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Variability in viral pathogenesis: modeling the dynamic of acute and persistent infections

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Virus infection often results in diverse outcomes. This variability of virus pathogenesis is not well understood. Here we revise theoretical arguments to further our understanding of factors controlling infection and its severity. We propose that variability in these factors results in different clinical outcomes, which ultimately ensure virus reproduction.

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Virulence versus transmission: a trade-off

A link between parasite virulence and its transmission efficiency is a paramount concept in modern epidemiology. The trade-off between these two pathogen's features has been studied and discussed for decades.

The original view that prevailed in 1880s–1990s was that pathogenicity (here and below also termed 'virulence') and transmission rates evolve independently. The best virus, according to this classical view, causes very small pathogenesis but replicates really well and therefore transmits at a high rate to other hosts (Figure 1a). Over time, the virus and the host coevolve and adapt to each other and the 'most convenient' strategy is to coexist in the long term. Historically this view was backed up by a classical in-nature experiment made on rabbit myxoma virus. When introduced in 1950 into Australia to limit European rabbit population, highly-virulent myxoma virus killed >99% of infected hosts. However, as the epidemic progressed, virulence appeared to decrease gradually within 15–20 years [1•].

An entirely different view on virulence and adaptation emerged in 1980s. A mathematical model predicted the existence of a trade-off between mortality and transmission [2•,3]. The hypothesis, introduced by Anderson and May [4••] and Ewald [5•], assumed that host resources that could be used by the virus are limited. Therefore, increasing viral replication – and thus transmission – without harming the host is not possible. Transmission increases as a function of pathogenesis.

The trade-off hypothesis is formulated in terms of pathogen's fitness. Fitness is defined as the 'reproduction number' (R_0), the average number of hosts newly infected with virus from a previously infected host [6]:

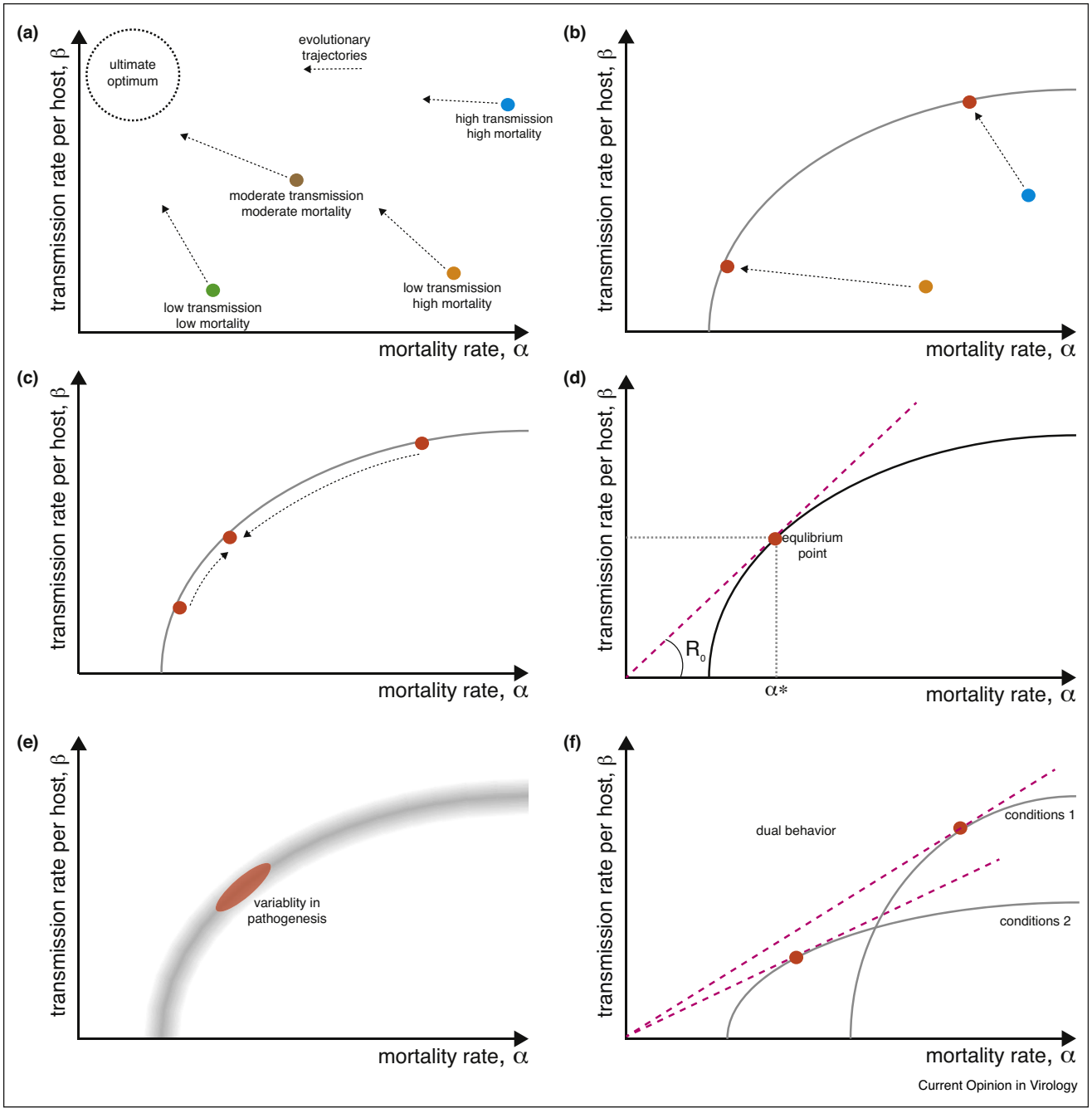
$$R_0 = \beta S/(\mu + \alpha + \gamma)$$

