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# Persistence pays: how viruses promote host group survival

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Recently, we have realized that viruses numerically dominate all life. Although viruses are known to affect host survival in populations, this has not been previously evaluated in the context of host group selection. Group selection *per se* is not a currently accepted idea and its apparent occurrence is explained by statistical gene frequency models of kin selection. Viruses were not considered in such models. Prevalent views associate viruses and disease. Yet many viruses establish species-specific persistent, inapparent infections that are stable on an evolutionary time scale. Such persistent infections can have large effects on relative reproductive fitness of competing host populations. In this essay, I present arguments on how persistent infections can promote population survival. Mouse hepatitis virus is used as well studied examplar to re-evaluate the theoretical basis of the mouse haystack model of M Smith. This virus-centric re-examination concludes that viruses can indeed affect and promote relative group selection.

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If one captures wild mice (*Mus musculus domesticus*) and brings them onto a laboratory-breeding colony, it is highly probable that reproductive collapse of the established breeding colony will ensue. Since persistent infection of feral mice with up to 20 known highly prevalent mouse-specific viruses is likely, an acute pathogenic infection of the established lab colony (especially in young) is also likely. Much to the horror of any veterinarian responsible for the maintenance of the lab colony, such an event would also result in a facility (habitat) that would be persistently contaminated by various types of tenacious virus, requiring the cessation of breeding, cesarean birth, foster mothers and rigorous decontamination to re-establish a virus-free colony. Yet in all likelihood, these feral virus-infested newcomers would be healthy, fit and survive a virus-contaminated facility with little problem. The viruses involved include a full spectrum of plus and minus strand RNA viruses (e.g. Theiler's virus, Mouse Norovirus, Mouse Hepatitis Virus, LCMV), dsRNA viruses (Mouse Reovirus), retroviruses (endogenous MMTV), and various small and large DNA viruses (Minute Virus of Mice, Mouse Parvovirus, Polyomavirus, Mouse Adenovirus, Murid Herpesvirus, Orthopox Virus), see [1] for natural prevalence. Although wild mouse populations differ in their specific virus composition, only some laboratory colonies are free of many, but not all, of these viruses (endogenous retroviruses are breed-specific). Thus some form of virus persistence is invariant in all natural murid populations and this persistence has big effects on the reproductive success of the population. Such inapparant viruses also have big effects on the innate and adaptive immune responses hence immunologist will insist on virus free mice to measure 'normal' immune responses and geneticist will insist on virus-free mice to measure 'normal' gene–phenotype relationships. In my judgment, however, this inapparant mouse–virus situation represents the norm for most life forms. We humans, for example, harbor eight types of prevalent persisting species-specific herpes viruses alone and one of these is known to be able to lethally infect gibbon ape colonies [2,3]. Similarly, human observers of wild gorilla populations should keep their distance in order to avoid exposing them to often-inapparent human viruses that can kill gorillas.

Most commercial 'practitioners' of life, whether they grow large vats of lactobacillus, study cyanobacteria, plants, mussels, shrimp, insects, fish, amphibians, or any mammal must contend with the real possibility of reproductive collapse following the introduction of feral, persistent virus-infested species that are related to those they are attempting to grow. And in some cases (i.e. mice), there may be no apparent genetic difference between populations that survive and those that collapse with virus exposure. The difference can be the relationship (transmission, immunity) between the same virus and the same host that allows the establishment of a persistently infected colony. Thus, this represents a difference in 'group state' relative to virus maintenance and the groups that are persistently infected with virus are the survivors—*survival of the persistently infected* [4–6]. This is not a small or isolated matter. Since our world is numerically dominated by viruses, they provide an inescapable selection on all life and it can be asserted that all extant organisms of Tree of Life are virus survivors. And virus can also matter for intergroup survival. None of the above assertions are likely to be startling or controversial to most

virologist, microbiologist or small mammal veterinarians. Yet from the perspective of accepted theory of evolutionary biology, there are some distinctly troubling issues raised and the assertion that group selection exists and can be mediated by virus will likely be contested. Below, I briefly outline how evolutionary biologist came to reject the notion of group selection and why I think their failure to consider the consequences of viruses to population survival (especially persistence) led them astray.

