Integrating across levels: What is the relevant level of organisation? Virulence evolution suggests it may not be so simple

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ABSTRACT

Part of the problems facing integrative biology is how to integrate across various levels of organisation. Some of these problems are already well appreciated in various domains such as epidemiology or biological control. In epidemiology, for example, much effort is currently devoted to understand how within-host processes are affecting the spread of parasites. In biological control, an important problem is to determine which measures of individual traits best predict the efficacy of introduced predators in suppressing a pest population. Classically, the problem is to link individual-level traits to population dynamics and eventually to ecosystem functioning. However, as I will discuss here, relevant levels of organisation are often in between the well-defined levels of organisms, populations and ecosystems. For example, in host-microparasite systems, one often takes the entire population of parasites infecting a given host as the relevant unit, but as often multiple infection is important, the relevant unit is something between the individual parasite and the population. In spatial ecology, the relevant unit to consider is not the individual, but rather a cluster of related individuals or even associated species. An important challenge is to determine the character of these relevant units.

INTRODUCTION

Modern biology faces the problem of integrating knowledge spanning wildly diverging levels of organisation, from the molecular level all the way op to the global ecosystem. One could simply state that 'everything is connected to everything' and leave it at that, but this is not going to yield much useful insight. Different levels are connected, but not all aspects from a lower level are relevant for a good understanding of a higher level. Some aspects of plant physiology, for example, must be taken into account to understand global energy cycles, but most detail is irrelevant at that level. This problem has been noted and discussed in depth by philosophers ever since it became clear that it was difficult to derive thermodynamical (high level) laws from the Newtonian dynamics of molecules (low level). An important part of ecology involves the similar problem of how individual level traits affect population dynamics and ecosystem function. To extend these links to even lower levels (physiology, genetics) and higher levels (global ecosystems, long-term evolution) is the daunting task faced by integrative biology.

Of course what level should be studied depends also on the problem at hand. A doctor designing a treatment scheme to cure an infected patient not normally considers its large-scale and longer-term consequences. A biologist developing fighting some agricultural pest usually is more aware of the large-scale consequences. Whatever, the problem, most biologists would agree that the relevant levels of integration (genes, individuals, populations, etc.) are well delineated. However, as I will argue here, sometimes relevant levels are rather blurred and in a way 'in between' the classical categories. This implies that for a good understanding of a given problem, also the relevant level needs to be determined, and currently few tools are available for this.

PARASITE VIRULENCE

A good example to consider is the problem of predicting the shorter-term (epidemiology) and longer-term dynamics (evolution) of parasites infecting a host population. Considering such interactions three distinct levels suggest themselves immediately: the level of the individual parasite (bacterium, virus particle, etc.), the level of the individual host they infect, and the level of the population. Pathogens can be fought at each of these levels, but the tools are very different, ranging from antibiotic treatment, *via* modification of host behaviour to population level vaccination campaigns. Working out the longer-term effects of these interventions is an urgent but certainly no easy matter (Anderson and May 1991).

Since Kermack and McKendrick (1927) the epidemiology of microparasites is usually modeled by keeping track of the state of the hosts in the population (Figure 1). This

