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Multiple infection theory rather than ‘socio-virology’? a commentary on Leeks *et al.*

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Abstract

Distinguishing social from nonsocial traits for microbial populations can be difficult in evolutionary ecology. This is particularly true for viruses because their obligate parasitic lifestyle de facto creates multiple levels of adaptation and puts contagion processes at the heart of their fitness. I argue that multiple infection frameworks developed in evolutionary epidemiology offer a range of theories, concepts, and tools that are particularly suited to capture the dynamics of diverse virus populations and study the evolution of their social traits.

Leeks et al. present recent studies on ‘the evolution of virus social traits’, which they define as ‘sociovirology’. This commentary attempts to complement their review in a nonoverlapping way. I first discuss what sociality means for virus traits. Then, by reflecting on the specificity of virus evolution and open challenges for modelling their life-history traits, I try to make a conclusion as to the usefulness and timeliness of the term sociovirology.

Are there non-social life-history traits?

The rich review by Leeks et al. is an opportunity to revisit the notion of sociality in the context of the microbial world. Throughout a century of experimental evolution [Mendelsohn, 2002], major contributions to the field of social evolution have come from microbial systems because of their rapid evolutionary rates and large population sizes. For viruses, the evolution of social traits has been the driving question in many studies, at least since the experiments on the sharing of intracellular products by phages [Turner & Chao, 1999]. The game-theoretical interpretation, published in this very journal [Brown, 2001], illustrates how influential this experiment was and how interweaved mathematical modeling and empirical approaches are in research on social evolution.

Leeks et al. define social interactions ‘when a trait carried by one individual affects the fitness of a different individual’. This definition originates from that of West et al. [2007], who refer to ‘social behaviours’ and specify that the fitness of the focal individual should be affected too. With both these definitions, and as suggested by the term ‘interaction’, it is difficult to picture what a nonsocial life-history trait might be.

According to the evolutionary ecology perspective, the environment in which individuals evolve is not constant. In particular, there is a feedback loop between ecological and evolutionary dynamics [Lion, 2018]. As popularized by the adaptive dynamics framework [Kisdi, 2020], the evolution of any life-history trait affects the population dynamics of the individual that bears it and, therefore, that of the other individuals in the population, thereby modifying all the selective pressures. In such a context, any virus life-history trait matches the above definition for social traits.

To address this problem, it is tempting to reduce sociality to direct interactions between viruses. However, some of the most classical and long-studied social interactions are indirect, for example, through the exploitation of shared host resources for the tragedy of the commons [Turner & Chao, 1999] or a host's immune response for apparent competition [Read & Taylor, 2001].

This debate is not new and was phrased almost in the same terms by Heino et al. [1998] in the context of frequency-dependent selection. Therefore, I do not have a satisfying alternative definition to put forward, and doubt that one even exists. Fortunately, this is more a problem for the definition of sociovirology rather for the study of the evolution of virus life history traits.

Viruses are parasites

Quoting Koonin et al. [2021],

Viruses sensu stricto are defined operationally by the ICTV [International Committee on Taxonomy of Viruses] as a type of MGE [mobile genetic elements] that encodes at least one protein that is a major component of the virion encasing the nucleic acid of the respective MGE and therefore the gene encoding the major virion protein itself or MGEs that are clearly demonstrable to be members of a line of evolutionary descent of such major virion protein-encoding entities. Any monophyletic group of MGEs that originates from a virion protein-encoding ancestor should be classified as a group of viruses.

This definition has the merit of being operational at a taxonomic level, but it does suffer from interpretability issues. The following addition made by the same authors helps to clarify the matter: 'the strict dependence on the host cell and intracellular reproduction remain universal traits of these replicators'. This parasitic nature of viruses shapes their physiology and represents a central point to understanding their evolution. In particular, it implies a virus traits cannot be studied independently of at least one host. Moreover, some life-history traits that we often implicitly associate with a virus genotype, such as virulence, are actually 'shared' with the host genotype.

Not only must a virus infect a host cell, but multiple host cells usually occur in close proximity, either because they all belong to a multicellular individual host or to a colony. This de facto creates two levels of adaptation [Lewontin, 1970], at the within-cell and at the within-host (or within-colony) level. In most natural systems, frontiers between levels of adaptation tend to be blurry, as illustrated by spatial structure [Lion & van Baalen, 2008]. Conversely, in the case of cells or hosts, these boundaries are as well-defined as the notion of individual [Pradeu, 2016b], which makes viruses ideal study systems for evolutionary biologists.

Anticipating which level of adaptation shapes the evolution of virus traits is not straightforward. Consider, for example, the case of an infected host living in a metapopulation. At least four levels of adaptation can be distinguished: within-cell, within-host, within-population, and within-metapopulation. The latter level is the most important for long-term persistence. However, evolution is short-sighted and, provided that the evolutionary speed is high enough, viruses may very well adapt to the population level or even to the within-host level, even if this represents an evolutionary dead end; a hypothesis that has been put forward to explain the existence of virulent yet poorly transmissible pathologies [Levin & Bull, 1994].

