the demography of at least one of the antagonists (see examples in Table 1).

In our opinion, such episodic perturbations in population size deserve particular consideration for our understanding of the coevolutionary process. Firstly, epidemics are common (and thus influential during evolution), as evidenced by a vast number of observations from medical epidemiology, agricultural and field studies (see Table 1) (Anderson and May, 1992; Dobson and Hudson, 1995; Hudson and Dobson, 1995). Secondly, such episodes

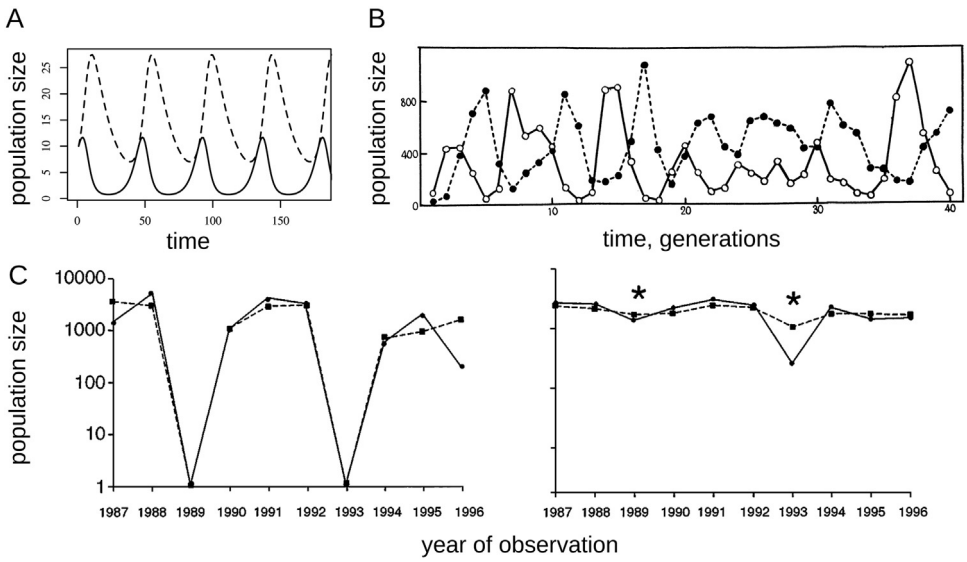

Fig. 2. Population size variations caused by interacting hosts and parasites. (A) Lotka–Volterra-type, interconnected population cycles of host (solid line) and parasite (dashed line). (B) Cyclical population size changes of azuki bean weevil (solid line, open circles) and its parasitoid wasp (dashed line, filled circles) in the Utida experiment (Utida, 1957). (C) Population cycles (left panel) in red grouse caused by its nematode parasite and their removal by anthelmintic treatment (right panel). Different lines indicate replicate populations. Asterisks designate the years when the treatment was applied (Hudson et al., 1998).

with their strong impact on parasite and/or host population size are very likely to coincide with intense selection and dramatic changes in allele frequencies (Duncan and Little, 2007; Gsell et al., 2013; González-Tortuero et al., 2016). Finally, high population dynamics and rapid evolutionary change due to host–parasite interactions are likely to coincide at single locations (similar to their temporal overlap) but can additionally show variation across space. Such spatial variation represents the core idea of the geographic mosaic theory of coevolution (Thompson, 2005). Here, the interacting species undergo antagonistic trait adaptation in some locations of a geographic mosaic (i.e., the so-called coevolutionary hot spots), but not in others (i.e., cold spots). With all other factors being equal, the populations in hot spots are more likely to experience changes in population size, because the ongoing trait co-adaptations reciprocally affect fitness. In cold spots, more stable population dynamics are expected since host and parasite fitness are less interconnected (Hochberg and Baalen, 1998; Thompson, 2005). Importantly, even a small number of hot spots within a geographic mosaic was shown to influence the global coevolutionary process (given strong selection and sufficient gene flow) (Gomulkiewicz et al., 2000). Consequently, population size perturbations restricted to a small number of coevolutionary hot spots may still have an effect on coevolution, even if the overall population size (across a geographic mosaic) remains relatively constant.