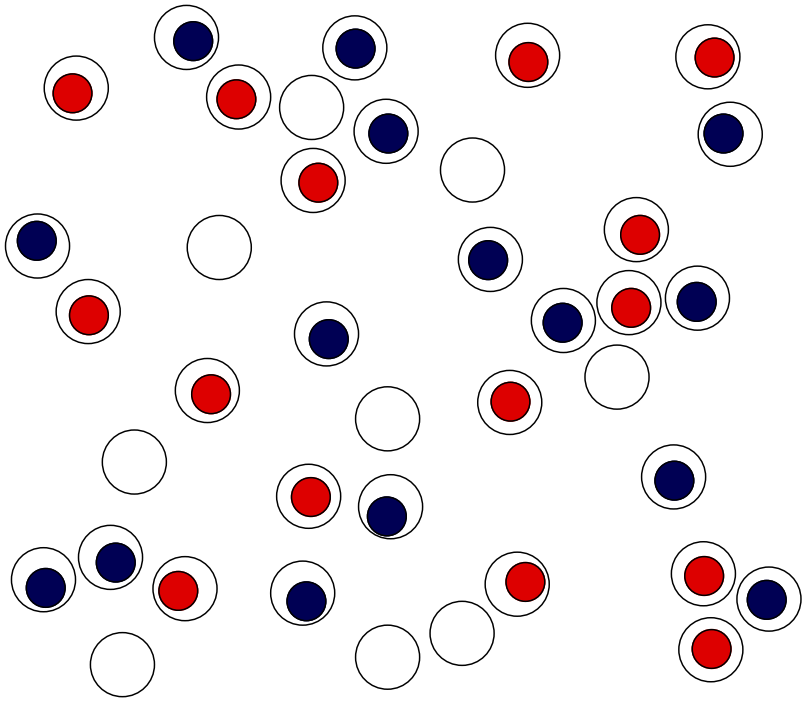

FIGURE 1. Hosts (circles) infected by single parasites. Which of the strains (indicated by light and dark shading) will eventually dominate will depend on how they exploit their hosts. The strain that strikes the optimal balance between infectivity and duration of the infection (virulence) will win.

implies that one focuses at individual hosts, thus effectively ignoring the lowest level. The justification is that that at the timescale of host-to-host transmission, within-host dynamics are extremely fast. This approach has led to many useful insights, the most important of which revolve around the notion of the basic reproduction ratio (commonly denoted R_0). If one want to carry out a vaccination program to extinguish a given parasite, one should work out how many new infections a single infection will cause, and vaccinate so many hosts that this number becomes less than one, even in an otherwise wholly susceptible population. Evolutionary epidemiologists quickly realised that a similar reasoning holds if one wants to determine what level of parasite virulence is favoured by natural selection: the strain with the highest R_0 replaces all other strains, thus producing the well-known dictum that 'parasites should maximize their R_0' (Bremermann and Pickering 1983, Anderson and May 1982)

Human life would probably be bleak if this were always true, however. As evolutionary biologist Ewald (1994) has argued, there are many instances of virulence evolution in response to changed conditions. According to the historian McNeill (1976) many of the

parasites that plagued humans have adapted and reduced their virulence even in historic times. Now, generally maximum R_0 is not affected by large-scale epidemiological parameters, and as a consequence, changes at this level (intentional or unintentional) should not provoke an evolutionary response.

WITHIN-HOST DYNAMICS

This conclusion does change, however, if some of the simplifying assumptions underlying the standard host-microparasite model are relaxed. From a purely pragmatical point of view only first infections are taken into account (why bothering following a few extra parasites in a host that already harbours millions of them?). However, the consequence is that from an evolutionary point of view, all parasites in a host are descendants of the original infection and can be considered as a single evolutionary unit. Under this scenario, maximizing transmission implies that all parasites 'cooperate' to optimally exploit a given host individual. Since there is only one optimum, associated virulence will not change when the host's external conditions change. If, however, one takes into account that hosts may be infected more than once (see Figure 2), the conceptual picture changes fundamentally (Eshel 1977). When multiple clones share the same host essentially a multilevel selection problem results. In general, a less virulent clone reduces its transmission rate but keeps its host alive longer. This is no problem if only single infections occur (and indeed, optimum virulence then requires striking the optimum balance between transmission and infection duration) but not a good idea if other parasites coinfecting the host (who also influence host survival). Under multiple infection, generally, more virulent strains are favoured as these get the benefit of increased transmission while the others pay the cost. Recently, it has been suggested that this conclusion may be too simplistic (Chao et al. 2000, Brown et al. 2002), but for the purpose of this argument the mere fact that multiple infection has evolutionary consequences is a most important conclusion. van Baalen and Sabelis (1995) have suggested that virtually *any* change at the population level will produce an evolutionary response, because such changes generally modify the intensity of infection and with it, the likelihood that two or more clones share the same host. Measures to fight parasites then may have a 'knock-on' benefit, as reducing their prevalence also allows individual clones to exploit their hosts more prudently and become less virulent (Gandon and Michalakis 1998).