Leeks et al. raise several issues revolving around levels of adaptation, although they do not phrase them as such. They first discuss it when mentioning 'timescales', which they do not define explicitly but equate to the ability to spread 'within and between hosts'. This may be confusing because a striking feature of infection dynamics is that these timescales can overlap, for instance if a host acquires a new genotype during an ongoing infection[Mideo et al., 2008]. Leeks et al.'s reflection on what viral organisms are also touches upon the notion of levels of adaptation, but, there, it gets eclipsed by the difficult and long-lasting debate on the notion of biological individuality[Pradeu, 2016b]. For some viruses such as multipartite viruses, which encapsidate different genomic fragments into separate virus particles [Sicard et al., 2015], this question is essential and still a major challenge for modellers. However, for most viruses, levels of adaptation represent a specific issue that requires a formal definition of fitness to be tackled.

How to measure virus fitness in a social context?

The review by Leeks et al. alludes to the difficulty of measuring virus fitness when presenting [Hamilton \[1964\]](#)’s inclusive fitness theory, which states that a focal individual has a direct fitness, through its offspring, and an indirect fitness, through the offspring of other individuals to which it is related. Expressing fitness is a key but challenging step for any social evolution analysis that wishes to go beyond verbal or qualitative reasoning.

As for most organisms, especially parasites, the main difficulty in expressing the fitness of a virus resides in ‘closing the life cycle’ [[Alizon & Michalakakis, 2015](#)]. For example, for vector-borne viruses, strong conflicting selective pressures can occur between the parts of the cycle taking place in different host species [[Vasilakis et al., 2009](#)]. This importance of the life cycle is even more striking for multipartite viruses, as illustrated by a plant nanovirus, whose ratios of copy number of each genomic fragment varies between the host plant and the aphid vector [[Sicard et al., 2015](#)]. These examples illustrate the problem qualitatively, but evolutionary epidemiology theory offers more quantitative formulations.

In epidemiology, we can express invasion fitness through the reproduction number (denoted R), which corresponds to the number of secondary infections caused by an infected individual over the course of its infection. However, it is important to go beyond the basic reproduction number (R_0), which is computed in a completely naive population, in order to capture the feedback loop between ecological and evolutionary dynamics [[Lion & Metz, 2018](#)]. In practice, this means estimating fitness as a function of the trait of a mutant strain (x_m) and that of a resident strain (x_r), that is, $R(x_m, x_r)$, instead of a value $R_0(x_m)$ that would only depend on the mutant trait. In the former case, the resident strain shapes the environment faced by the mutant, for instance through the density of susceptible or immune hosts, whereas in the latter, the environment is constant.

Although classical epidemiology formalisms typically assume single infections, how many genotypes share a cell, a host, or a host population shapes the selective pressures undergone by a virus population. This echoes the concept of relatedness, which is central in social evolution [[Hamilton, 1964](#)]. Building on the seminal work by [Frank \[1996\]](#), many studies make the simplifying assumption that the relatedness between two viruses at one level of organization, e.g. within a host or within a host population, is fixed. From this, and with a few assumptions discussed by [Taylor et al. \[2007\]](#), it follows that for n genotypes (or strains) with different phenotypic trait values x_i and present at a density N_i in a population of total size $N = \sum_i N_i$, the relatedness r at the level of the trait can be written as

$$r = \frac{1}{N} \frac{\partial}{\partial x_i} \left(\sum_{i=1}^n N_i x_i \right) \quad (1)$$

Coming back to the definition of a social trait, Equation [equation 1](#) illustrates how the value of an individual’s trait (x_i) shapes its relatedness to other individuals. Following [Hamilton \[1964\]](#)’s theory, this hence affects the indirect components of the individual’s inclusive fitness.

Many studies assume r to be constant and often equate to $1/n$ thereby assuming that all genotypes are present at equal frequency. This can lead to insightful results on virus evolution, as illustrated by [Brown \[2001\]](#) or by the review from Leeks et al. who clearly show how ‘ploidy’, to use their terminology, shapes population dynamics. However, relatedness is a dynamic variable: in the short term, there can be temporal fluctuations, and in the long term, the value of the trait of interest is likely to shape the equilibrium density of each of the genotypes. Furthermore, the number of genotypes n present at a level of adaptation may itself vary over time, for example, if a host becomes infected by another genotype.