## A brief history of the rejection of group selection

In 1932, Haldane used the term 'altruistic' to explain self-sacrifice among genetically different individuals as a way to account for group-related selection (see [7]). Although Haldane also considered the possibility that viruses might participate in the origin of life (see [8,9], such thinking was subsequently dismissed and not included in group selection theory. Since Darwinian natural selection operates via competition between fittest individuals, the existence of altruism might seem to require some principle other than genetic relatedness and natural selection to explain group cooperation and survival. Until the early 1960s, some field biologists still thought group selection could be experimentally observed in field studies (i.e. artic birds) and proposed group advantages in selection (see [10] and [11]). But such views were challenged as having weak theoretical foundations and as being inconsistent with modern evolutionary thinking in that they lacked a role for Darwinian natural selection and competition between individuals. By the mid-sixties, there followed a series of publications that incorporated a role for natural selection in apparent group selection. Hamilton published his landmark paper on inclusive fitness theory, also known as kin selection and Maynar Smith (a student of Haldane) developed a mathematical model for the analysis of altruism [12]. Smith proposed a hypothetical haystack, colonized by a single fertilized female mouse, resulting in a population that colonizes additional haystacks. He used this model to evaluate the statistical gene frequencies that might contribute to population behaviors (altruistic genes) of genetically related individuals. Thus a statistical foundation was applied to natural selection of individuals, expressing fitness in absolute, reproductive terms (see [13]). The model evaluated the expected frequency of 'altruistic' alleles in these haystack colonies using established population genetic approaches of Nomura and concluded that altruism would be generally unfavorable outside of close kin. Then, in 1967 George Williams published his influential book ('Adaptation and Natural Selection' [14,15]) and defend the field against the 'heresy of group selection' (see Steve Rose commentary; Guardian, April 23, 2004). This book successfully convinced the field to dismiss the idea of group selection, outside of natural selection. Thus, although the existence of group selection in evolutionary biology was initially debated, it is now generally dismissed. Yet the ongoing field studies of social interactions amongst animals (sociobiology), continues to assert that the rejection of group selection needs to be revisited [16]. As this literature is not likely to be highly familiar to many microbiologist, the bullets below summarize the key developments:

- Early reports argued for the existence of group selection
- Such assertions lacked a Darwinian theoretical foundation (i.e. natural selection)
- Mathematical models suggest natural selection can promote altruistic traits
- Evolutionary biologist were thus convinced group selection *per se* does not exist
- Social biologist still question the absence of group selection

## Persistence as symbiotic; a group selective state

Symbiosis can be defined as the mutual existence of two organisms that had a distinct genetic origin, a definition that includes genomic and extragenomic persistence by viruses [17]. However, owing to the needed transmission between individuals, a host 'population' is the essential entity required to support the stable colonization by viruses. In this we start to see the relationship of virus transmission to group selection in that group selection requires the ability of one individual to regulate the outcome (survival) of another individual within the group. Virus colonization provides this feature and can have major impact on population-based competition and population-based survival (see [4]). As noted above, destructive acute infections with the same persisting virus can cause reproductive collapse of noncolonized host populations. But such infections are often derived from populations of related species that harbor a persisting nonpathogenic version of these same viruses. Because they are transmissible, viruses have inherent tendencies to promote the establishment of group or population-based relationships that can be both protective (i.e. persistent infections) and harmful (i.e. acute infections) to their host. By doing so, they can potentially provide a distinct theoretical foundation that promotes the origin and evolution of group traits that are stable in evolution [6].

## The haystack model revisited: adding virus to the haystack

The haystack mouse model originally proposed by M Smith was 'aviral'. This mathematical model imagined a mouse population residing in an imagined haystack where mice expressed individual fitness in absolute reproductive terms. Thus relative fitness was not included. However, high reproductive rates alone should not insure survival if other (similar) organisms bare alternative traits that are more 'relatively fit' [18]. Persisting and acute

