Trends in Parasitology

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Opinion

Host-Manipulation by Trophically Transmitted Parasites: The Switcher-Paradigm

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Host-manipulation by trophically transmitted parasites is thought to always predispose the intermediate hosts to enhanced predation by definitive hosts ('enhancement'). However, theory predicts that enhancement can disrupt stable, bottom-heavy predator–prey ratios, leading to fluctuation-driven extinction of intermediate hosts and parasites. How then can enhancement persist in nature despite this apparent instability? We address this paradox and conceptualize the 'switcher-paradigm', a novel framework incorporating sequential phases of reduced predation ('suppression') followed by enhancement. Theoretical models within the framework that consider 'switching' from suppression to enhancement indicate that switching likely increases parasite persistence and, in some circumstances, cancels out the effects of strong enhancement, leading to bottom-heavy predator–prey ratios. The switcher-paradigm confronts interdisciplinary research challenges, linking ecological processes across scales from within-host to community-wide dynamics.

Highlights

Monotonic predation enhancement induced by trophically transmitted parasites can impair persistence of both hosts and parasites.

Host-manipulating parasites might commonly successively exhibit predation suppression followed by enhancement with maturation.

A novel framework to fully capture varying degrees of host-manipulation strategies is proposed.

Paradox of Host-Manipulation by Parasites in Trophic Dynamics

Parasites that induce phenotypic changes in their hosts (e.g., in morphology and behaviors) complete their life cycles via **trophic transmission** (see Glossary), which often involves increased predation of the intermediate hosts by definitive hosts (i.e., **enhancement**) [1–7]. This process has attracted broad interest in biology. Historically, the majority of research into host-manipulation by parasites has focused on understanding the proximate and ultimate causes of enhancement [8], but, more recently, interest in understanding the trophic consequences of enhancement has grown [1,9–12]. Trophically transmitted parasites exhibiting enhancement ('enhancer-parasites') can make up a large proportion of the parasites in food webs [13–16]. Also, the prevalence of enhancer-parasites in intermediate hosts (i.e., the proportion of intermediate host individuals infected supposedly by enhancer-parasites) is relatively high, for example, 33% in acanthocephalan [17], 44.9% in microsporidia [18], 35.1% in nematodes [19], and 33% in protozoans [20], albeit with a substantial variation in prevalence within and between parasite taxa. Collectively, enhancement can alter predator–prey interactions via profound energy-flow pathways across food webs [21–23], thereby shaping community structure and ecosystem processes [6,24–26].

In direct contrast to the evidence for the prevalence of enhancer-parasites in natural systems, theoretical work suggests that enhancer-parasites are unlikely to persist [10,27]. This is because strong enhancement, along with a relatively high abundance of infected intermediate hosts, cannot only help parasites spread within host populations [27] but also cause a top-heavy predator–prey biomass ratio (i.e., a proportion of definitive compared to intermediate hosts), which is vulnerable to fluctuation-driven extinction of intermediate hosts and parasites [1]. Combining trophic and epidemiological dynamics, Fenton and Rands [10] predicted that extensive enhancement would destabilize predator–prey dynamics and lead to parasite extinction. Thus, researchers are faced with a

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paradox: how can we reconcile the ample evidence for strong enhancement in empirical studies with the theoretical prediction that enhancer-parasites should be uncommon in ecological systems?

Host-Manipulation Varies with Time: Cryptic but Common?

The current view of host-manipulation by trophically transmitted parasites largely rests upon the *a priori* idea that it always shows enhancement (but see [28–30]). Based on this working hypothesis, empirical studies have often quantified enhancement at a given timepoint, and theory has assumed that enhancement is constant across the duration of infection [1,9,10]. However, this is not always the case. Several empirical studies have shown that some parasites switch from **suppression**, during the noninfective phase, to enhancement upon maturation in the infectivity to definitive hosts (we refer to these parasites as '**switcher**-parasites', Figure 1A, Table 1). Such parasites' strategy, namely **switching** (i.e., imposing suppression when immature but enhancement upon maturation), has been recently reported in empirical studies (reviewed in [31]). For example, Dianne and colleagues [32] experimentally showed that acanthocephalan parasites (*Pomphorhynchus laevis*) suppress the activity of their amphipod intermediate hosts (*Gammarus pulex*) and reduce the predation by fish (definitive host), until *P. laevis* reaches maturation (Figure 1B; see [33] for review).