Host–parasite interactions not always result in coevolutionary adaptations. The likelihood for coevolution increases when two species coxist for longer time periods and strongly affect the fitness of one another (Woolhouse et al., 2002). Similarly, host–parasite interactions do not always have an effect on population size; however, they are more likely to do so if the antagonistic interactions have a strong impact on fitness. In fact, many key assumptions underlying antagonistic coevolution (including those used in the common mathematical models on the topic) rather favor demographic changes than constant population size, such as the assumptions of strong reciprocal selection, rapid evolution of fitness-related traits (as in RSS dynamics) and also parasite specialization on the most common host genotype (as under NFDS and RSS). The latter point is particularly important, as it increases the likelihood that the parasite-induced fitness reductions in individual hosts translate into demographic changes at the population level. This relationship is expected to be especially strong for host taxa with generally small population size, usually *K* strategists, although it is also possible for *r* strategists (Gokhale et al., 2013).

Thus, we conclude that host–parasite coevolution should frequently generate demographic perturbations at both the level of single populations and within the geographic mosaic.

3. Bottlenecks are part of a parasite's life cycle

Parasites are commonly viewed as having superior adaptive potential in comparison to their hosts due to their larger population size, shorter generation time, and usually high frequencies of horizontal gene transfer (Woolhouse et al., 2002). At the same time, parasites are likely to be subject to extreme changes in population size during the interaction with a single host and also during transmission between hosts. The resulting higher influence of genetic drift can then limit the parasite's ability to adapt rapidly.

In detail, a strong reduction in abundance (i.e., a bottleneck) can occur at different points of a parasite's life cycle. For certain parasites, infection of a new host can be initiated by as few as 1-10 infectious particles or cells (Jones et al., 2005; Schmid-Hempel and Frank, 2007). During within-host proliferation, a parasite, especially viruses or bacteria, multiplies reaching quantities which can be many orders of magnitude larger than the original inoculum. At this point, another parasite bottleneck may be caused by the host immune system, which can minimize overall parasite load and simultaneously select for a more immune-resistant genotype (Levin et al., 1999). Another bottleneck may occur during the transmission process, depending on a variety of factors, especially host density, the proportion of susceptible hosts, host contact rates, and persistence of transmissible stages (Anderson and May, 1992; McCallum et al., 2001). Furthermore, many parasites possess a complex life cycle, involving multiple intermediate hosts or vector species. Such a life history can potentially increase the number of bottleneck events, resulting in complex patterns of demographic changes for the parasite (Woolhouse et al., 2001; Criscione and Blouin, 2005).

Moreover, contrary to their hosts, parasites usually do not show a continuously high abundance at a certain geographic location or time period. Instead, they can show dramatic demographic

Table 1
Examples of variations in population size as a result of host–parasite interactions.[1]