Here S is the density of susceptible hosts in the population, β is the transmission rate of virus per susceptible host per unit time, μ, α and γ are host's rates of natural death, the death rate due to infection, and the recovery rate from infection. The combined parameter βS represent the average number of new individuals infected by a single infected host per unit time and $(\mu + \alpha + \gamma)^{-1}$—the average time of host's exposure to infection.

According to the trade-off hypothesis, higher transmission comes at a cost to the host fitness. In other words, there is a minimal harm that pathogen must inflict on the host. The basic Susceptible-Recovered-Infected models [2] measure the minimal pathogenicity as a reduction in either the host lifespan or host reproduction due to the viral infection, or both. The transmission rate plotted against the minimal pathogenicity is called 'the tradeoff curve' (Figure 1b, dashed curve). This curve limits the area on the chart potentially accessible to a pathogen. The existence of that limited area expresses the main idea by Anderson and May [4••] and Ewald [5•] that one cannot have very high replication and transmission without causing high pathogenicity.

In the long-term, as we discuss below in more detail, the system host-pathogen arrives at an equilibrium represented by a point on the tradeoff curve (Figure 1b). In this situation, the variant composition in the virus population [7,8] are in transient equilibrium with the host. As time passes by, the transient equilibrium point slides along the tradeoff curve until it arrives at the ultimate long-term equilibrium (Figure 1c). The coordinates of the

Figure 1



(a) Hypothesis of avirulence of well-evolved viruses. All viruses are evolving to lower their virulence (here virus-related mortality rate per time unit, α) and increase transmission (rate per susceptible host per time unit, β). This assumes independent evolution of these two parameters. Dots show different virus strains or species. **(b)** Hypothesis of tradeoff (interdependence) of virulence and transmission due to host-scale factors. Paths show direction of dynamics of host population toward local equilibrium. Curve with dots: different possible local equilibria (depending on initial values α and β). Thus, virulence and transmissibility, although defined on the epidemiological scale, are mutually restricted due to underlying host-scale factors. **(c)** A single tradeoff point. The arrows along the curve show direction of long-term genetic evolution toward stable end-point equilibrium. **(d)** Long-term equilibrium. μ and γ are natural mortality and recovery rates correspondingly. The straight line is the tangent of the curve. Fitness (R_0) could be found as a tangent of this curve. **(e–d)** Hypothesis: variability in ecological factors leads to a fluctuating of tradeoff curve resulting in viruses with variable pathogenesis (d). Existence of two sparse conditions results in two tradeoff curves and viruses with dual pathogenesis (e).

ultimate equilibrium can be found graphically as a tangent of the curve that passes through the origin of the chart (Figure 1d). Intuitively, the tangent (R_0) is the maximum ratio of transmission to pathogenesis that can be achieved.

One strategy for a virus to increase the transmission to pathogenesis would be to prolong the virus existence within a host (*i.e.*, minimize $\alpha + \gamma$) as illustrated with arboviruses that persist in mosquitoes and HIV in humans. However, since many viruses are unequipped to establish lifelong persistence, they may evolve to maximize their yields within limited time windows (*i.e.*, maximize β). In this connection, while describing possible virus strategies, Alizon et al. [2] allude to the Achilles' dilemma, a choice between a short and bright life (*i.e.*, brief acute infection with high virus loads) versus a long but inglorious one (persistent infection with low virus loads excreted during longer periods). Severe symptoms or even the death of hosts may be evolutionarily beneficial for a virus if they increase the resulting number of infectious particles excreted and transmitted.