Combining the evolutionary epidemiology approach and its feedbacks with the frameworks classically used to study social evolution, such as kin selection or group selection [[Lion et al., 2011](#)], has rarely been attempted explicitly (but see [Alizon & Lion \[2011\]](#) or [Lion \[2013\]](#) for exceptions). In theory, this only requires accounting for multiple infections, while describing interactions between an arbitrary number of genotypes within hosts [[Sofonea et al., 2015](#)]. However, many challenges remain for achieving such integration.

Outstanding challenges for models of virus social evolution

Encompassing multiple levels of adaptations

As mentioned above, trait evolution is shaped by selective forces occurring at distinct levels of adaptation. Considering each level separately is possible but, as illustrated with our Equation 1, has little relevance in the context of social evolution because it means assuming that genetic diversity at the level considered (the cell, the host, or the population) is constant.

An answer to this issue can come from the so-called ‘nested models’, which have been developed in evolutionary epidemiology to specify which interactions take place at one level and readily integrate these in another level [Mideo et al., 2008]. The multiplicity of hypotheses that can be made at each level may seem daunting at first. However, once we factor in biological relevance, the diversity of outcomes reduces. For example, in a simple setting with only two genotypes, only seven nontrivial multiple infection patterns can be generated from basic within-host interactions (competition for resources, production of spite and public goods molecules) [Sofonea et al., 2017]. Two of these patterns are actually mentioned by Leeks et al., namely co-infection and priorinfection (referred to by them as ‘superinfection exclusion’). Therefore, within-host processes shape virus epidemiology and multiple infection frameworks can be used to formalize problems revolving around the evolution of virus social traits.

Overlapping timescales

Another limit common to most frameworks is that, even when they do consider multiple levels of adaptation as Alizon & Lion [2011], they typically assume a strict separation of timescales to analyse the dynamics taking place at each level separately. This simplification is useful to formalize biological hypotheses but, in some cases, it can lead to missing important population dynamics feedbacks, and multiple infections are one of these cases. An elegant answer to this overlap comes from the so-called Price equation approach, which combines epidemiology and quantitative genetics and, therefore, follows trait evolution and population dynamics simultaneously [Day et al., 2020]. In particular, some of its developments have shown how within-host dynamics can be summarized and integrated into an epidemiological model using temporal covariance terms [Day et al., 2011]. This makes this framework particularly well suited to incorporate empirical data. However, current Price equation models only consider single infections and new extensions are needed in order to capture virus genetic diversity both at the within-host and at the between-host levels. More generally, a limit of this approach is that it only provides insights on the short term, unless there is enough information to update the genetic covariance matrixes.

Short-sighted evolution

Capturing the overlap between population dynamics taking place at different levels of adaptation would only partially address the problem of conflicting selective pressures acting at these different levels. Indeed, due to their rapid evolutionary rates, some viruses can adapt to ‘lower’ levels in a short-sighted manner [Levin & Bull, 1994]. This rapid evolution has been studied mostly using simulation-based approaches designed for human viruses such as Human Immunodeficiency Virus (HIV) or Hepatitis C Virus [Bonhoeffer & Nowak, 1994, Poon et al., 2007, Luciani & Alizon, 2009, Lythgoe et al., 2013, van Dorp et al., 2014] and not in the context of social evolution.

These multiple timescales indirectly bring us back to the notion of individuality, or perhaps, more precisely, that of units of selection [Lewontin, 1970]. In their review, Leeks et al. present in exquisite detail the variety of strategies viruses have evolved to be transmitted in groups, or ‘collective infectious units’. At the other extreme, they mention the puzzling case of multipartite viruses that transmit parts of their genomes separately. This resonates with analyses from philosophers of science, according to whom ‘it is extremely difficult to determine where and when a virus starts and ends, and what it means for one virus to remain the

same through time’ [Pradeu et al., 2016]. One of their proposed solutions is to consider them as processes involving their host instead of things [Dupré & Guttinger, 2016], a task for which evolutionary epidemiology formalisms can help. For example, the probability of cotransmitting can be included in multiple infection models [Alizon, 2013]. The more this probability tends towards 1, the more the genotypes behave as one organism and the system resembles a single infection system. In the case of a ‘helper’ virus coevolving with a satellite (or cheating) virus, increasing this cotransmission leads to a decrease in the virulence of both viruses [Alizon, 2013]. The issue is more delicate with rapid within-host evolution because the genetic sequence of the virus that caused the infection can differ from that that infects a new host. For human viruses, this has been studied in the context of the ‘heritability’ of virus traits from one infection to the next [Leventhal & Bonhoeffer, 2016]. As mentioned above, this problem has been tackled with simulations but also, more rarely, with analytical models, especially in the case of HIV Lythgoe et al. [2013]. However, a more formal integration with social evolution is still lacking.