Typically, suppression is less obvious than enhancement and, thus, has been poorly recognized until recently (see Table 1 for the summary of empirical evidence for switcher-parasites). In agreement with the empirical evidence, a seminal, theoretical study by Parker *et al.* [28] has shown that (i) enhancement is likely favored whenever it increases transmission success to make up for any of its associated costs with increased mortality of intermediate hosts and parasites, and (ii) suppression can increase the survival of intermediate hosts and parasites until maturation. Parker *et al.* [28] omitted explicit dynamics of trophic interactions between intermediate and definitive hosts; in context of resulting predator–prey dynamics, however, enhancer-parasites should be rare because they can disrupt stable prey–predator ratios, suggesting that considering trophic dynamics (i.e., ecoevolutionary dynamics) be needed to better understand the evolution of switchers [10]. Finally, more recent theory [34] suggests that switching can lead to higher parasite persistence. Hence, considering the trophic dynamics underpinning enhancement-suppression behavior is a crucial prerequisite to understanding the evolution of switchers.

The Switcher-Paradigm

A General Framework beyond the Enhancer-Biased View

In this paper we conceptualize the role of switcher-parasites in trophic dynamics, that is, how the successive phases of differential predation pressure on intermediate hosts affect the community-wide consequences of parasite persistence and predator–prey ratios. To illustrate this, we propose a general framework for incorporating the varying degrees of suppression and enhancement into trophic dynamics (referred to as the 'switcher-paradigm'; Box 1),

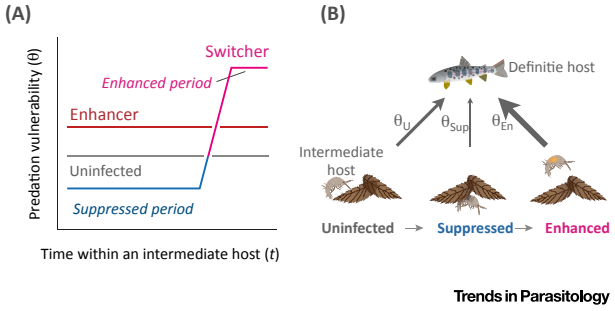

Figure 1. Schematic Diagrams of Switchers and Enhancers. (A) Predation vulnerability (θ) of intermediate hosts infected by enhancer and switcher-parasites, and uninfected intermediate hosts. (B) Temporal changes in prey–predator interaction between intermediate and definitive host with a switcher-parasite. Amphipod-Fish-Acanthocephalan parasite was used as a model system [31]. Gray and orange ovals inside the intermediate hosts are parasites that are uninfective and infective to the definitive hosts, respectively.

Glossary

Basic reproductive number: the average number of secondary infections produced by a parasite in a nonparasitized population, calculated as the leading eigenvalue of the linearized community dynamics around nonparasitized equilibrium.
Enhancement: host-manipulation by parasites that increases the predation vulnerability of intermediate hosts to definitive hosts.
Extended phenotype: a phenotype of an organism that is physically apart from the actual expression of the phenotype.
Noise predation: predation on intermediate hosts by non-host species, particularly through the exploitation of enhanced phenotype of the intermediate hosts.
Suppression: host-manipulation by parasites that decreases the vulnerability of intermediate hosts to their potential predators (including definitive hosts).
Switcher: manipulative parasites that first express suppression (before maturation) and then switch to enhancement following reproductive and/or developmental maturation.
Switching: successive stages of manipulation of hosts phenotypes, such that parasites first exhibit suppression and then enhancement.
Trophic transmission: parasite transmission from prey (intermediate hosts) to predators (definitive hosts).

Table 1. Examples of Manipulative Parasites Adopting Temporal Assortments of Manipulation Strategies

