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Making (good) use of *Wolbachia*: what the models say

Fabrice Vavre and Sylvain Charlat

Wolbachia, probably the most common animal endosymbiont, infects a wide range of arthropods as well as filarial nematodes. Generally vertically transmitted from mothers to offspring, it has evolved various strategies, ranging from brutal male-killing to mutualism, which facilitate invasion and persistence of the infections within host populations. Current interest in *Wolbachia* as a potential control agent against harmful nematodes and arthropods makes it important to be able to predict *Wolbachia* epidemiology and evolutionary trajectory. Here we highlight recent theoretical developments and suggest future modelling and empirical directions for basic and applied research in this domain.

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Introduction

Wolbachia bacteria form a diverse clade of obligate intracellular Rickettsiales, hosted by a wide range of nematodes and arthropods, with incidence estimates reaching 70% in insects [1]. While generally vertically transmitted from mothers to offspring, this symbiont regularly captures new hosts through horizontal transmission [2]. *Wolbachia* is best known for manipulating its hosts' reproduction through various effects including male-killing, feminization of genetic males, parthenogenesis induction (PI) and cytoplasmic incompatibility (CI), which leads in its simplest form to sterility in crosses between uninfected females and infected males [3]. All these effects endow the symbiont with invasive dynamics, possibly extremely rapid, but also potentially generates conflicts with the host nuclear genes [4••]. In some cases *Wolbachia* has evolved mutualistic relationships with its hosts, notably in filarial nematodes, but also a few insect species [3]. Recent findings also demonstrate that *Wolbachia* can confer resistance to its host enemies such as RNA viruses, bacteria, fungi and protozoans [5]. These various properties make *Wolbachia* a potentially powerful control agent against pest, pathogen and pathogen-vector species [6]. One method of population suppression, analogous to the Sterile Insect Technique, simply relies on the mass release of CI-*Wolbachia* infected males to reduce population size (e.g. [7]). Other stratagems necessitate the stable introduction of *Wolbachia* in previously uninfected populations to limit host competence for onward transmission of pathogens [8•]. The short and long-term success of such inoculative programs requires control of the initial invasion process and predictions on the evolution of the newly created *Wolbachia*-host associations. Here we summarize recent developments in this field, where the practical needs of applied programs are boosting the theoretical understanding of *Wolbachia* epidemiology and evolution.

Wolbachia spread across time and space

Theoretical models on the epidemiology of *Wolbachia* in host populations date back to the very birth of the *Wolbachia* research field (reviewed in [4••]). Recent developments have been largely motivated by the possibility of utilizing CI to spread useful *Wolbachia* strains into populations where they were initially absent, with two main strategies envisioned. The first relies on the introduction of life-shortening *Wolbachia* into vector populations, which could modify the age structure of the host. Because onward transmission of pathogens occurs through old females, reduction in longevity can reduce the effective transmission of pathogens such as Dengue virus in *Aedes aegypti* [9]; this method engenders only mild selection for host resistance, making it potentially long lived in the field [10•]. The second strategy builds upon the ability of *Wolbachia* to reduce pathogen load in arthropod vectors and onward transmission to vertebrate hosts, demonstrated in natural [11,12•,13] as well as newly created associations [14,15].

In both cases, the success of the method critically depends on the local spread and spatial diffusion of the infection from initially low infection frequency at points of release. Epidemiological modelling provides a principled means to guide the insect release methodology. The *Wolbachia* in these cases drives into populations through its CI phenotype: *Wolbachia* induces embryonic mortality in crosses between infected males and uninfected females so that infected females, on average, produce more offspring. This benefit to infected females is stronger when most uninfected females mate with infected males, that is to say when infection is prevalent. Such positive frequency-dependent selection generates