AMONG-HOST TRANSMISSION

The usual interpretation of Ewald's claim goes like, 'if we make it more difficult for parasites to transmit themselves from one host to the other, we force them to be more

careful with their current host.' As we have seen, however, in the most basic case of host-microparasite interactions this conclusion does not hold. We obtained support for Ewald's claim by incorporating the fact that parasites may compete within hosts. Does this mean that if multiple infections are rare there is no scope for 'virulence management?'

Another assumption that underlies the Kermack and McKendrick's (1927) formulation of host-parasite dynamics is that of homogeneity in contact rates. That is, the model assumes that it suffices to keep track of global densities (or numbers) of hosts. In particular, any infected host has an equal chance to meet and infect any susceptible host in the population. This amounts to stating that the number of other hosts a given host meets will be proportional to host density. Clearly, for many if not most host species this will not hold true: doubling the overall population is likely to increase but not necessarily double the encounter rate among hosts: people living in big cities tend to have about the same number of social contacts as people living in small villages. The consequences for modelers of relaxing the homogeneity assumption are serious. Most of the tools developed for analysing population are based on analysing differential equations, and these, in turn, are based on the assumption of homogeneous mixing. To study the consequences of non-homogeneous contact structures one can choose to let go of all means to aggregate individual-level events into larger wholes and carry out extensive individual-based simulations. Comparison of such simulations with equivalent well-mixed populations has given us many insights into where the consequences will make themselves feel most clearly. A problem with this approach is that simulations may help us to develop insight but but provide little analytical knowledge. Modern methods borrowed from statistical physics help to fill the gap.

A striking result from both simulation and analytical studies is that deviations from homogeneity may have important consequences, both on the short and on the longer time-scales. On the short time-scale, the traits that allow a parasite to maintain itself in a spatially homogeneous host population are not at all comparable to the traits that are needed to ensure transmission across a contact network (Figure 3). Consider a parasite that has just been introduced into a susceptible population. If there is no spatial or contact structure the infecteds will dilute themselves into the population at large, implying that infected individuals will keep on average meeting susceptibles until the epidemic takes on serious proportions. In contact-structured populations, however, a initial infection will cause a cluster of infections to the effect that individuals in the center no longer meet susceptibles to infect. The self-shading that occurs in 'small world' social structures severely limits the capacity for parasites to create large-scale epidemics.

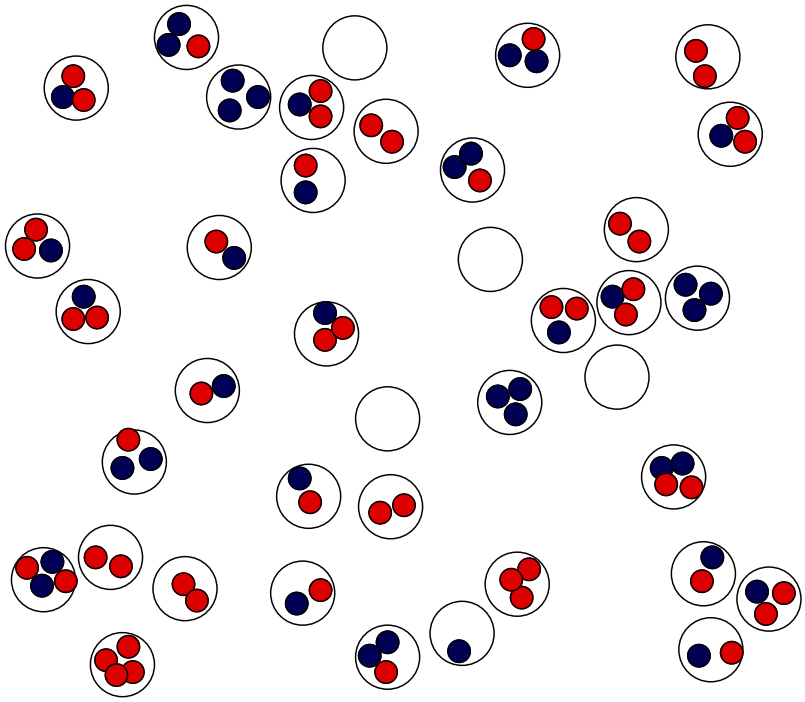

FIGURE 2. Hosts (circles) infected by multiple strains (clones) parasites. Which of the strains (again indicated by light and dark shading) will eventually dominate will not only depend on how the combination of strains exploit their hosts but also how the clones interact within the hosts.