Parasite	Host	Manipulation strategy	Details	Refs
Acanthocephala				
Polymorphus paradoxus	*Gammarus lacustris* (Amphipoda)	Temporal enhancement	Predation enhancement is switched only after the parasites become infective to their definitive hosts.	[69]
Pomphorhynchus laevis	*Gammarus pulex* (Amphipoda)	Switcher[a]	Gammarids parasitized by noninfective stage of the parasite hid more under refuges than did uninfected ones, which resulted in less predation by trout. When the parasite reached the infective stage to its final host, it enhanced vulnerability of its gammarid host to predation.	[32]
Pomphorhynchus laevis	*Gammarus pulex* (Amphipoda)	Switcher	Gammarids parasitized by noninfective stage of the parasites showed an increase in refuge use and reduction in activity and food intake, irrespective of predator presence and food availability.	[70]
Polymorphus minutus	*Gammarus pulex* (Amphipoda)	Switcher[a]	Noninfective stage of the parasite induced a stronger positive geotaxis, which presumably results in protecting the amphipod hosts from bird predation. Once the parasites have become infective, the parasites induced a negative geotaxis, which predisposes the hosts to predation by birds, the definitive hosts.	[71]
Aconoidasida, malarial parasite				
Plasmodium yoelli	*Anopheles stephensi* (Diptera, vector mosquito)	Switcher	Female mosquitoes infected with malarial parasites rarely bite humans during the parasites' noninfective stage (oocyst stage), but frequently do when the parasites reach the infective stage (sporozoite stage).	[72]
Plasmodium gallinaceum	*Aedes aegypti* (Diptera, vector mosquito)	Switcher		[73]
Cestoda				
Schistocephalus solidus	*Gasterosteus aculeatus* (Gasterosteiformes, Stickleback)	Temporal enhancement	Predation enhancement is switched on only after the parasites become infective to their definitive hosts.	[69]
Schistocephalus solidus	*Macrocyclops albidus* (Copepoda)	Switcher	Copepods harbouring noninfective cestodes were less frequently predated by stickleback predators than were uninfected copepods. The strength of predation suppression was similar in cestodes and nematodes (see below for the same reference), suggesting the potential evidence of convergent evolution.	[74]
Nematoda				
Camallanus lacustris	*Macrocyclops albidus* (Copepoda)	Swicher	Copepods harboring noninfective nematodes were less frequently predated by stickleback predators than were uninfected copepods.	[74]
Trematoda				
Microphallus sp.	*Potamopyrgus antippodarum* (Gastropoda, Freshwater snail)	Switcher	Snails infected by noninfective trematoda larvae stay under rocks (supposedly showing supression), whereas snails infected by infective larvae forage more on the rock during the foraging period of their definitive hosts (waterfowl).	[75]
Diplostomum pseudospathaceum	*Oncorhynchus mykiss* (Salmoniformes, Rainbow trout)	Switcher	Young-of-the-year rainbow trout harbouring a moderate number of noninfective meatacercariae were significantly less captured by the dip-net catch (simulated predation) and less active in terms of the horizontal movement.	[69]

[a]A full factorial design was not used to evaluate the manipulation effects; that is, infection status (infected vs. uninfected) × parasite-stage (noninfective vs. infective to the definitive hosts).

Box 1. Theoretical Framework

We model the dynamics of trophically transmitting parasites using ordinary differential equations (ODEs; Figure I). The dynamical system involves definitive hosts (DHs), intermediate hosts (IHs), and environmental parasite-pool (E; Figure I), with (i) D_P: the density of parasitized DH; (ii) D_U: the density of unparasitized DH; (iii) I_U: the density of unparasitized IH; (iv) I_{Sup}: the density of suppressed, infected IH (suppressed IH); (v) I_{En}: the density of enhanced, infected IH (enhanced IH); and (vi) E: the parasite-density in environmental parasite-pool. A remarkable feature is that the infected, intermediate hosts are either suppressed or enhanced by parasites. The transience from I_{Sup} to I_{En} occurs at a constant rate k (**Equation I**), and thus $\frac{1}{k} = T_{Sup}$ represents the average suppression period.

ODE then reads (Figure I; Equation I):

$$\frac{dD_U}{dt} = r_{DH}(1 - q_{DH}\cdot(D_U + D_P))\cdot(D_U + D_P) - d_{DH}D_U - \beta_{DH}\alpha D_U\theta_{En}I_{En} + e\alpha D_U\cdot\left(\theta_{Sup}I_{Sup} + \theta_U I_U\right) + e\alpha D_P\cdot\left(\theta_{Sup}I_{Sup} + \theta_{En}I_{En} + \theta_U I_U\right) \quad [I]$$

$$\frac{dD_P}{dt} = \beta_{DH}\alpha D_U\theta_{En}I_{En} - (d_{DH} + v_{DH})D_P$$

$$\frac{dI_U}{dt} = r_{IH}\left(\sigma_U I_U + \sigma_{Sup}I_{Sup} + \sigma_{En}I_{En}\right)\cdot\left(1 - q_{IH}\left(I_U + I_{Sup} + I_{En}\right)\right) - \alpha\cdot(D_U + D_P)\cdot\theta_U I_U - \beta_{IH}I_U E$$

$$\frac{dI_{Sup}}{dt} = \beta_{IH}I_U E - \alpha(D_U + D_P)\theta_{Sup}I_{Sup} - \left(d_{IH} + v_{Sup} + k\right)\cdot I_{Sup}$$

$$\frac{dI_{En}}{dt} = kI_{Sup} - \alpha(D_U + D_P)\theta_{En}I_{En} - (d_{IH} + v_{En})I_{En}$$

$$\frac{dE}{dt} = \lambda D_P - d_E E$$

where: reproduction (σs), predation vulnerability (θs), and disease-induced mortality (vs) differ among I_U, I_{Sup}, I_{En}. Here, rs are growth rate, qs are density-dependent regulation, ds are death rate, βs are transmission rate, e is conversion rate, α is the basic predation rate, and λ is production of parasite propagules from parasitized, definitive hosts.