Plasticity in host-virus interactions

In their seminal co-infection model, van Baalen & Sabelis [1995] already account for the importance of the plasticity of the parasite exploitation strategy by assuming that a strain can shift strategy if the host is co-infected by another strain. Some studies have pursued this line of research in social evolution. For example, Taylor et al. [2006] show that, when introduced at the level of the host–parasite interaction, plasticity is predicted to select for decreases in parasite virulence and in host clearance rate. Microbial trait plasticity is more associated with bacteria [Kümmerli et al., 2009] but recent studies show that some phage traits can also be interpreted as such [Duddy & Bassler, 2021]. Some adaptive dynamics models include it in models of virus evolution [Choua & Bonachela, 2019] but adding multiple infections, an important upgrade to study social evolution, largely remains an open challenge.

Population structure

Classical social evolution models can readily incorporate metapopulation or network structure, even in the context of infections [Lion & van Baalen, 2008]. However, these rarely allow for multiple infections, which limits the possibility for virus interactions. We introduced such a framework using an individual-based approach, but the evolutionary perspective consequences of the combination of spatial structure and multiple infections remain to be investigated [Selinger & Alizon, 2021]. At the theoretical level, the main challenge is to capture the fact that virus traits shape infection spread and, therefore, the spatial structure seen by an infected host [Lion & van Baalen, 2008]. This leads to an interesting feature because relatedness between viruses can then be defined at the within-host level and at the between-host level (in a well-mixed model the relatedness between two hosts is trivial and only depends on the type). Experimental work on this topic is more advanced, with studies showing how the viscosity of the host environment shapes the evolution of virus virulence [Boots & Meador, 2007, Berngruber et al., 2013].

Most studies combine within-host and between-host levels but similar frameworks can be deployed at the within-host level, where infected entities are cells rather than individuals. Since seminal work by Frank [2000], few models have attempted it. There are, however, exceptions in the case of HIV [Althaus & De Boer, 2012], for which genetic recombination is a major component of the life cycle. Recent work also shows that the layout of the target cells shapes virus within-host evolution [Saeki & Sasaki, 2018].

Towards a multi-specific approach

Finally, Leeks et al. mention virus–virus co-evolutionary issues in the context of satellite viruses, which can be seen as viral parasites of viruses (they require ‘helper’ viruses for their genome replication). The latter issue is even more general since multiple infections between different parasite species. Modelling trait co-evolution in this context calls for a specific formalism [Choisy & de Roode, 2010], which has rarely been

applied to the evolution of social traits except in the context of co-transmission [Alizon, 2013].

This co-evolutionary dimension goes beyond microbial interactions. First, the diversity of hosts encountered in terms of immune defences or life-history traits is likely to shape virus evolution [Williams, 2012]. Second, for some host types or over long timescales, co-evolutionary host–parasite dynamics can take place that are known to lead to a range of outcomes, from peaceful coexistence to arms race [Van Baalen, 1998]. Adding superinfection into the model and, therefore, increasing the opportunities for interaction between genotypes seems to favour the latter equilibrium [Kada & Lion, 2015]. Allowing for co-infections and different within-host interactions remains to be done but these could lead to a diversity of evolutionary outcomes and help understand the evolution of mutualistic viruses [Pradeu, 2016a].

Is it time for ‘sociovirology’?

The term ‘sociovirology’ seems to have first appeared in the literature in a Commentary in 2017 [Díaz-Muñoz et al., 2017]. In spite of the undeniable beauty of the word itself, the elements listed in this commentary suggest that it may be premature to refer to it as a field or a subfield for theoretical and historical reasons.

The features that make virus evolution such an appealing topic for social evolution are shared by other organisms since microsporidia or bacteria such as *Chlamydia trachomatis* or *Bdellovibrio bacteriovorus* are also obligate intracellular parasites. Therefore, one can wonder whether ‘socio-microbiology’ or ‘socio-parasitology’ might not be more accurate terms, with the caveat that all seem to currently share a lack of clarity about what a social trait is. Furthermore, the parasitic lifestyle implies that virus life-history traits cannot be defined independently of a host, de facto creating a social interaction, albeit between different species. In addition to a potential lack of specificity, a risk that should not be neglected is to appear as presenting reinterpretations of known features in virology as novel findings. Nearly half a century ago, the coining of sociobiology undoubtedly generated intense debates in the following years, but the term is now rarely used in article titles and this episode led to durable antagonism between evolutionary ecology and other fields in social sciences [Yudell & DeSalle, 2000]. Overall, insights from historians and philosophers of science could prove valuable on this delicate matter, especially given their growing interest in viruses [Pradeu et al., 2016].

Conversely, evolutionary epidemiology in general and multiple infection theory in particular, represent rich and lively frameworks to capture the spread of interacting genotypes in populations that can be instrumental to understanding the evolution of virus life-history traits. Better integration of the tools and concepts developed by epidemiologists and infectious disease biologists can be inspiring for evolutionary biologists and virologists.

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