



Editorial

Host–parasite coevolution—rapid reciprocal adaptation and its genetic basis



1. Introduction

Coevolution between hosts and their parasites (here defined in a broad sense, including viruses, bacteria, fungi) provides fascinating examples of evolutionary adaptation. Host–parasite coevolution is predicted to be dynamic and rapid, mainly because fitness costs caused by parasites are high, parasites are ubiquitous, and they often evolve rapidly due to short generation times, large population sizes and flexible genomes. Studies of host–parasite coevolution can thus provide powerful and versatile models for analysing the causes and processes of evolutionary adaptation more generally.

With the recent availability of new sequencing technologies, it has become possible to study ‘evolution in action’, i.e. the genetic changes underpinning evolutionary processes. This approach is particularly fruitful when complemented with theory-based, novel and hypothesis-driven thinking in conjunction with a deepened knowledge of the phenotypic processes involved. Funding for such an approach was provided through a priority programme of the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) between 2009 and 2015 (SPP 1399 on host–parasite coevolution). The present special issue of ZOOLOGY provides a collection of 18 reviews and research papers written by researchers of this priority programme.

2. Host defences – the role of immunity in host–parasite coevolution

Evolution is driven by changes in the genetic composition of populations. However, selection acts on phenotypes, and, thus, adaptation may also be achieved at the phenotypic level only. Such phenotypic plasticity or flexibility has been well characterised for the immune system, and hence a key trait for a host’s interaction with parasites. A number of articles in the present issue are specifically devoted to the architecture of host immune responses at both genetic and phenotypic levels. They provide impressive examples of the high degree of phenotypic flexibility with which hosts counter-act the enormous genetic versatility of parasites. Even invertebrate hosts show vast immunological plasticity.

In this context, [Yang et al.](#) explore the immune regulatory capabilities of a seemingly simple host, the nematode *Caenorhabditis elegans*, when confronted with gut pathogens. They take advantage of a comprehensive database of more than 1800 published transcriptomic data sets for *C. elegans* and demonstrate that tran-

scription factors containing the GATA motif, and in particular ELT-2, serve as key regulators for these immune responses.

Within-generation plastic immunological regulation could culminate in individualised immune responses, such as the highly specific immune memory in the vertebrate adaptive immune systems. [Milutinović et al.](#) discuss accumulating evidence that not only vertebrates, but also invertebrates possess some kind of immune memory, often denoted as ‘immune priming’ in arthropods. Priming subsumes a large set of potentially very diverse phenomena. Both the phenotypic characteristics and the mechanisms of priming seem to be highly divergent for different host–pathogen combinations and for different routes of infection, which could limit the success of approaches based on candidate genes. More intricate methodologies such as selection for priming ability might prove useful to gain a deeper knowledge of the peculiarities and evolutionary potential of immune priming.

Phenomena of immune priming are also observed within the innate immune system of vertebrates, and in both invertebrates and vertebrates, immune priming has been shown to be transferable to offspring. Particularly interesting are examples where not only the mothers, but also the fathers transfer resistance to offspring. [Beemelmans and Roth](#) report of a unique example, the sex-role reversed pipefish, where offspring are raised within the father’s brood pouch. Using two bacterial species for testing maternal, paternal and bi-parental priming effects on offspring immune gene expression, they show that the effects on offspring are not simply additive, but bacteria-specific. Moreover, maternal and paternal effects differ, with stronger paternal contributions, as expected for this sex-role reversed animal. A particularly interesting question is whether such trans-generational influences might be caused by epigenetic regulation. Indeed, the authors found paternal effects on the expression of genes for histone acetylation/deacetylation.

A review by [Vilcinskas](#) discusses the role of epigenetics for host–parasite coevolution more generally. The author suggests that some of the changes observed in host adaptation might be too rapid for evolution to take place on the genetic level, and could rather be explained by epigenetic adaptations. The different processes involved in epigenetic regulation, such as DNA methylation, histone acetylation/deacetylation and microRNAs, are presented and examples from the author’s research are discussed, where epigenetic modifications were found in the greater wax moth and the red flour beetle upon exposure to fungi and bacteria. Epigenetics

of rapid host–parasite adaptations are clearly an emerging field for future studies.

The diversity of potential immune outcomes indicates that there is obviously strong variation in the way in which individual responses to infection translate into host fitness. Organisms can either resist an infection, clear it upon infection or, alternatively, tolerate low to moderate infection levels. In contrast to classical immunological function, tolerance is only recently coming into the fore of research. Basic concepts are therefore urgently needed, and the distinction between resistance and tolerance clearly is such an approach that is increasingly being used. **Kutzer and Armitage** review the literature on host tolerance, which is the ability of a host to limit the negative fitness effects of a given parasite load, while resistance describes a host's ability to reduce parasite load, e.g. using its immune defence. This distinction is obviously important for studies of host–parasite coevolution, since, in contrast to resistance, tolerance may only have a negligible negative effect on parasite prevalence and is unlikely to lead to selection against common host genotypes on the population level, i.e. we may not expect strong negative frequency-dependent selection (NFDS) when hosts are tolerant. The article points out that important aspects of tolerance still need to be addressed in the future. For example, just as resistance, we can expect that tolerance will also vary for host genotypes and environmental conditions, as well as for different parasite genotypes.