The model (Equation I) covers a wide range of ecological situations. For instance, assuming that the transience from suppressed to enhanced occurs fast (taking $\frac{1}{k} \to 0$) corresponds to the dynamics of enhancer-parasites (without a suppression stage). Also, setting $r_{DH} = 0$ represents the situation in which DH is a specialist predator on IH, as is usually assumed in previous theory [10,34].

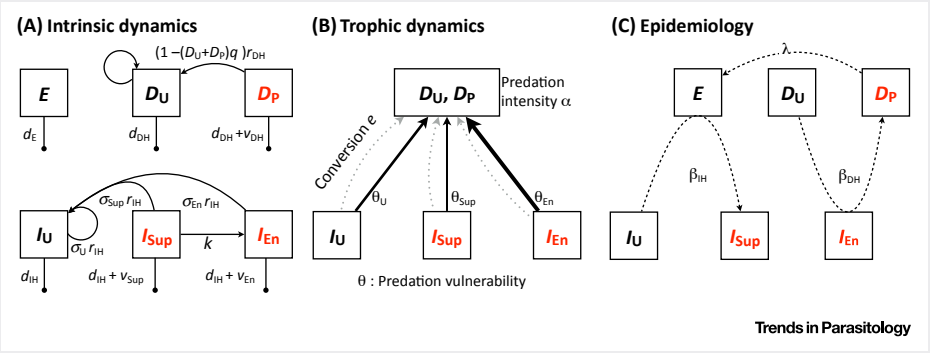

Figure I. Model Structure.

generalizing the previous theoretical models [34] (note, however, that de Vries and van Langevelde [34] assumed that definitive hosts are specialized to intermediate host species, which can consequently evoke classic, predator–prey oscillations). A key feature of this framework is that it allows one to examine the conditions for which strong suppression may allow parasites to express extensive enhancement in succeeding life cycle stages. Also, within the framework, one can examine the possibility of parasite persistence (with the basic

reproductive number, R_0) and the stability of hosts' population dynamics, thereby resolving the paradox for the persistence of enhancer-parasites with strong enhancement in nature despite the apparent instability in trophic context [10].

In addition, the present paradigm can offer a benchmark to investigate the trophic consequences (persistence, steady-state abundance of parasites and hosts, and predator–prey ratios) of diverse host-manipulation strategies, from pure enhancement to prolific switching. For instance, the framework allows for further extensions to include more realistic complexity in parasite life cycles and/or evolutionary dynamics of switchers [24] (in particular under explicit trophic interactions [10]).

Switchers Are Adaptive

Dawkins included manipulated host behavior as one component of the **extended phenotypes** of a manipulative parasite [35]. In particular, suppression might simultaneously magnify opportunities for trophic transmission for the parasite, while also bringing about evolutionary benefits for the intermediate host. For example, suppression could modify hosts' habitat selection (reviewed in [36]), which could potentially result in higher reproductive success of infected hosts (while suffering successive exploitation by parasites). Consequently, there would then be fewer conflicts of interest between hosts and parasites. This coadaptive view of hosts aiding manipulation has been overlooked so far (but see [4,37]).

Predictions of the Trophic Consequences of Enhancer and Switcher-Parasites

We can assess the impacts of switcher- and enhancer-parasites (Boxes 1 and 2). A key prediction is that the sequential phases of suppression and enhancement allow parasites to achieve more efficient trophic transmission, largely due to strong enhancement being imposed at later time points. Specifically, suppression reduces predation pressure such that it may

Box 2. Basic Model Output

By nullifying the right hand sides on **Equation I**, we can obtain the equilibrium values and thus possible ecological regimes. We found that two regimes can exclusively occur:

- **Parasite-free regime(PFR):** $D_U^{(0)} > 0, I_U^{(0)} > 0, D_P = I_{Sup} = I_{En} = E = 0$;
- **Stable coexistence regime (SCR)**: $D_U > 0$, $I_U > 0$, $D_P > 0$, $I_{Sup} > 0$, $I_{En} > 0$, $E > 0$;

where R_0 represents the **basic reproductive number** of parasites, accounting for a measure for parasites persistence.