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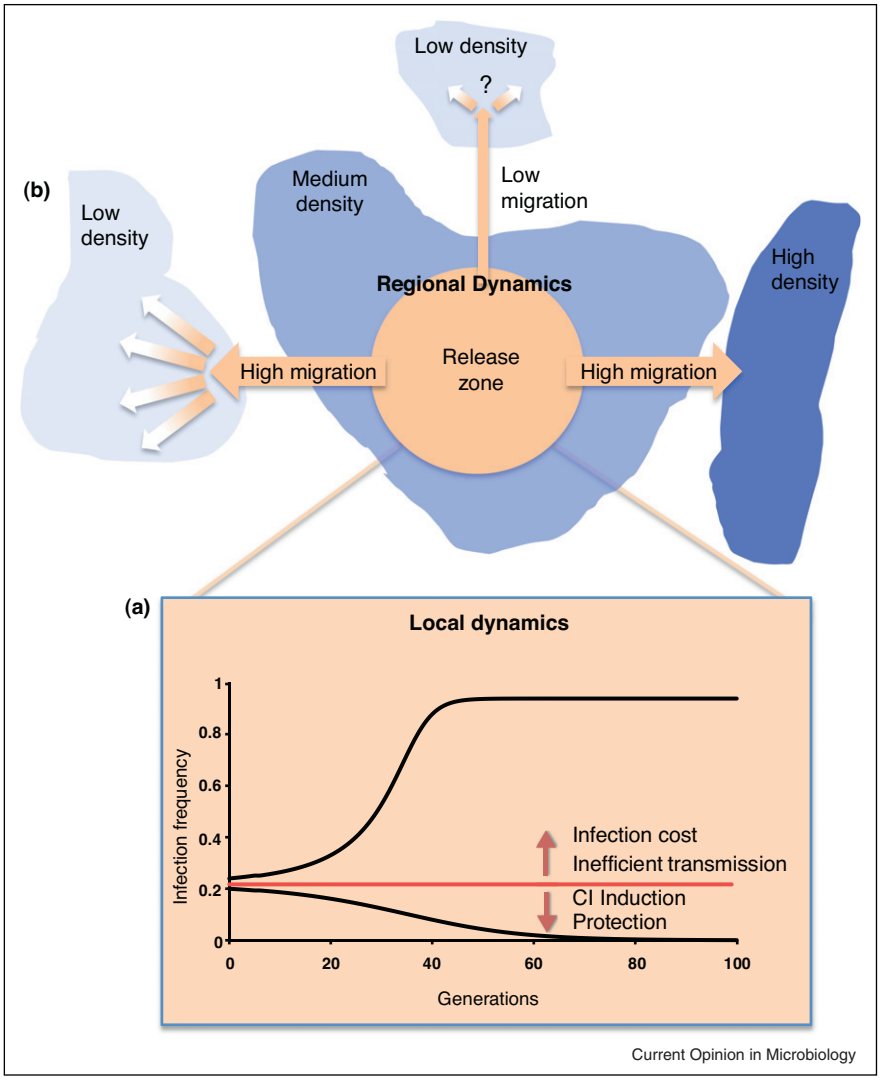
so called bistable dynamics when infection is costly to the host and/or imperfectly transmitted. Thus, the infection frequency either collapses to zero or approaches fixation, depending on its initial value, below or above a threshold frequency (Figure 1).

The original models of CI dynamics were based on closed free mixing populations, and took no account of host population ecology (host populations were presumed fixed in size). However, natural populations of insects are not like this – they are structured in geographical space, with each population having an independent dynamic, but connected to other populations through dispersal. In predicting release dynamics, it is important to understand how this spatial structure impacts *Wolbachia* dynamics [16]. Population subdivision can either facilitate or hinder invasion depending on several factors, such as the size of subpopulations and the associated stochastic demographic effects [17,18] or patterns of migration and dispersion modes [19] (Figure 1). Importantly, local invasion of *Wolbachia* is not necessarily sufficient to produce the diffusion of the infection over space. Modelling of