The evolutionary consequence of this clustering is that (even in absence of multiple infections) the relevant unit is no longer the clone infecting a single host but rather the cluster of hosts infected with the same strain of parasites. Those clusters that are most proficient in transmitting themselves across the new network and thus create new clusters are favoured by natural selection. This effectively creates new 'units of selection' and the consequences may be far-reaching. For example, Boerlijst et al. (1993) noted that species taking part in so-called hyper-cycles form spiral structures when allowed to develop in a spatial domain, and that it was the characteristics of the spirals they created that determined their evolutionary fate. The resulting selective pressures turned out to be rather counterintuitive. For example, a species may evolve higher mortality rates, which would never occur in spatially homogeneous settings. Yet increased mortality makes the spiral turn faster, and rotation rate turns out to be a spiral-level trait that is strongly selected. Rand et al. (1995) found that spatial structure may impose an upper limit to transmissibility favoured by natural selection: a parasite strain that is highly transmissible will simply 'burn through' (and

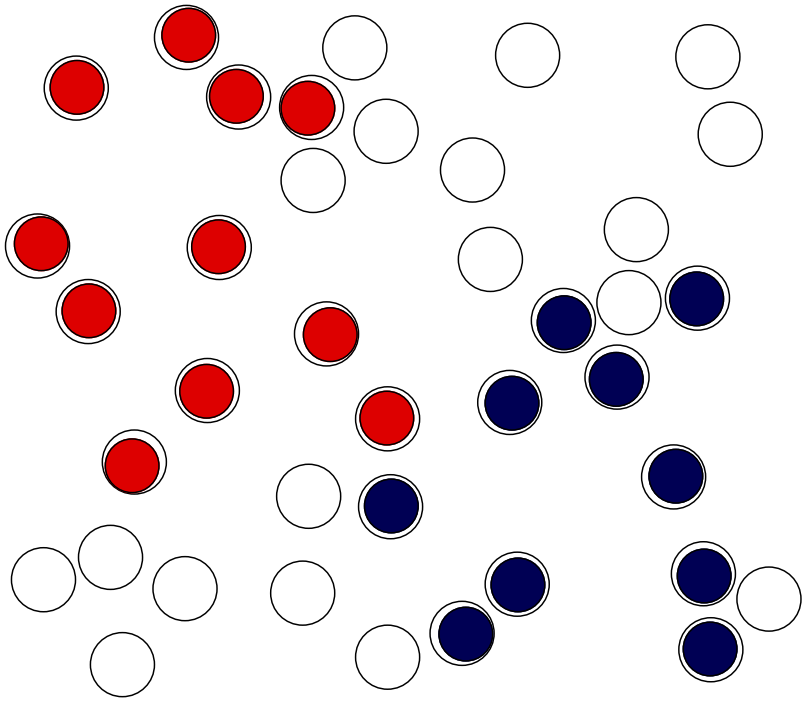

FIGURE 3. Parasites can only infect nearby susceptible hosts. Which of the strains (indicated by light and dark shading) will eventually dominate will depend on how the host cluster they create competes with other clusters. (Note that multiple infection of individual hosts, if it occurs, will not be a strong evolutionary force as multiple infections are likely to be with parasites from the same strain and therefore essentially indistinguishable from single infections.)

eventually kill) a cluster of hosts it infects before this cluster has mingled with new, susceptible clusters and thus deprive itself of means to propagate itself across space. Moderately transmissible parasites allow their host cluster to reproduce and can thus hitchhike across space. When virulence and transmissibility are linked (as might be expected in most cases) this effect will even be more pronounced. Virulence then strongly depends on the contact structure in the host population (van Baalen 2002).

In terms of relevant levels, this result implies that sometimes the relevant level to consider is *above* the clone infecting individual hosts. In particular with epidemic diseases (diseases that form local outbursts and then die out) such larger-scale considerations will be necessary to understand their evolution. A problem again is the identification of the right level. Individual hosts are readily recognizable, and we all think know what we mean by 'the population'. Dealing with and characterizing the relevant intermediate levels, if they occur, is not so easy, however. van Baalen and Rand (1998) suggested that invasion

analysis can be used to provide formal definitions of these fuzzy intermediate structures. One of their conclusions was that these structures have a close relationship to inclusive fitness in what Hamilton (1967) called 'viscous' populations. Being in a cluster (or any other intermediate level structure such as a spiral) implies that an individual is likely to have relatives in its neighbourhood. Intermediate-level selection that arises therefore is similar in its effects to what evolutionary biologists know as 'kin selection' where individuals will pay a cost to benefit a larger whole.