Applying the next-generation theorem in epidemiology [67,68], we obtain the basic reproductive number (**Equation II**):

$$R_0 = \frac{\lambda}{d_E} \cdot \left(\frac{\alpha \beta_{DH} D_U^{(0)} \theta_{En}}{d_{DH} + v_{DH}} \right) \cdot \left(\frac{\beta_{IH} I_U^{(0)}}{\alpha D_U^{(0)} \theta_{Sup} + k + d_{IH} + v_{Sup}} \right) \cdot \left(\frac{k}{\alpha D_U^{(0)} \theta_{En} + d_{IH} + v_{En}} \right) \quad [II]$$

where, at PFR, the density of unparasitized definitive or intermediate hosts is given by Equation III:

$$D_U^{(0)} = \frac{q_{IH} r_{IH} (r_{DH} - d_{DH}) + e\alpha\theta_U (r_{IH} - d_{IH})}{r_{DH} r_{IH} q_{DH} q_{IH} + e\alpha^2 \theta_U^2}$$
$$I_U^{(0)} = \frac{q_{DH} r_{DH} (r_{IH} - d_{IH}) - \alpha\theta_U (r_{DH} - d_{DH})}{r_{DH} r_{IH} q_{DH} q_{IH} + e\alpha^2 \theta_U^2} \quad [III]$$

See the Appendix in the supplemental information online. If $R_0 > 1$, the dynamics leads to SCR; otherwise, PFR is attained. Equation II tells us that parasite persistence becomes more likely with a stronger θ_{En} by promoting trophic transmission (Figure IA) and with a stronger suppression (i.e., smaller θ_{Sup}; Figure IB). In particular, a longer period of suppression (or a larger $1/k$) makes the persistence less likely (Figure IB).

Numerical investigation reveals that the total density of the intermediate hosts at SCR can increase with weaker enhancement and with stronger suppression (Figure IC; but note that this is not a monotonic trend). Finally, the predator–prey ratio skewed heavily either towards predator (top-heavy) or prey (bottom-heavy; Figure ID), depending on the assortments of the predation suppression and enhancement Hence, switcher-parasites dramatically modify the trophic structure by directly increasing the abundance of the intermediate hosts.