Host	Parasite	Patterns in population dynamics	Time period	Reference
Field observations				
diatom *Asterionella formosa*	chytrid fungus *Zygorhizidium planktonicum*	seasonal parasite outbreak followed by host decline	spring in 1978–1980	Donk and Ringelberg, 1983
	chytrid fungus *Rhizophydium planktonicum*	two epidemics coincide with host decline	Apr–Jul in 1984	Bruning et al., 1992
11 phytoplankton species	fungal infections, mainly *Rhizidiaceae*	diverse epidemic patterns, often strong effect on host density	1987–1989	Holfeld, 1998
leopard frog *Lithobates yavapaiensis*	chytrid fungus *Batrachochytrium dendrobatidis*	seasonal variation in host abundance with high winter mortality attributed to the infection	2006–2010	Savage et al., 2011
red grouse *Lagopus lagopus scoticus*	nematode *Trichostrongylus tenuis*	cyclic oscillations of host and parasite	1977–1989	Dobson and Hudson, 1992
European rabbit *Oryctolagus cuniculus*	myxoma virus	strong decline in host population followed by recovery as a result of evolved resistance	1950–1997	Fenner and Fantini, 1999
Soay sheep *Ovis aries*	nematodes *Trichostrongylus axei*, *Trichostrongylus vitrinus* and *Teladorsagia circumcincta*	fluctuations in host and parasite densities; host population crashes resulting from winter weather, malnutrition, and parasitization	1988–2012	Hayward et al., 2014
Laboratory experiments				
flavobacterium *Cellulophaga baltica*	viruses ΦS_T and ΦS_M	initial drop in host density and following recovery via accumulation of resistant clones	18 host generations	Middelboe et al., 2009
cyanobacterium *Synechococcus* sp. WH7803	virus RIM8 (*Myoviridae*)	coevolution in chemostat; initially extreme changes in population densities tend to stabilize	170 host generations	Marston et al., 2012
dinoflagellate *Alexandrium minutum*	protist *Parvilucifera sinerae*	perturbations in population dynamics depending on the combination of host and parasite clone	16 days	Råberg et al., 2015
common housefly *Musca domestica*	parasitoid wasp *Nasonia vitripennis*	cyclic oscillations in host and parasite	80 weeks	Pimentel, 1968
azuki bean weevil *Callosobruchus chinensis*	parasitoid wasp *Neocatolaccus mamezophagus*	cyclic oscillations in host and parasite	51 host generations	Utida, 1957
moth *Plodia interpunctella*	parasitoid wasp *Heterospilus prosopidis*	cyclic oscillations in host and parasite	112 host generations	Bjornstad et al., 2001
water flea *Daphnia magna*	White Bacterial Disease, bacterium *Pasteuria ramosa*, fungus *Metschnikowiella biscuspidata*, 3 microsporidia sp.	different outcomes depending on the pathogen ranging from extinction to co-existence	8-10 host genrations	Ebert et al., 2000
Mass extinctions				
a variety of amphibian species from Mesoamerica	chytrid fungus *Batrachochytrium dendrobatidis*	host decline coincides with an increase in the parasite prevalence	1964–1999	Cheng et al., 2011
seal *Phoca vitulina*	phocine distemper virus	up to 60% extinction of North Sea host population	1988, 2002	Härkönen et al., 2006
house finch *Carpodacus mexicanus*	bacterium *Mycoplasma gallisepticum*	up to 60% decline in abundance compared to expected values	since 1993	Hochachka and Dhondt, 2000

[1] The first two parts summarize field and laboratory observations where population dynamics has been recorded for at least a few host generations, i.e. opening the possibility for genetic adaptation. The last part provides some examples of devastating effects of parasites on host populations.

changes during an epidemic (i.e., emergence of new parasites or complete extinction), invasion of new host populations, and host shifts (Altizer et al., 2003) (Fig. 3). Examples for this are the re-occurring outbreaks of measles, mumps and pertussis in human populations, which were most pronounced before the introduction of mass vaccination (Anderson et al., 1984). Another example of a complex spatio-temporal parasite occurrence is found in a 'travelling' infection wave, such as that described for raccoon rabies spreading across the eastern USA (Biek et al., 2007) or various human diseases influenced by complex human mobility patterns (Brockmann, 2009).

Parasites are represented by a diverse spectrum of species which can have very different life histories and genome organisations. Accordingly, population size and adaptation dynamics can vary considerably for different parasite types, for example viruses versus helminths or bacteria versus insect parasitoids. In turn, the differences in parasite trait characteristics, especially those relating not only to population size itself but also to transmission mode, infection cycle or genome size, are central determinants of their ability for evolutionary adaptation (Barrett et al., 2008). Consideration of these differences is thus also important for an improved understanding of the evolution and population biology of specific parasite taxa. These differences further emphasize that the frequently made assumption of infinite parasite population size and superior adaptation potential does not necessarily apply to all taxa (Criscione and Blouin, 2005).