Figure 1



Local and regional *Wolbachia* epidemiology.**(a)** Local dynamics. CI *Wolbachia* increases the relative reproductive success of infected females because only them can successfully reproduce with infected males. If *Wolbachia* is frequent enough (above the red line), this benefit is sufficient to counterbalance any infection cost or loss through imperfect transmission. Protection against a virulent pathogen, if it provides a net benefit, reduces this threshold frequency and thereby facilitates *Wolbachia* spread.**(b)** Regional dynamics. The figure illustrates the consequences of host population density variation across space (blue intensity) and migration rate (arrow size) on regional invasion. Once *Wolbachia* has spread in the release zone population, its ability to invade neighboring populations will depend on migration rates and host population densities. High migration into a low-density population (left part) leads to spatial spread while high migration into a high-density population (right part) does not. The upper part illustrates an intermediate situation, with uncertain outcomes.

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infection waves is required to determine the minimal number of individuals to be released, and ascertain the conditions under which diffusion could be stopped [20••]. Recent developments thus incorporate more explicitly the host population dynamics, integrating effects such as reduced lifespan, altered development time or population age structure [21,22], but also demographic factors like density-dependence [23]. This is clearly a direction that has to be pursued to integrate more thoroughly the reciprocal effects of symbiont and host population dynamics.

Dynamics in natural populations are obviously complex, and sensitive to the interplay between many aspects of host and *Wolbachia* biology. Often, these are difficult to estimate empirically, and one should not aim to use models as safe quantitative predictors of the infection spread. However, theory provides explicit guidance by which to assess the feasibility of introduction programs, and highlights critical parameters. As an example, models indicate that life-shortening strains are commonly able to invade locally following inoculation, but would probably not generate an infection wave leading to regional invasion [20••]. Indeed, spatial invasion by a CI-*Wolbachia* is only possible when the infection threshold (below which infection is lost) is far below 0.5, which is not the case for a strain halving its host lifespan. Models also provide explicit information on the required insect release effort as a function of individual dispersion [20••]. Encouragingly, results from experimental introductions in greenhouses or natural populations are in good accordance with theoretical expectations, suggesting that rather simple parameter estimates can be sufficient to optimise and assess the feasibility of population transformation programs [14,24••].

Wolbachia and pathogen dynamics in '*menage a trois*'

An emerging picture in the world of insect symbiosis is that vertically inherited symbionts, of which *Wolbachia* is one, often protect their hosts against natural enemies [5]. Theory shows that protection itself may drive the spread of otherwise costly vertically transmitted symbionts, if the infection generates a net benefit [25,26]. The dynamics of such protective symbiont is very similar to the one of a costly resistant nuclear allele: it will reach an equilibrium prevalence that depends on the balance between the costs of the symbiont and the benefits of protection, with the only distinction of imperfect maternal inheritance. Protection may also exist alongside other effects such as reproductive manipulations. In the case of CI-*Wolbachia*, the benefit of protection facilitates invasion by lowering the threshold frequency [27•]. As soon as this threshold is passed, CI allows *Wolbachia* to reach high prevalence independently of the protective phenotype. Facilitation by protection is more pronounced when the pathogen is highly prevalent and virulent, that is, if the net benefit of protection is high. In most cases, among which the promising *A. aegypti* system, it has been shown that the symbiont blocks the replication of the pathogen, but the actual protection (i.e. the reduction in the cost inflicted by the pathogen) remains to be assessed, and the prevalence of pathogens (Dengue and Chickungunya viruses) appears to be low in the field. Notably, protection may also act on other (non-targeted) pathogens through cross-reactions [15], which could increase the net benefit of protection.

In turn, the spread of a protective symbiont affects the pathogen dynamics (Figure 2). If the protective symbiont does not induce CI, the pathogen prevalence decreases [25,26]. When protection is associated with CI, the high prevalence reached by the symbiont may even lead to pathogen extinction, a situation of particular interest for applied perspectives [27•]. However, reduction in pathogen prevalence may produce undesirable outcomes if the pathogen has a marked effect on host population density: a denser population, and therefore a larger number of hosts carrying the pathogen [26]. This process might be further amplified by cross-reactions between *Wolbachia* and other natural pathogens. Beyond the existing, very generic, models, more explicit predictions would require the integration of the recent developments, highlighted above, on *Wolbachia* invasion dynamics, together with parameters relevant to particular systems (e.g. transmission to vertebrate host, interference with other natural pathogens).