Biological factors that may promote long term evolutionary stability in highly virulent viruses

In contrast to the classical view that prevailed over a century, some highly virulent viruses retain high pathogenicity in the long-term. The trade-off models [3] help to understand this observation. Below we describe several sets of potentially important factors driving benign/virulent infection equilibrium:

a. A major group of factors are biochemical and physiological limitations of virus replication within its host. Although understanding of these factors is far from being complete, it is clear that some viruses persist for life while the others are incapable of establishing long-term persistence. In addition some viruses kill rapidly, while the others can hardly cause an apparent disease. These observations imply that different areas on the trade-off chart (Figure 1b–f) are differently accessible to various virus species (at least within the visible evolutionary timeframes), affecting their final choice of the replication strategy.
b. Another group of factors are parameters of host's population, such as its density. It is very important that the 'tempo' of pathogen expansion into a host population depends on the average number of susceptible hosts that come in contact with an infected host (denoted S in the equation above). A virus strategy that involves fast and severe pathogenesis should be more efficient in very dense populations where the hosts are contacting each other more frequently. Highly pathogenic viruses should also benefit from the high rate of host's reproduction, as this masks the declines in host's numbers caused by infection-related death. However, such viruses indirectly limit their own progression by decimating the host population (*i.e.*, by decreasing S), making lethal diseases a poor long-term strategy. In contrast to this common-sense notion, some pathogens, such as smallpox virus or foot-and-mouth disease virus, in real life cause harsh symptoms in their native hosts. The trade-off models help to understand the evolutionary basis of these observations.
c. In some cases, more complex trade-offs are taking place. Sometimes, severe pathogenesis itself helps virus to disseminate. One example is the behavioral change occurring in carnivorous mammals upon rabies virus infection [9]. Rabies virus shortens host's lifespan by increasing the transmission efficiency of excreted particles, since the aversion to swallowing liquids leads to spread of infectious saliva. Also, the changed behavior of active search and biting increases the number of contacts with susceptible hosts. Another well-known example is prion disease Kuru, which was infecting the Fore people in Papua New Guinea. Since its transmission was coupled with funerary cannibalism, the premature death of the host augmented pathogen spread [10]. The multi-biolevel approach, including intra-cell, inter-cell, host, and population levels, is required to integrate all these diverse groups of factors within a single modeling framework.

Viruses with variable pathogenesis: 'accidental' events or multiple equilibria?

So far we have discussed why some well-evolved viruses retain high level of pathogenesis despite they have reached a steady state in adaptation. The basic version of the tradeoff model(s) predicts a single dot on the transmission/pathogenesis chart upon reaching the evolutionary equilibrium (Figure 1c). This is well explained by the existing basic models [2].

The issue that so far received little theoretical attention is that some pathogens are known to show extremely different pathogenic forms ranging from benign to lethal in the same host population. In the chart 'transmission-pathogenesis', this observation implies multiple equilibrium points or even whole continuous equilibrium regions on the tradeoff curve of the chart (Figure 1e,f). One of such examples is bluetongue virus infecting ruminants (cows, sheeps, deers, *etc.*). Infection of the susceptible hosts of the same breed results in a broad range of pathological consequences [11]. Some viral diseases are known to exist as several discrete forms (Figure 1f) rather than with a continuous gradient of symptoms' harshness. The best understood examples are lysogenic bacteriophages, which are 'benign' while host bacteria are growing on rich medium and 'acute' when hosts are starving. Interestingly, a recent report showed intercommunication between bacteriophages allow them to choose the most effective infection strategy, lytic or lysogenic [12•]. Dual