Taken together, the temporally and spatially variable nature of parasitism and the numerous constraints during the parasite life cycle strongly suggest that extreme variation in population size represents a universal characteristic of parasite biology with a potentially strong influence on its evolution.

4. Varying population size influences reciprocal adaptation

Population size is one of the key parameters that determines the availability of genetic diversity and also the intensity of genetic drift and selection. Classical population genetic theory explicitly defines the relationship between population size and different evolutionary forces. Yet, to date, the specific effect of temporal variation in population size on evolutionary adaptation is still largely unexplored.

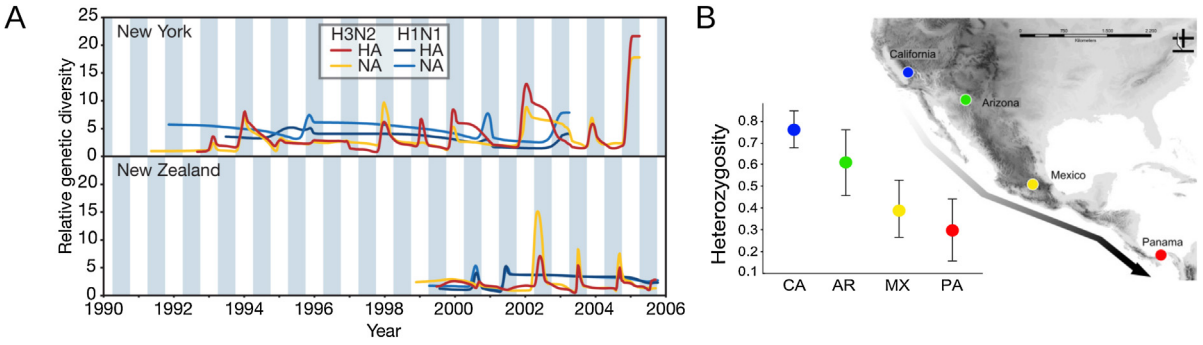

Fig. 3. Bottlenecks experienced by parasites. (A) Bottlenecks among successive epidemics of influenza virus H3N2 and H1N1, each time followed by winter outbreaks that coincide with increases in genetic diversity (Rambaut et al., 2008). (B) Bottlenecks during the geographic expansion of the deadly amphibian pathogen *Batrachochytrium dendrobatidis* from Northern to Central America cause a decrease in genetic diversity (heterozygosity) (Velo-Antón et al., 2012).

4.1. Genetic diversity and changing population size

Population size variation may affect genetic diversity by (i) scaling the rate of producing novel variants (i.e., through influencing the effective mutation/ recombination rate) and (ii) influencing the maintenance of genetic diversity already present in a population. The number of mutations produced de novo is proportional to the population size, thus small populations would almost exclusively rely on standing genetic variation. Genetic diversity in small populations is then likely to decrease, because of increased drift effects. Moreover, if genetic diversity is low, the population is likely to suffer from high parasite prevalence due to the inability to counter-adapt. Such a situation is frequently observed in endangered species, where low diversity often correlates with high parasite load (Coltman et al., 1999; Hoffman et al., 2014). Equivalently, an increase in population size should provide a population with a larger number of mutations, ultimately leading to high levels of genetic diversity. This has been repeatedly reported for growing parasite populations, especially during an outbreak, when increases in genetic variation may enhance the parasite's adaptive potential. In particular, peaks in genetic diversity of A/H3N2 and A/H1N1 influenza viruses coincide with annual outbreaks during the winter season (Rambaut et al., 2008) (Fig. 3A). Diversification in some phylogenetic trees of viruses correlate with the onset of an epidemic (Biek et al., 2007; Tee et al., 2010). Within-host proliferation of a parasite can similarly increase genetic diversity, as documented for HIV in recently infected patients (Maldarelli et al., 2013).