viruses can provide precisely such relativistic group associated traits. With over 100 years of collective breeding experience, it is well established that interactions between wild mouse (*mus musculus*) populations and breeding colonies must always be strictly controlled (quarantined) to prevent an inevitably reproductive collapse. Even the very first established inbred mouse strains (Balb/c) suffered colony collapse from the milk-borne infection of young mice by endogenous MMTV. Yet, most wild caught mice are healthy (seldom showing acute viral disease) and are clearly fit relative to any inbred lab strains. Thus wild mice are reliable colonized by an array of mouse-specific persisting inapparent viruses that cause havoc when introduced into a naive breeding colony. Yet even wild mouse populations (i.e. islands) have been occasionally observed to collapse when initially exposed to common mouse viruses, establishing that population collapse is not peculiar to laboratory mouse colonies. Indeed, commercially grown colonies of most any animal species will often experience major collapse due to introduction of wild species (or populations) with new persisting viruses. For example, Japanese hatcheries (fish and shellfish) have long known that they must screen for inapparent persistent viruses to avoid large-scale population crashes of farmed fish and shellfish [19]. Survival of the specific population is thus relative to both the viruses they support and those they are exposed to. What then would be the consequence to a haystack model if we include these virus-mediated relative population effects?

## Premises of haystack model; adding relative 'viral' fitness

The haystack model considered a mouse population that lives as a colony in one haystack, founded by one fertilized female [12]. This population grows for an unspecified number of generations from which another single female can disperse to form other new colonies at adjacent haystacks. The interest was to calculate the distribution (frequency) of altruistic genes on the basis of various selective assumptions (such as dominance or recessive coefficients), using the mathematical methods of population genetics. The assumption of Darwinian selection is that a single line of heredity is being traced by measurements within groups. Thus, the classic concepts of 'altruistic' gene frequency (X) is applied from this perspective. In this, it is assumed that there is a cost $c$ to donor and benefit $b$ to recipient of altruism. The goal is then to calculate P of X or frequency to altruistic allele by applying the formula of Crow and Kimura for population genetics [20,21]. Group selection, however, as defined by Wilson and Wilson, is the evolution of traits based on differential survival and reproduction of groups [16]. For it to exist, it must involve measurable within-group selection versus between-group selection. Such putative group-based selection would have an inherently relative character as it is not determined by individuals, but by intergroup selection. However, if persistent virus colonization were involved in group selection, we immediately see that a basic tenant of Darwinian selection has been violated since symbiotic merger of virus–host fitness and genomes and horizontal transmission is not the product of a single ancestral line of heredity. The survival of a virus colonized or uncolonized host population depends very much on the relative (stochastic) exposure to related viruses.

## The MHV examplar; a realistic virus-infested haystack

Let us now consider an empirical and virus-centric perspective on group selection and add virus infection to the model. Operationally, we already know that moving mice between separate colonies can pose serious risks to those populations that are free of a specific virus. The outcome of haystack colonization by a pregnant female should thus be strongly affected by virus status. Since essentially all measured feral populations of mice appear to harbor various mouse-specific viruses, this is an empirically realistic premise [1,22,23]. A most prevalent and well-studied mouse virus is mouse hepatitis virus (MHV, a coronavirus, relative of SARS virus) [24]. How then does the presence or absence of MHV in the pregnant female founder affect the haystack model? Is there a differential survival or breeding success related to the colony that depends on MHV presence? Can the presence of this virus affect population-based survival and also affect group (altruistic) behaviors? If so, does the concept of persistent 'virus addiction' apply to or provide an alternative theoretical frameworks for understanding such group-based selection, as I have previously proposed [4]?