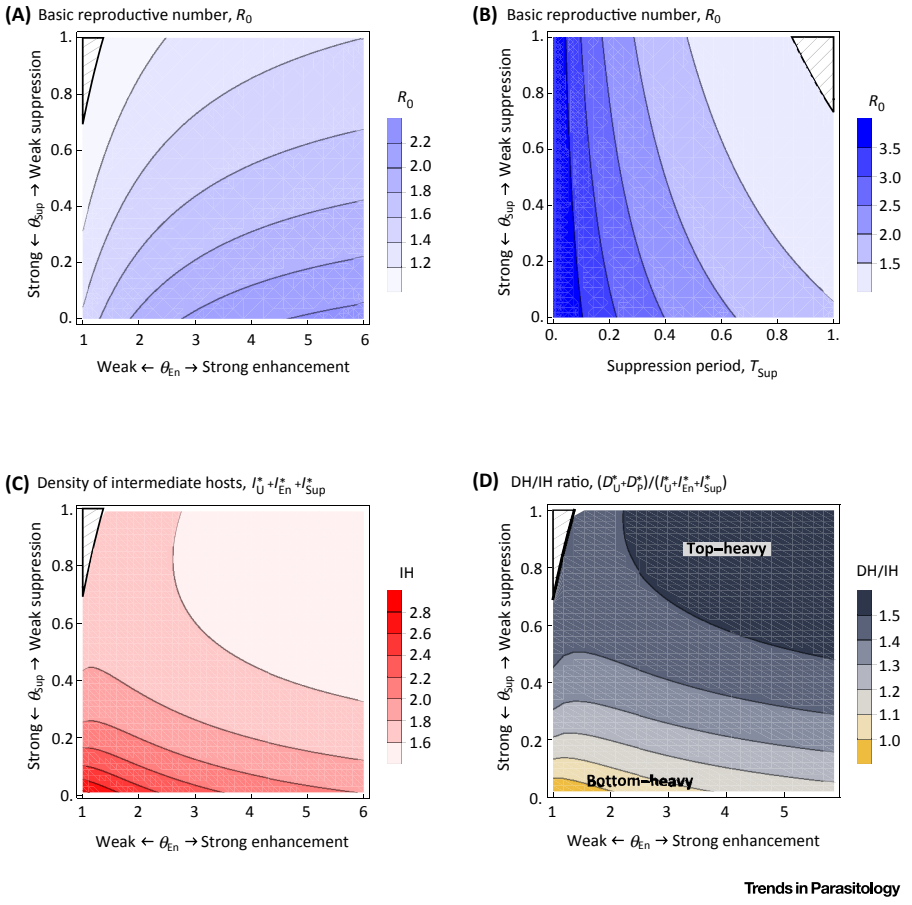

Figure I. Steady-State Outcomes of the Model. IHs: intermediate hosts; DHs: definitive hosts. The hatched region represents PFR (parasite-free regime); that is, $R_0 < 1$. Model parameter values are shown in the Appendix in the supplemental information online.

cancel out the effect of enhancement, even when enhancement is strong, therefore resolving the paradox of the prevalence of enhancer-parasites in nature (Figure I in Box 2). Note that the outcomes of the present models quantitatively differ from those in de Vries and van Langevelde [34]. This discrepancy could be partially attributed to their presumption that definitive hosts are specialized to intermediate hosts with the resulting predator–prey oscillations.

In addition, the present paradigm allows predictions of how a variety of host-manipulation strategies affect parasite persistence and hosts' abundance (Figure I in Box 2, A–D). In contrast to the previous theory [1,10], a striking implication of our work is that even weak suppression can result in a bottom-heavy predator–prey biomass ratio (i.e., a greater proportion of intermediate compared to definitive hosts; Figure I in Box 2, C). Collectively, our theoretical findings suggest that switcher-parasites may play an important role in community composition and support the empirical evidence for switcher-parasites (Table 1).

Within the present theoretical framework there are several unresolved issues that should be addressed to better understand long-term dynamics of host–parasite systems. For example, successive suppression and enhancement, manipulation costs, parasite prevalence with

seasonally limited epidemiology, and community context (e.g., coinfection and noise predation) would largely affect model predictions, but there are scarce empirical data to parameterize those variables. Empirical studies relevant to those variables will be necessary to move the field beyond a loose assemblage of case studies and lay a groundwork for comprehensive understanding of the cause and consequences of host-manipulation in nature. Below, we provide a number of suggestions for future studies stemming from the switcher-paradigm.

Finding Switchers with Dynamic Mechanisms

Biological assays

Quantitative tools

First, the evolution of switching will require that parasites possess recognition mechanisms for the transition from suppression to enhancement (Figure 2A). Recent studies have been increasingly focused on the physiological [38] and molecular [11] mechanisms of enhancement [39,40]. Also, Adamo [38] provided a systematic review on the (i) psycho-neuroimmunological, (ii) neuro-pharmacological, and (iii) genomic- and proteomic-based pathways to host-manipulation. For instance, studies have shown that serotonin production in gammarids is a phylogenetically common trait among manipulative parasites [41,42], suggesting that neurochemical costs might be inexpensive (see also [24]). Also, some parasites can upregulate the expression of activity-related genes of the hosts, including proteins and neurotransmitters in the hosts' brain during enhancement [40,43–46]. It would be informative to test whether they can also downregulate the expression of these same molecules encoding suppression. Knowledge of the mechanisms underlying these processes will shed light on the relative strengths of suppression and enhancement for switchers. For instance, if resource limitation affects the degree of suppression and enhancement (e.g., if producing neurotransmitter is costly; [43,44]), stronger suppression might then lead to weaker enhancement (or vice versa), thus posing a life-history trade-off. By contrast, if suppression and enhancement share common mechanisms, then the evolutionary shift from enhancer to switcher would be highly likely. Therefore, developing biological assays for quantifying the suppression and/or enhancement across the taxa of manipulative parasites would be crucial. Trematode and acanthocephalan parasites (which show strong enhancement) would offer excellent model systems.