An extreme form of population size variation is a bottleneck event, which has a direct influence on genetic diversity, usually leading to a loss thereof. This has, for example, been reported for an isolated population of the African lion in the Ngorongoro Crater, which preserved only 30% of its original diversity after the severe bottleneck caused by the epizootic of biting flies (Wildt et al., 1987). Bottlenecks experienced by parasites in the course of repeated infection cycles (Zwart et al., 2011) or in the process of geographical expansion lead to founder effects (Fig. 3B) (Velo-Antón et al., 2012). In some cases such bottlenecks are the prime determinants of evolutionary dynamics. In a recent study, artificially induced bottlenecks qualitatively changed the outcome of bacterium–phage coevolution. More specifically, the joint action of strong selection for resistant clones and large bottlenecks rapidly eliminated susceptible clones from the bacterial populations, which, in turn, led to the extinction of the phages (Hesse and Buckling, 2016).

Population size and resulting variations in genetic diversity are additionally likely to influence the evolution and maintenance of sexual reproduction, especially in connection with the strong selective influence of coevolving parasites (Hamilton et al., 1990; Lively, 2010). Sexual reproduction and recombination can generate novel genetic variants resistant against parasites, which is of most importance to eukaryotic hosts with small population sizes. Thus, even if genetic diversity is limited, sexual reproduction would help small host populations to combat parasites. Such an advantage of sex and outcrossing in the host could indeed be confirmed for several host–parasite systems (Dybdahl and Lively, 1996; Lively and Jokela, 2002; King et al., 2009; Morran et al., 2011), although not for all of the studied cases (Ben-Ami and Heller, 2005; Killick et al., 2008). We here argue that interaction-induced population size changes should additionally enhance the selective advantage of sex. This aspect has not yet been tested empirically. However, it is supported by theoretical work, which highlighted that population size dynamics has a large influence on the competition among sexual and asexual individuals (Lively, 2009, 2010; Ashby and Gupta, 2014).

4.2. Selection and genetic drift under the influence of changing population size

Apart from affecting genetic diversity, variation in population size can determine the efficiency of selection. According to Kimura and Ohta (1969), the probability of fixation of neutral alleles is the inverse of the population size. In addition, the time to fixation of neutral or nearly neutral loci is proportional to the effective population size. At small population size (e.g., after a bottleneck), selection becomes weak and random genetic drift becomes stronger, favouring the accumulation of deleterious mutations and an associated fitness decline, as known for many viruses (Chao, 1990; Escarmís et al., 1996). As an alternative, bottlenecks can also facilitate purging selection, as reported for plant viruses (Visser et al., 1999; Miyashita and Kishino, 2010).

Population size similarly influences the spread of a selectively favoured allele. The fixation probability (ϕ) of a new mutation is usually predicted by the relationship between effective population size (N_e) and census size (N) multiplied by a selection coefficient (s): $\phi = 2s\frac{N_e}{N}$ (Kimura, 1970), valid for small s and sufficiently large N. The effective population size N_e of a cycling population is then often approximated by a harmonic mean of census sizes, $N_e = (\sum_i 1/N^i)^{-1}$ (Ewens, 1967; Kimura, 1970). Thus, the harmonic mean approximation allows us to study evolutionary processes under changing population size by applying standard techniques, which are based on the assumption of constant population size. This obvious convenience may mislead us to ignore some restrictive assumptions behind the theory. For example, the harmonic mean approximation performs poorly if the amplitude of population cycles is large and selection is strong (Otto and Whitlock, 1997), as is likely the case for coevolving antagonists. In addition, the probability of fixation deviates from estimates made for constant population size in a variety of demographic scenarios, for instance

during exponential and logistic growth or a bottleneck (Otto and Whitlock, 1997; Patwa and Wahl, 2008; Parsons et al., 2010).