## Colony fitness as relative and epigenetic: MHV colonization as 'virus addiction'

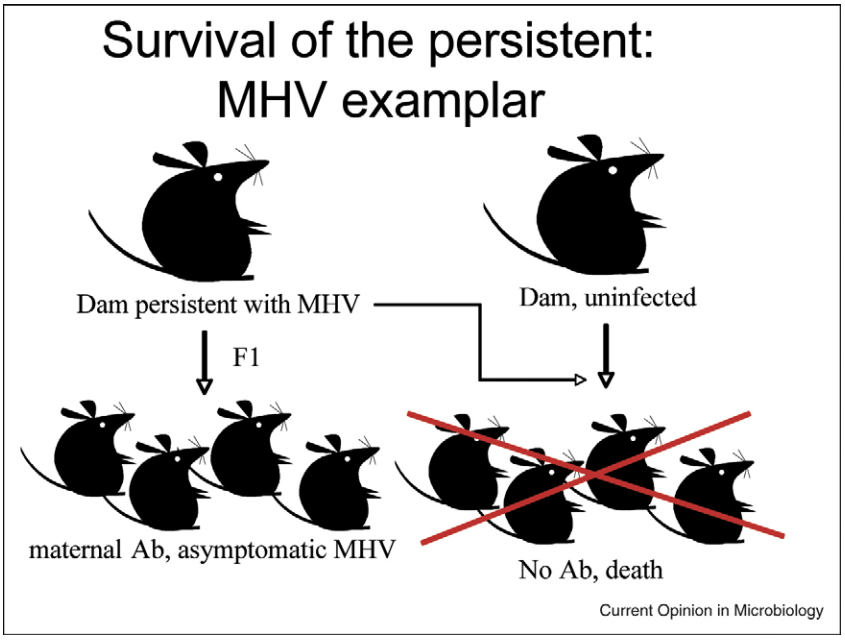
A transmissible extra-genomic agent like MHV, with variable prevalence and relativistic (state dependent) disease outcome does not fit the basal assumptions of any of the above mathematical models. One significant problem is that stable MHV persistence is an epigenetic dependent state [24–26]. By this, I mean that whether the virus establishes either inapparent persistence or acutely kills the colony is determined by differential (often non-genetic) circumstances that involve the same virus and the same host. What differs is the state of virus persistence, especially as found in mother and its young: a state that has major consequences to host population survival. A protective (persistent) state results when a persistently infected mother nurses the newborns of the colony, passively transmitting immunoglobulins through the milk that prevent lethal gut and CNS MHV infection of young thus promoting the establishment of persistence enteric infection in the next generation [27,28]. By contrast, a virus free mother, or one that does not transmit virus and protective immunoglobulins to the young of the colony (an occasional event) can lead to the establishment of a colony that is MHV free and susceptible to severe acute

MHV enteric and CNS disease. Consistent with this dual role, MHV from field isolates appears able to exist in two distinct population structures (biotypes). One (more prevalent type) is associated with persistence in enteric tissue [24] and has considerable genetic stability [29]. The other (less prevalent type, ~10%) is seen in acute CNS-mediated disease and this virus is a less stable quasispecies [24,30]. A virus-free colony (if isolated) would probably have somewhat higher reproductive success, since persistent MHV does have some measurable reproductive cost. However, as MHV is highly prevalent in wild populations, reproductive collapse is expected when an isolated virus-free mouse population encounters an infected population [31–33]. Thus wild mice harboring persistent but disease free MHV are the norm and must therefore be considered relatively fit. In addition, the elimination of MHV from a mouse colony often requires extended cessation of mouse breeding [34], so virus maintenance, habitat occupation and breeding success are also linked. Since mothers must provide immune milk to their young to establish persistence, a mother's altruistic behavior is also important, although foster (non-genetic) mother's can also provide passive protection against MHV by nursing genetically distinct pups [28]. A schematic of the differential survival of an MHV persistently infected 'haystack colony' is shown in Figure 1. This examplar also defines a generalized state of 'virus addiction' in that the persistent virus infection must be retained to protect the breeding colony from severe acute disease by this same prevalent virus [4,6]. The resulting group fitness is relative since an adjacent uncolonized population is threatened only if exposed to this virus. Also, in an MHV 'addicted' colony, any individual that 'cheats', such as a mother that clears the MHV infection or stops producing or offering immune milk will also fail to protect her young from acute viral disease that is stable in the habitat and population. Viral 'addiction modules' are thus inherently intolerant of 'cheaters' of the required group traits and such states are also robust and stable.