Kurze et al. also make use of the concept of tolerance and transfer it to the colony level in a social insect, the honeybee. They argue that colony level outcomes may differ from the responses of the individuals that constitute the colony. This is because in addition to individual responses, a colony can react with social defences, for example hygiene behaviours such as grooming or killing infected individuals, medication or swarming, leaving infected brood behind. With respect to the colony behaviour, honeybee breeds seem to differ in their defence against *Varroa* mites and *Nosema* microsporidians.

3. Arms races and a running Red Queen – on the genetics of host–parasite coevolution

The in-depth study of host immune responses, and also of parasite counter-adaptations, even in non-model organisms, is clearly a research trend that has an enormous potential to yield insights into the physiological processes governing host–parasite coevolution. Next-generation sequencing (NGS) methods are being used by an increasing number of researchers. A review by **Greenwood et al.** gives an overview of the types of data relevant for host–parasite coevolution studies, the computational approaches that are used to analyse such NGS data, and suggested novel routes to be taken. They highlight the potential and challenges of dual RNA-sequencing of host and parasite and a likely role of non-coding RNA for host–parasite coevolution.

The study by **Haase et al.** makes use of NGS data and compares two transcriptomic or RNAseq data sets that were produced within the priority programme. Stickleback fish were experimentally infected with two different species of helminth parasites, the eye fluke *Diplostomum pseudospathaceum* and the tapeworm *Schistocephalus solidus*. The data showed that the responses to the two parasites differ largely, and that there is only a small core set of genes generally involved in helminth defence. This may not come as a large surprise, as the infection routes and residence organs of the two parasite species are quite different. Host gene expression responses to different genotypes of *D. pseudospathaceum* varied almost as much as those to the two different parasite species, supporting the notion of a very diverse and customised immune system in fish hosts.

Transcriptomic data can provide important insight into responses to infection and point to genes and gene-regulatory networks of potential relevance during host–parasite coevolution. On the population level, neutral markers can inform about the potential evolutionary dynamics of host–parasite coevolution when used to detect specific genotypes. Parasite-driven negative frequency-dependent selection (NFDS) on host genotypes is expected when genotypes carrying rare alleles provide an advantage to the host because parasites have adapted to the most frequent host genotypes. In turn, rare parasite genotypes might have an advantage because hosts have evolved resistance to the common parasite genotypes. **González-Tortuero et al.** tested for such selection against common parasite genotypes in *Caullerya mesnili*, an endoparasite of *Daphnia* water fleas. They found that the most frequent parasite genotypes decreased, while rare genotypes increased in frequency over the course of the study, i.e. four years.

Over longer evolutionary time scales, NFDS and other forms of balancing selection (such as heterozygote advantage) will maintain alleles in the population, while directional selection would lead to the fixation of alleles. Tests for balancing selection on genes in a population can therefore distinguish between the two main models of host–parasite coevolution (trench warfare or Red Queen dynamics based on NFDS vs. arms races based on recurrent selective sweeps) and also point to the kind of genes that are under selection. **Croze et al.** review the literature on balancing selection on immunity genes and then perform a study in *Drosophila melanogaster*. In contrast to vertebrates that show evidence for balancing selection on many immunity genes, they find a relatively low number of candidate genes under balancing selection in their *D. melanogaster* populations, and only one directly related to immunity. While further genes such as those for olfactory receptors might in fact have pleiotropic functions in immunity, the low total number of genes under balancing selection is still puzzling, but might be explained by more frequent fixations of host genes under drift.

In their review, **Papkou et al.** emphasize the relevance of population size for the question whether arms races or Red Queen dynamics prevail in host–parasite coevolution. The strong selection pressure of parasites on hosts and vice versa will often lead to fluctuations in population size, yet the interaction of demographic fluctuations with the dynamics of coevolution are usually ignored. Changes in population size associated with host–parasite coevolution can have strong effects on genetic diversity, drift and selection. The resulting coevolutionary dynamics are thus expected to differ from those under constant population size, potentially favouring recurrent selective sweeps rather than ongoing Red Queen oscillations.

Multiple infections are another, often neglected factor that can strongly influence coevolutionary outcomes. While most theory on host–parasite coevolutionary dynamics deals with single host–single parasite genotype associations, multiple infections are probably widespread in nature. The interaction among the different parasites that infect a host could then range from competition to cooperation. Parasites could compete for host resources or even show spiteful behaviour, but they could also use host resources prudently. **Bose et al.** give an overview of available empirical studies on multiple infections and their virulence in comparison to single infections and conceptualise the various possible outcomes.