pathogenesis is also known for animal pathogens, for example, Drosophila C virus displays two drastically different pathogenic patterns, lethal and persistent, in genetically identical hosts depending on the route of infection (intra-haemocoelic versus oral) and input virus load. Persistently infected flies display minor pathogenesis, little if any lifespan shortening and sometimes increased fecundity [13]. Acutely infected animals succumb rapidly, producing enormous amounts of virus (more than in 3 orders of magnitude exceeding those in benign infections) [14•]. Out of human pathogens the extensively studied example of the 'dual behavior' is poliomyelitis, a disease caused by a benign gut virus that sporadically penetrates into central nervous system and induces acute encephalitis, which leads to flaccid paralysis and sometimes death, in less than 1% of infected human hosts [15]. Curiously, dual behavior of poliovirus seems to be evolutionary conserved. Experiments suggest that neurotropism of poliovirus can be compromised by mutations [16] or even by reducing diversity in virus' quasispecies populations [17]. Currently used live poliovirus vaccines are replication-competent and can be transmitted from human to human, but are not capable to induce flaccid paralysis. However, these attenuated viruses rapidly revert to strains again capable to induce severe disease [18]. These observations, taken together with polio-like flaccid paralysis symptoms documented already by Ancient Egyptians, argue the polio-derived pathology is an evolutionary stable adaptation rather than a coincidence. However the exact evolutional benefit of acute poliovirus infection is unclear. One is tempted to speculate that It might relate to specific behavioral reactions of prehistoric humans to paralysis in their infants. Many researchers consider poliovirus neurovirulence an 'accidental' event [19]. They argue that neuroinvasion is not needed for successful polio replication and occurs largely independent on host's parameters (age, gender, *etc.*) while its retention in evolution is a coincidence as it is believed to happen for neutral adaptations [20], for example, by occasional genetic linkage with the function that is vital for reproduction. Existence of a minority of patients with severe symptoms (polio, influenza A H1N1 and B, *etc.*) is clearly a major concern for public health that requires to be studied and explained. Even more importantly, acute viruses (such as Ebola [21], West Nile [22], tick-born encephalitis [23], Crimean-Congo hemmoragic fever [24], MERS-CoV [25] and many others) can infect humans without any symtoms as judged by seroconversion analysis. Humans asymptomatically infected with dengue [26] and Zika [27] viruses were directly shown to spread the pathogens. Thus variability in pathogenesis is an almost universal feature, but in most cases virus-driven variability is difficult to differentiate from genetic or epigenetic variations in the hosts. This problem is also poorly addressed in animal models since often invariable experimental systems are used. The focus of this article is to discuss the possible theoretical tools that might address this type of phenomena from an evolutional perspective.

Basic tradeoff models do not take in account a variety of biological parameters, such as: host population structure, social behavior, genetic, ecological and immune inhomogeneity, environmental factors, affecting virus containment and transmission, and so on. Real-life tradeoff curve shown in Figure 1d is a superposition of plethora multidimensional transient tradeoffs, change over the time therefore changing the position of maximal accessible R_0 (Figure 1f). If these transformations are occurring regularly over time and space (due to seasons, oscillations of population density, *etc.*) virus might occupy a wider region of expected equilibria on the tradeoff chart, rather than to continuously evolve toward the sliding short-term punctiform equilibrium. We propose that variation in virulence, usually considered by most researchers as an outcome of biological noise affecting pathogenesis, could in some part come from an implementation of intrinsic virus strategy. Moreover these two possibilities are not mutually exclusive: viruses can intentionally exploit variability and biological noise by making their replication machinery specifically sensitive to variable factors, as in case of bacteriophages, or even employ the stochasticity, as it is believed for poliovirus. Taking in account that virus pathogenesis on the organism level in some cases might depend on infection outcome in a small groups of susceptible cells (*e.g.*, endothelial cells, organizing blood-brain barrier in mammals), it is possible that the pathogenesis on the host level could have a stochastic component, as it has been recently demonstrated on the single-cell level [28•]. In this case virus might adapt a dual strategy composed of majorly conservative choices (low risk-low reward) and a small proportion of highly risky behavior (high risk-high reward), alternating stochastically.

To conclude, the simplest models of trade-off (such as shown in Figure 1) are not capable of explaining the rich variety of observations regarding the evolutionary stability of the viruses with dual or continuous variation in pathogenesis. Regular variations in ecological factors may affect the shape of trade-off curve and create multiple equilibrium points making pathogens to adopt more complex replication strategies.

The central questions that have to be addressed are:

(i) Can 'dual' or 'multiple' pathogenesis be evolutionarily stable? If the latter is true, which ecological factors are the most critical?
(ii) How viruses choose between 'acute' and 'benign' strategies at multiple levels of biological organization: signaling networks and RNA expression in a cell, inter-cell transmission, within-host inter-host transmission, and epidemiological level. How to couple these levels, input to output?

(iii) At each scale the system is non-uniform (within-cell structures, different cell tissue within host, topographic and ecological subdivision of populations). What are the simplest generalizations of the basic SIR models that take this into account?

Future experimental research coupled to modeling will shed light on these issues.

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