Co-evolution in '*menage a trois*'

Beyond the field of *Wolbachia* applied biology, co-evolution between reproductive parasites and their hosts can lead to spectacular co-evolutionary dynamics, in particular when symbionts produce a female-biased population sex-ratio. The paucity of males engenders a nucleo-cytoplasmic conflict of rare intensity, selecting for nuclear alleles that eliminate the symbiont or inhibit its action [28]. The extremely rapid spread of such resistance alleles has been monitored in the interaction between the butterfly *Hypolimnas bolina* and its male-killing *Wolbachia* [29,30]. Interestingly, this male-killer expresses CI when placed in a resistant host background [31], which impedes the spread of resistance when *Wolbachia* prevalence is low (because resistant males cannot reproduce with uninfected females), but leads to its fixation when prevalence is high [32]. The host evolutionary response to *Wolbachia* is also patent in the haplodiploid species carrying parthenogenesis inducing (PI) *Wolbachia*, which allow females to produce daughters without mating. In most PI-*Wolbachia* systems, only females are found in infected populations. Although males can be obtained through antibiotic curing, sexual reproduction is impossible: strikingly, males are often able to reproduce sexually, but females refuse to mate (e.g. [33]). It is proposed that the rapid evolutionary loss of female sexual abilities results from the biased population sex-ratio, because male rareness selects for

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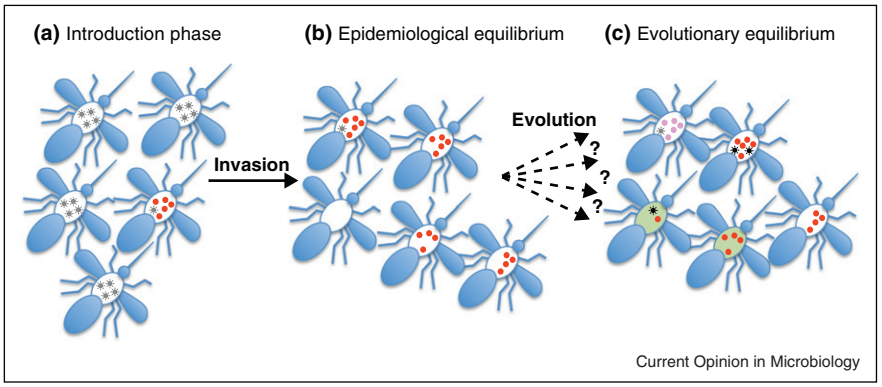
Figure 2



Epidemiology and evolution of a tripartite association: host, pathogen, and CI-inducing protective *Wolbachia*.
(a) *Wolbachia* (red dots) is first introduced in a pathogen vector (the host) carrying a pathogen (gray stars). If the pathogen is virulent, *Wolbachia*-mediated protection acts in synergy with CI to facilitate *Wolbachia* spread. If protection does not confer a net benefit (e.g. if it is costly and/or if the pathogen is not highly virulent or prevalent), *Wolbachia* invasion can occur through CI alone. Cross-reaction against other pathogens (not shown) can facilitate the spread.
(b) The high equilibrium prevalence of the protective *Wolbachia*, determined by CI, keeps the targeted pathogen (and potentially other pathogens) at low prevalence, with possible effects on host population density and interference with other biocontrol methods.
(c) Genetic variation in the host, the pathogen and the *Wolbachia* (symbolized by color variation), and potentially interactions between them, can alter pathogen virulence as well as the efficiency of the protective phenotype. As discussed in the main text, the evolutionary stable strategies in such tripartite systems remains largely unexplored by current models.

females that refuse to mate and thereby produce more sons [34–36]. These 'virginity mutants' can spread rapidly even at high cost and lead to a peculiar outcome: the loss of sexual reproduction and the concomitant strict dependence upon *Wolbachia* for reproduction.