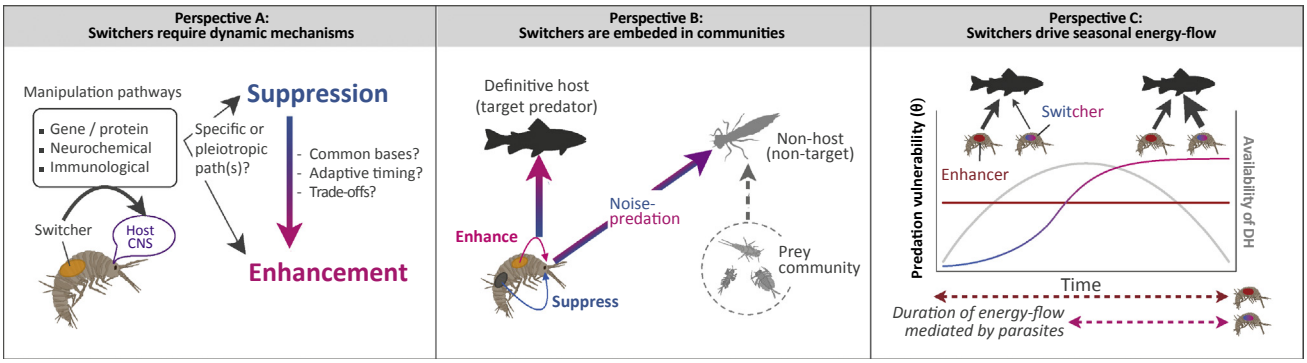

Figure 2. Three Perspectives on Host-Manipulation Studies across Scales. Perspective A: identification of mechanistic bases of switchers entails interdisciplinary approach. Perspective B: switchers can have wide consequences for communities, from within-hosts to food webs (ovals with different colors represent different parasite individuals being subjected to intra- or interspecific conflicts over host-manipulation timing). Perspective C: switchers can modulate temporal attributes (e.g., magnitude, peak timing, and duration) of energy flow within or across ecosystems. Red line and a line with blue and pink gradation represent the expected seasonal changes in predation vulnerability (θ) of intermediate hosts to definitive hosts that mediate seasonal energy flow. The effects of switchers on the energy flow should be regulated by seasonal epidemiology, for example, availability of definitive hosts, DHs (i.e., gray line).

Switcher-parasites can cause strong heterogeneity in the exposure of intermediate hosts to predators due to changing manipulative behavior. In practice, however, the effects of individual heterogeneity are difficult to assess. To overcome this issue, recent advances in quantitative tools can help to define critical parameters in ecological and evolutionary dynamics. For instance, Briggs *et al.* [47] developed quantitative models for amphibian chytrid fungus (*Batrachochytrium dendrobatidis*; Bd) and showed that epidemic and endemic host–pathogen dynamics likely explain amphibian decline. Also, more recently, integral projection models of host–parasite dynamics that account for within-host temporal changes in infective stages and disease progression have proven useful [48–51], allowing for parameterization of complex factors of disease dynamics. Finally, individual-based simulations are now well used in evolutionary ecology [52]; they can incorporate realistic and complex disease dynamics (see [53] for the practical, statistical analysis of stochastic simulations in general). Combining these quantitative tools for the complex life cycles of switchers offers a promising research opportunity to understand the mechanistic causes and community-wide consequences of switcher-parasites.

Switchers Embed Themselves into Complex Communities

Multiple Predators and Prey

Enhancement might promote predation by nontarget predators via **noise predation** (reviewed in [54]; Figure 2B), a controversial concept discussed in the literature [55–57]. As was previously examined both empirically [56] and theoretically [57], the total benefit of enhancement can overcome the costs associated with noise predation. Based on the switcher-paradigm, it would be interesting to set up experimental communities involving switcher-parasites, definitive hosts, and nontarget predators to investigate if suppression can protect intermediate hosts from both types of predators (definitive host and non-host predators; reviewed in [58]). Being validated, this hypothesis would suggest that switcher-parasites might pay lower costs of suppression by reducing noise predation.

Also, although we introduced a minimal number of species into the food web to reduce complexity in the theoretical model (Box 1), incorporating multiple predators (one definitive host with a non-host) as well as non-host prey could yield unexpected outcomes. For instance, switchers can provoke the functional responses of other predators, thereby modifying the predation intensity upon other prey species at the same trophic level as the intermediate hosts. Recent food web studies have shown that manipulative parasites are often found in community modules of tightly linked species [14], suggesting that shifts in predator functional responses caused by host-manipulation may have widespread consequences for entire food webs. Furthermore, our theory can help to predict the trophic consequences of varying degrees of suppression and enhancement under a variety of ecological situations. Therefore, it is interesting to consider what types of host-manipulation strategies should be found at certain locations within food webs. To address this issue, further theoretical and experimental studies are required to assess the impacts of switchers on complex, multi-trophic dynamics.