The ultimate consequences of a bottleneck on selection and drift may be more complicated as they can be influenced by several factors simultaneously. These factors can include the proportion of parasite individuals/particles within an infected host contributing to new infections (size of a transmission bottleneck), population distribution of new infections coming from a single source, the likelihood of superinfections, and mixing of infectious propagules from different sources during the transmission bottleneck. Small transmission numbers, large variance in the number of new infections, and low levels of gene flow within a parasite meta-population would all result in increased genetic drift (Criscione and Blouin, 2005). A good illustration of how such transmission bottlenecks can shape parasite evolution is provided by HIV-1. With its fast replication cycle and high mutation rate, HIV easily overcomes human immune defences in a process of within-host adaptation. However, with only about one million infected people in the US, the rate of adaptive evolution at the population level is extremely small, especially when compared with rates of within-host adaptation. This surprising difference is explained by a strong transmission bottleneck, where a new infection is usually established from only a single lineage, which effectively prevents selection from acting on the population level (Lemey et al., 2006; Pybus and Rambaut, 2009).

4.3. *Eco-evolutionary feedback during host–parasite coevolution*

Variation in population size during host–parasite coevolution is usually not independent of selection, as outlined above. This implies that coevolutionary adaptations and population dynamics can interact. A fitness improvement in response to selection may compensate for the negative effects of a population decline, because at least some individuals in the host population would possess advantageous resistance traits (Gomulkiewicz and Holt, 1995). For example, after the myxoma virus had been introduced to the rabbit populations of Australia in 1950, the first epidemic was characterized by high mortality and a devastating effect on host density (Fenner and Fantini, 1999). In the following years, the rabbits increased resistance and the virus became less virulent, which eventually led to recovery of the host population. Thus, genetic adaptations in the rabbit–myxoma system resulted in stabilization of the host population. Eco-evolutionary feedbacks may also result when interaction-induced population dynamics is coupled with changes in population density. In particular, reduced densities can lower parasite transmission rates and automatically increase host survival, which in turn may affect the potential of both host and parasite to adapt to the antagonist. For example, virulence may be most pronounced at higher host densities (Lively et al., 1995; Bell et al., 2006). Incorporation of density-dependent virulence in a coevolutionary model can change the outcome of competition among sexual and asexual hosts (Lively, 2009). Moreover, eco-evolutionary feedbacks were shown by using a mathematical model to attenuate pathogen virulence when transmission is density-dependent (Lenski and May, 1994).

In addition, the combined action of population dynamics and coevolutionary selection should potentially favour a much larger variety of evolutionary pathways compared to populations evolving at constant size. Firstly, changes in population size increase overall stochasticity, making evolutionary trajectories less deterministic. Secondly, changing population size does not only influence the amount of available genetic variation but also modifies the way this variation changes in response to selection (i.e., it affects trait heritabilities) (Roff, 1997, pp. 285–338). Thirdly, bottlenecks can affect the evolution of genetically correlated traits, as previously demonstrated experimentally (Whitlock et al., 2002). Consequently, because of different population dynamics, otherwise identical populations under the same selective pressure can follow distinct evolutionary trajectories.

Taken together, numerous studies highlight that changes in population size induced by host–parasite interactions can have a strong effect on genetic diversity, drift and selection, and, thus, are likely to shape eco-evolutionary feedback. As a consequence, coevolutionary dynamics are not identical under changing and constant population size, potentially making the latter an inaccurate approximation of the natural situation.

5. Future directions in studying host–parasite coevolution

The exact traits, the involved genes, and the underlying selection dynamics represent central topics of particular current interest for our understanding of host–parasite coevolution. Future research at both the theoretical and the empirical/experimental level should address these topics in consideration of temporal variations in population size. It would be of particular value to assess to what extent different types of parasites (e.g., micro- versus macro-parasites) vary in their effects on host population dynamics, as these usually have different population sizes themselves and may thus differ in their ability to respond to an adapting host.