Current application plans mostly rely on CI-inducing, protective, *Wolbachia* strains. Anticipating the durability of these programs would require predictions on the evolution of (i) pathogen virulence (and prevalence) and (ii) *Wolbachia*-mediated protection. A full theoretical framework, integrating the contribution of the three partners on the evolution of these key parameters is still lacking (Figure 2). One critical and unexplored point, probably impacting the evolutionary stable strategy of the different players, is that the protective effect is not necessarily the force determining the protective symbiont prevalence if CI is also at play.

Focusing on the evolution of pathogen virulence, one study investigates the co-evolutionary fate of an horizontally transmitted pathogen and a non-protective sex-ratio biasing vertically transmitted symbiont competing for the same hosts [37]; two other studies explore the co-evolutionary dynamics when the vertically transmitted symbiont protects its host from pathogen infection but does not induce CI or other reproductive manipulation [25,38••]. In all cases, it is suggested that the protective symbiont selects for higher pathogen virulence. In the case of CI-inducing protective *Wolbachia*, where CI drives the symbiont to very high prevalence, such selection on the pathogen for high virulence might be further intensified. This may represent a problematic perspective for applied purposes, especially if the introduction of the protective symbiont does not readily lead to pathogen extinction. Anticipating the consequences of such an evolutionary trajectory on (i) the efficiency of pathogen transmission to the definitive vertebrate host and (ii) the virulence in the definitive vertebrate host seems critical, and would require empirical assessments of trade-offs between all these parameters.

One valuable property of CI-inducing protective *Wolbachia* is their ability to reach high prevalence even if the protective effect is overall costly to the host. In an evolutionary perspective, one should note however that such costly protection is unlikely to be maintained, because selection on both *Wolbachia* and its host will tend to reduce any cost associated with the infection [39]. As an example, in the association between *Drosophila simulans* and the *w*Ri *Wolbachia* strain, the symbiont was costly to its host 20 years ago, but has since evolved to become beneficial [40]. In the wasp *Asobara tabida*, which cannot produce eggs if deprived of its *Wolbachia*, it is suspected that the dependence upon the symbiont is owing to the evolution of host compensatory mechanisms (i.e. tolerance) to limit the impact of *Wolbachia* on oxidative stresses [41,42]. Importantly, *Wolbachia*-mediated protection may be at least partly attributable to immune priming in newly created associations [15,43,44], a phenomenon more rarely seen in co-evolved associations [45,46]. If the constitutive cost of this immune reaction to *Wolbachia*

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is larger than the net benefit of protection (which is perhaps likely, else the organism would not have maintained an inducible system), the expectation is that the host will evolve tolerance to *Wolbachia* infection and a concomitant reduction in the protection against pathogens. In support of this hypothesis, no obvious interference has been observed between Dengue virus and natural *Wolbachia* infection in naturally infected *Aedes albopictus* [47], but protection appeared and was accompanied by immune priming after injection of another *Wolbachia* strain [48]. On a more optimistic tone, pathogen blockade, not only relying on immune priming, has been demonstrated in some co-evolved associations [11,12•,49]. Here again, it appears critical to assess possible cross-reactions between *Wolbachia* and other, non-targeted pathogens, as these will affect the cost and benefit (and therefore the durability) of the protective effect.

Conclusion

Both empirical and theoretical studies highlight the great potential of *Wolbachia*-based strategies as new tools to fight pests, vectors and vector-borne diseases. Additional theoretical development is however needed to better understand the evolutionary trajectories of these systems, which will affect the protective effect of the symbiont, the virulence of the pathogen in the vector and potentially in the vertebrate host. Empirical studies are also needed to evaluate the net benefit of *Wolbachia*-mediated protection, which will depend on the protection mechanism, the pathogen virulence and prevalence, as well as cross-reactions against other natural, non-targeted pathogens. Beyond *Wolbachia*, addressing these issues will be valuable for any symbiont-based biocontrol programs.

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