## MHV-mediated colony survival is one way

Suppose mated but genetically identical (inbred) dams establishing two respective colonies; one persistently infected with MHV and the other is not (as outlined in Figure 1). The separate haystacks should support equivalent colonies resulting from these dams and if anything, the MHV free colony would have a slight reproductive advantage. If incoming males to these colonies are not persisting with MHV, they are at risk of some viral disease (normally a limited infection in adults), but should still succeed in impregnating females. However, their offspring should be MHV protected and their sired colony survive but be MHV persistent. However, if any male from MHV positive colony contacts or mates with MHV negative colony, this will probably result in acute MHV introduction and reproductive collapse of the entire uninfected colony. Surviving mice, if any, will probably have become MHV colonized. Thus two haystack populations with identical founder genetics are expected to have very different outcomes depending on states of MHV persistence. Survival of the persistent population is expected. Since this is a population-based phenomenon, this also represents a form of group survival.

**Figure 1**




Schematic outline of how persistent infection by a virus (MHV) can affect relative population survival that is dependent on epigenetic states.

## MHV can mediate survival of an otherwise 'less fit' colony

In a second scenario, consider a wild (reproductively fit) but MHV negative mouse colony adjacent to inbred (reproductively less fit) but MHV persistent colony. In the absence of MHV, we clearly can expect that a wild population will out compete the inbred colony. However, since MHV can mediate the collapse of a wild mouse population [32], we would predict that communication between these two groups will result in the collapse of the MHV negative wild-type colony. Thus, in this scenario, we would initially expect the relative survival of the otherwise 'less fit' inbred but persistently infected colony (survival of the persistent). Here too we can also see that the outcome of competition between these colonies is not necessarily due to the exact genetic composition of the MHV positive mouse. The successful population must allow or support viral persistence. In this requirement, however, host immune genes are not simply opposing viral disease, as commonly believed, but must support stable persistence in the appropriate group. For example, if an innate immune gene is altered by mutation to no longer allow persistence, severe disease could be expected to result with corresponding poor survival in the wild. Observation with neurotropic herpes viruses in both mouse and humans appear to support this idea, as it appears mutations in various innate immune genes result in failure to establish herpes persistence, inducing acute often fatal CNS disease [35–37]. Indeed, it has been suggested that neurotropic persisting herpes viruses have contributed to the maintenance of otherwise 'redundant' innate immune genes in humans [38].

## Generalizing viral-mediated group selection

In summary, persistent viruses have provided us with a distinct perspective form which to understanding a haystack model and how virus can affect the relative reproductive success of mouse groups or colonies. The mouse MHV-haystack examplar clearly shows us that the reproductive success of a colony can depend on various viral, epigenetic and population-based parameters. Although it is clear that many of the exact characteristics that we see with this MHV-mouse example do not specifically apply to other persisting viruses (even of mice), it is nonetheless clear that all the other mouse-specific persisting viruses are highly adapted stable states that are specific to peculiar populations and that these viruses also tend to affect breeding success. Thus strong selective group-based advantages should be associated with stable persistent infections that can also be harmful to competing populations. Indeed, such agents can selectively sweep and may even exterminate specific and sometimes competing populations (such as British red squirrel [39]). The occurrence of species-specific persisting viral agents is well established in most natural populations of animals. However, in evolutionary biology, such states are not generally considered as a significant issue of relevance to population dynamics. Persistent viral states do not adhere to the usual predators/prey like models of virus/host dynamics as persistence is generally stable and specific to host populations. Also, in contrast to acute infections, persistence seldom jumps between species. In some species (e.g. mice and sheep) viruses (i.e. endogenous retroviruses) also persist in genomic DNA but can also emerge to acutely infect competing host populations, see [40].

Although viral persistence is highly prevalent in nature, its inherently silent character has historically limited its study. We often find these agents only by accident. Thus the overall viral consequences to long term survival of host populations are largely underappreciated, especially in evolutionary biology. Indeed metagenomic and transcriptomic screens do find much viral derived material but generally dismiss this as often silenced junk. However, the regulatory consequence of this material and its ability to modify information networks is just now starting to receive serious attention. When persistent viral states and populations are disturbed, such as from the introduction of new species, the introduction of feral members, new interactions between groups, or commercial growth of large virus-free and homogeneous populations, we often observe large and devastating consequence to populations that do not harbor the virus. All populations in our virus-dominated world have thus been virus molded. And the ability of such viruses to affect host survival appears never ending as seemingly every week agents continue to emerge from persistent states and threaten other populations.

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