The question of who is ahead in the coevolutionary race of hosts and parasites is an interesting one that is mostly answered in favour of the parasite. However, **Joop and Vilcinskis** show that it may depend on the starting situation, in particular when coevolution is staged in the laboratory. In their system of the entomopathogenic fungus *Beauveria bassiana* experimentally coevolving with the greater wax moth *Galleria mellonella* and the red flour beetle *Tribolium castaneum*, the fungus was found to be initially ahead in

Galleria, but the lepidopteran was able to catch up during the experiment, while this was reversed in the beetle, a result that argues for the careful interpretation of such data, since only snapshots in time are usually obtained. *Galleria* also provides a nice example of a coevolutionary interaction that can be traced down to the molecular level: fungal virulence factors, proteinases that enable *Metarhizium anisopliae* to penetrate the insect cuticle and damage the host immune system, are counteracted by means of an insect metalloproteinase inhibitor (IMPI).

Experimental coevolution studies are a powerful tool for analysing coevolution under controlled laboratory conditions. **Strauß et al.** emphasise the need for mathematical models that explicitly take the experimental conditions into account. For example, most epidemiological models assume that parasite transmission follows the mass action principle, which is violated in controlled infection protocols that are often used in experimental coevolution. They therefore design a model that specifically takes into account the experimental conditions of the coevolution studies that were performed within the SPP 1399, with *C. elegans* and *T. castaneum* as hosts, and *B. thuringiensis* as the parasite. With this model, they can reproduce results from the actual coevolution experiments, and also derive further predictions that could be tested in future experiments. A close collaboration of theoreticians with empiricists has the potential to deepen our understanding of the exact processes shaping host–parasite coevolution.

4. Host–parasite coevolution goes wild – insights from field studies

Experimental host–parasite coevolution studies in the laboratory allow us to control ambient conditions and test specific predictions. However, only micro-evolutionary processes can be studied within the time frame of such experiments. Sometimes nature seems to perform experiments for us that encompass longer time periods. For example, in the case of invasive species the invasion history is often known quite well, and separate invasion events may almost resemble repeated experiments. **Feis et al.** focus on the mussel *Mytilus edulis* and compare two invasions of the parasitic copepod *Mytilicola intestinalis*, which reached opposite ends of the Wadden Sea (i.e., Texel and Sylt). Bringing hosts and parasites into the laboratory for experimental cross-infections, they find that mussels from Texel and Sylt seem to vary in their evolutionary response to the invasive parasite: hosts from Texel have evolved resistance, whereas hosts from Sylt have evolved tolerance.

Focusing on different natural populations of sticklebacks and their macroparasites, in particular *D. pseudospathaceum* and *S. solidus*, **Scharsack et al.** review the evidence for local adaptation in these populations and highlight the beauty of the stickleback model: natural populations can be studied in combination with the possibility for controlled laboratory infections. The authors emphasise the possible influence of environmental factors on host–parasite interactions. For example, elevated temperature seems to increase the virulence of *S. solidus*, an effect that has the potential to also influence coevolutionary outcomes.

Such environmental effects on the interaction of parasite and host genotypes bear the potential for the speciation of both parasites and hosts. **Brunner and Eizaguirre** argue that increased parasite virulence or host resistance, due to environmental change,

should accelerate speciation if even slight differences between populations lead to different evolutionary trajectories.

Such differences between populations are likely to exist: **Rahn et al.** present a case study on stickleback macroparasite communities on North Uist, Scotland. They find huge variation in parasite communities on a small geographic scale, which was found to be related to the population genetic differentiation of the host. Most likely, small-scale differences in individual lake characteristics that also influence intermediate host availability shape the parasite distribution on this island.

5. Summary and outlook

The reviews and research papers in the present issue of *ZOOLOGY* highlight the breadth of approaches used, and also needed, to study the causes and consequences of host–parasite coevolution. It becomes evident that often the different organisms with their different characteristics, such as tractability in the laboratory, generation time and availability of ‘-omics’ resources dictate which questions can be addressed. Nevertheless, some generalisations are possible. For example, the genetic underpinnings of coevolution may differ largely for the different systems and time scales that are studied. However, only few examples are currently understood at the molecular level. It is noteworthy that for host–parasite coevolution a rich theoretical body of literature can provide concepts, i.e. predict which evolutionary processes could occur, such as arms races through repeated selective sweeps or Red Queen processes based on NFDS. Nevertheless, the gap between theoretical predictions and empirical support is still huge. In particular, the question which genes are directly involved in coevolutionary adaptation is still open in almost all cases. Second, except for some experimental coevolution systems, the dynamic nature (i.e., arms race or frequency-dependent selection) is still elusive. NGS approaches on experimental coevolution studies clearly provide resources that can be exploited further to shed light on the genetic basis of coevolution, but even with such rich data it remains a challenge to identify the loci that are actually coevolving. The emerging role of epigenetic processes will not simplify this task. On the other hand, population genetic methods can help to infer which loci show an evolutionary history of selection. Combining these approaches might yield a promising research avenue for the future.

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