Coinfection

At microscales, it is challenging to take into account the interactions among parasites within a host that determine the temporal attributes (i.e., magnitude, direction, and timing) of suppression and enhancement (reviewed in [4,59]; Figure 2B). For instance, the enhancement mediated by trematode metacercaria in the brain of killifish increases with their infection intensity [60]. On the other hand, acanthocephalans at different developmental stages in their intermediate hosts (Gammarid) would be exposed to the conflicts over their transmission timing to the definitive host [61]. Similar interactions can also occur with heterospecifics; for instance,

experimental studies [62–65] using copepods (*Macrocyclops albidus*) as an intermediate host species showed that cestodes (*Schistocephalus solidus*) can reduce the enhancement manipulated by co-occurring heterospecific parasites (nematode; *Camallanus lacustris*). Taken together, these studies suggest that some parasites are capable of facultatively expressing suppression, as well as enhancement. Priority effects, where first-arrived parasites dominate the manipulation over second-arrived parasites, also likely play a role. Therefore, exploring the mechanisms behind whether the parasites modulate or 'sabotage' the manipulation can offer an excellent opportunity for studying the proximate causes of switching. Along with these proximate mechanisms, identifying reasonable parameters to predict the dynamic consequences of coinfection would be intriguing and pose new research questions.

Switchers Can Drive Seasonal Trophic Flows

In general, temporal attributes (magnitude, duration, and timing) of resource pulse can have dramatic impacts on various scales of evolutionary and ecological dynamics [66]. If prevalent in a given ecosystem, switcher-parasites could temporally modulate abundances of intermediate hosts in the system, thereby impacting predator–prey dynamics between intermediate and definitive hosts (Figure 2C). To assess this possibility, researchers will need to understand the strength of predator–prey interactions across a parasite's life history, as temporal changes in manipulation will determine the magnitude, duration, and timing of prey availability to the predator. The impact of switchers or enhancers on trophic dynamics will heavily depend on the role of seasonality in the epidemics; specifically, if opportunities for infection and transmission are seasonally limited (e.g., definitive hosts might be absent in some seasons), then the schedule of switching from suppression to enhancement could synchronize with seasonal infection opportunity, which can result in accelerating temporal dynamics of predator–prey interaction. In contrast, if the duration of epidemiological events is constant, then the effects of switching might be averaged out over time, and their impacts on predator–prey dynamics would not differ significantly with those caused by enhancers. Finally, the schedule of switching might completely synchronize among intermediate hosts; in such a scenario, resulting predator–prey oscillations can differ quantitatively from the previous theory (including [10,34]). Thus, the incorporation of seasonal epidemiology into trophic theory, potentially in combination with the multitrophic dynamics mentioned above, represents a promising new avenue for understanding quantitative differences in the impact of switcher versus enhancer-parasites on trophic dynamics in seasonally changing environments (Figure 2C).

Concluding Remarks

Classically, host-manipulation studies have strived to identify 'adaptive' host-manipulation strategies, mainly enhancement for effective trophic transmission. In part due to the rapid advances in molecular biology, increasing numbers of studies have begun to reveal proximate and/or ultimate mechanisms of enhancement across diverse host–parasite systems, such as those involving acanthocepelans, trematodes or *Toxoplasma* [11]. The trophic theory we proposed predicts that the enhancement can be more efficient when coupled with the seemingly contradictory strategy of suppression, resolving a paradox of frequent strong enhancements observed in nature. We hope that this opinion will inspire new research avenues for elucidating the optimal schedule of suppression and enhancement, and the trophic consequences of such switching strategies in natural ecosystems. To this end, progressing techniques in molecular biology will greatly help to carry out quantitative and more mechanistic investigations of host-manipulation by parasites (see Figure 2 and Outstanding Questions). By integrating ideas and techniques across disciplines, we hope to get closer to comprehensive understanding of host-manipulation, one of the most fascinating life history strategies in nature.

Outstanding Questions

Can we quantitatively define enhancer and switcher?

How can we quantify the relative strength and timing of suppression and enhancement (Figure 2A)?

Do suppression and enhancement share common bases or require independent pathways, thereby being subject to trade-offs (Figure 2A)?

Do matured, first-arrived parasites dominate over immature, secondarily-arrived parasites (Figure 2B)?

Do switchers escape noise predation more successfully than enhancers (e.g., by temporal assortments of enhancement or temporal synchronization with definitive host availability; Figure 2B)?

Do switchers indirectly modify other prey–predator interactions (e.g., by functional responses of target and/or nontarget predators) and thus trophic cascade (Figure 2B)?

Do switchers alter the temporal feature of energy flow more intensively than enhancers (Figure 2C)?

When seasonality limits the transmission opportunity (e.g., availability of DH), do switchers then synchronize the timing of switching and subsequently enhance temporal energy flow (Figure 2C)?

Does the effect of enhancers and switchers on temporal energy flow depend on the seasonality in epidemiology (Figure 2C)?

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Supplemental Information

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