INTERMEDIATE-LEVEL PHENOTYPES

Currently, however, very little insight exists into what are possible intermediate-level structures and what are the 'traits' of these structures that are favoured. As mentioned before, Boerlijst et al. (1993) identified rotation rate as an important phenotypic trait (faster spirals replace slower ones) but at the same time they noted that fast-rotating spirals have a tendency to fly apart and disintegrate. Among 'artificial life' biologists, this tendency is called 'evolution towards the border of order' (a reference). This in itself is a fascinating conclusion but without more firm ideas about what determines these structures (in particular, how they depend on the interplay between the characteristics of constituent entities and large-scale dynamics) discussion will remain rather academic. van Baalen and Rand (1998) propose a method to identify the unit of selection in simple viscous populations, but this method is unwieldy and difficult to apply to interacting populations.

INTEGRATIVE BIOLOGY ACROSS LEVELS

We have seen that host-parasite interactions require consideration of what happens at multiple scales. With respect to the evolution of virulence, often the relevant level is taken to be that of the individual host interacting with a single clone of parasites. Under those conditions, virulence reflects optimum host exploitation, which is difficult to interfere with and does not depend on higher levels. However, as soon as simplifying assumptions are relaxed the relevant levels (for understanding both short-term epidemiology and longer-term evolution) may be either below or above this traditional level. That is, the relevant level may consist of smaller units (clones) coinfecting the same hosts but just as well it may consist of clusters of nearby hosts carrying the same strain of parasites (Figure 4). At present, there exists no easy way to determine what is the relevant level, except considering the interaction in some detail. Ideally one would consider all levels spanned by the interaction and determine from this at which level reside the relevant processes.

This is not just an academic issue, but it has important practical aspects. We have seen that Ewald's conjecture that parasite virulence may be manipulated only holds if relevant

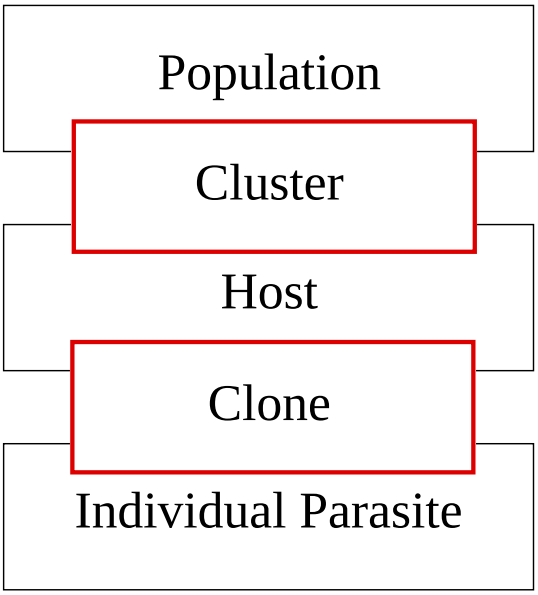

FIGURE 4. The hierarchy of organisation in host-parasite systems, with the levels that are usually well-distinguished but may be linked through intermediate levels. Parasites can be fought at any of these levels, but which one should focused on is not easy to decide straight away.

levels are either below or above the level of the population infecting a host. In designing interventions to fight parasites it is very important to know *which* of these is the most important. If it would appear (as may well be the case for many parasites) that within-host competition is the structuring process, then our relevant level is below. If, on the other hand, it is the larger scale structure of a patterns of infection that determines the fate of parasites, then it is the higher level that should form the basis of our conceptual parasite. Both cases involve Hamilton's (1964) concept of relatedness (of parasites within hosts and among hosts) and are in a way conceptually similar. Yet at one level is by host social social behaviour is the key parameter whereas at the other requires consideration of the physiological details of the individual hosts' immune systems.

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