So far, an enormous wealth of theoretical work has been produced on host–parasite coevolution. Several models allow for interaction-induced changes in population size, even though most of these models do not specifically assess their effect on the coevolutionary dynamics. The available models are based on different approaches, including game theory and adaptive dynamics (Lenski and May, 1994; van Baalen, 1998; Dieckmann, 2002; Gandon et al., 2002; Restif and Koella, 2003; Best et al., 2009, 2010; Boots et al., 2014), or they explicitly define the genetic basis of the interaction (e.g., matching alleles or gene-for-gene interaction types) (Frank, 1991, 1993; Gandon et al., 1996; Hochberg and Moller, 2001; Day and Gandon, 2007; Gandon and Day, 2009; Gokhale et al., 2013; Ashby and Gupta, 2014; Song et al., 2015). Different approaches all come with specific advantages for characterizing host–parasite coevolutionary dynamics; however, genetically explicit models are particularly useful because they can capture non-equilibrium population dynamics and thus allow a more straightforward comparison with empirical data (Day and Gandon, 2007; Gandon and Day, 2009). A particular challenge for the future is to assess the relative influence of both interaction-induced population dynamics across time and the resulting stochastic effects on the process of co-adaptation. Such an assessment requires that results are compared from models with and without interaction-induced population size changes and also with and without stochastic processes, especially genetic drift (Parsons et al., 2010; Black and McKane, 2012). To date, such comparisons have only rarely been undertaken. In fact, only few modelling approaches simultaneously take into account both changing population size and stochasticity (Dieckmann and Law, 1996; Dieckmann, 2002; Quigley et al., 2012; Gokhale et al., 2013). One of these studies indeed identified a dramatic effect of these two factors on coevolutionary dynamics (Gokhale et al., 2013). In particular, the combination of stochasticity and changing population size can enhance fast allele fixation (consistent with RSS dynamics), while the same model with constant population size or the deterministic version produces the pattern typical for NFDS. In the former case, the fixation events coincide with antagonist-mediated selection during a population bottleneck, suggesting strong interactions between selection and population size variation (Gokhale et al., 2013). These approaches clearly need to be extended to allow for more complex genetic interaction patterns and/or more realistic population structures.

Similarly, to date there is also only very little empirical data which directly tests the influence of interaction-induced popula-

tion size changes on the coevolutionary process. Ideally, population dynamics should be recorded along with temporal evolutionary or genetic characteristics of the studied populations (Duncan and Little, 2007; Gsell et al., 2013; Auld et al., 2014). Changes in parasite abundance are particularly difficult to measure. Fortunately, novel approaches, such as phylodynamics and skyline plots (Biek et al., 2007; Pybus and Rambaut, 2009; Ho and Shapiro, 2011) can be used to reconstruct population history based on genetic information. Another interesting technique is a combination of sequence 'barcoding' and deep sequencing which has been used to infer the founding population size of *Vibrio cholerae* during the onset of infection (Abel et al., 2015). In fact, the recent advances in NGS-genotyping, bar-coding and related techniques will facilitate the generation of longitudinal data from coevolving host and parasite populations, even though detecting signatures of coevolution from genome sequences is not a trivial task (Tellier et al., 2014; see also Croze et al., 2016). Although difficult to obtain, such type of data would help to elucidate the patterns of population dynamics in coevolving populations and, most importantly, evaluate its effect on evolution of traits and genetic diversity.

The effect of self-governed population dynamics on coevolution can also be assessed through evolution experiments by comparing a treatment where population size is externally controlled with a treatment where population dynamics is determined directly by the interaction. This can be achieved, for example, by using microorganisms evolving in a chemostat, where population and adaptation dynamics are monitored in parallel (Middelboe et al., 2009; Marston et al., 2012). Such an experimental approach has the advantage that confounding influences can be minimized, facilitating inference of cause-effect relationships and, specifically, the exact influence of interaction-dependent demographic changes and associated stochastic effects on the process of coevolution.

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