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Theoretical approaches to disclosing the emergence and adaptive advantages of multipartite viruses

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Multipartite viruses have a segmented genome encapsidated in different viral particles that, in principle, propagate independently. Current empirical knowledge on the molecular, ecological and evolutionary features underlying the very existence of multipartitism is fragmented and puzzling. Although it is generally assumed that multipartitism is viable only when propagation occurs at high multiplicity of infection, evidence indicates that severe population bottlenecks are common. Mathematical models aimed at describing the dynamics of multipartite viruses typically assign an advantage to the multipartite form to compensate for the cost of high multiplicity of infection. Since progress in the theoretical understanding of the evolutionary ecology of multipartitism is strongly conditioned by empirical advances, both aspects are jointly revised in this contribution.

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Introduction

Among multicomponent viruses, multipartite viral species stand as the most puzzling ones. The need for complementation demands a high multiplicity of infection (MOI) that does not seem to be always guaranteed under propagation in the wild. Also, the advantages of multipartite viral species with respect to potentially competing monopartite forms are unclear. Still, current evidence supports that multipartitism has emerged independently a number of times along evolution, representing over 16% of viral species described to date [1••]. As an adaptive strategy, it undeniably yields highly successful viruses which, however, seem to be strongly biased towards infecting plants, followed by fungi [2].

The very existence of multipartite viruses poses many more questions than answers. Which are the specific advantages conferred by multipartitism? Are those advantages enjoyed by all such species? Which are the qualitative and quantitative differences between multipartite viruses and segmented viruses? How is the loss of information due to population bottlenecks overcome? Which are the features of the ecological niche occupied by this strategy? All these questions, though important not only to understand multipartitism, but to the adaptive and evolutionary processes overall, have received limited attention in the literature. However, the interest of the community has been stirred thanks to new empirical results and fresh conceptual viewpoints. First, the host range of multipartite species has been extended significantly [3], suggesting that transmissibility costs need to be reconsidered; secondly, the unbalanced presence of the different segments in the host, which can be seen in some early experiments [4,5], has been carefully quantified, leading to challenging hypotheses regarding its adaptive meaning [6•,7,8]. Finally, new models which address the evolutionary strategy deployed by multipartite viral species in an ecological context hint at possible advantages of opportunistic behaviour [9].

Empirical observations

As of today, quantitative data on multipartite viruses and their adaptive advantages is meagre, and to a large extent regard the molecular properties of those viruses [10,11]. Main empirical findings are summarized in this section and in Table 1. We do not intend to be exhaustive, rather focusing on the observations that improve our understanding of the evolutionary and adaptive mechanisms behind multipartitism.

Multipartite viruses were indirectly detected through experiments showing a relationship between viral dose and number of local lesions steeper than predicted by the independent-action hypothesis model [12], which assumes that different viral particles do not interact during the infection process. A nice summary of this initial discovery and the additional research it triggered can be found in [13]. Only three families (seven genera) of multipartite viruses, all having ssRNA genomes of positive polarity, were known in the early 1980s. The first multipartite virus with DNA genome described was a begomovirus [14], and few years later a bipartite ophiovirus with an ssRNA genome of negative polarity was the first example with a filamentous nucleocapsid [15].

Table 1

Main properties of mathematical models dealing with different features of multipartite virus (white background) and main empirical highlights (green background). For the former, we show the nomenclature used to name the multipartite viruses (there is no unique term used in the literature), the factor that each model introduces to reinforce the segments versus the monopartite type in order to compensate for the disadvantage of complementation, the model type and the main novelty of each work; for the latter, we explain the main observation and list the viruses used in the experiments

Reference	Nomenclature	Advantage of segments	Type of model	Novelty and/or empirical basis
Price and Spencer, 1943 [12]	*The relationship between the dose and the number of local lesions for different plant viruses is steeper than predicted by the independent-action hypothesis model* ***alfalfa mosaic virus, tobacco necrosis virus, tobacco ringspot virus***			
Haber et al, 1981 [14]	*First description of a multipartite virus with ssDNA genome* ***bean golden mosaic virus***			
Pressing and Reaney, 1984 [42]	Multicompartment virus	Increase in copying fidelity under high mutation rate	Quasispecies model, included thermodynamics of the (noisy) replication process	First quantitative model. Most multipartite viruses described at the time had an RNA genome
Nee, 1987 [36]	Covirus	Higher copying fidelity and replication rate	Stable states of the competition between mono- and multipartite forms. Individual selection	Weighted the opposite effects of MOI and mutations. Followed arguments in [42]
Derrick et al., 1988 [15]	*First description of a ssRNA multipartite virus of negative polarity and of the virion as a filamentous nucleocapsid* ***citrus psorosis virus***			
French and Ahlquist 1988 [4]	*They first shown the different accumulation levels of genomic segments for the tripartite* ***brome mosaic virus***			
Iltis et al., 1989 [38]	Multicomponent virus	,9-	Probabilistic, included viral interference	Dynamics of infection-dilution in cell culture series. Motivated by [12]
Nee and Maynard Smith, 1990 [48]	Covirus, multicomponent virus	Higher copying fidelity	Deterministic, game theory	Overall and integrative review of molecular parasites. Discussion of pros and cons of multipartitism
Chao, 1991 [35]	Multi-component virus	Reduced mutational load, enhanced sex as re-assortment	Stable states of the competition between mono- and multipartite forms	Complementation/reassortment as a form of sex. Follows [36] and includes frequency-dependent replication
Szathmáry, 1992 [43]	Covirus, multicompartment virus	Local clustering	Structured deme model, game theory	Local replication, effects of compartmentalization in the establishment of defective viral forms and covirus
Nee, 2000 [44]	Covirus	Higher colonization probability	Ecological and epidemiological model	Virus-covirus coexistence is unlikely, in agreement with observations
García-Arriaza et al, 2004 [16]	*An evolutionary transition from a monopartite to a fitter bipartite viral form is possible and spontaneously arises in laboratory conditions under high MOI* ***foot-and-mouth disease virus***			
Timchenko et al, 2006 [18]	*Several genome segments are dispensable to develop infection in laboratory conditions, though they are maintained in vivo* ***faba bean necrotic yellow virus***			
Moury et al, 2007 [21]	*Narrow bottlenecks exist during vector transmission of a plant virus. The average number of particles transmitted by an aphid is 0.5-3.2* ***potato virus Y***			
Miyashita et al, 2010 [27]	*Narrow bottlenecks exist in cell-to-cell movement during tissue infection, promoting superinfection exclusion, though it does not affect genome complementation* ***soil-borne wheat mosaic virus***			
Ojosnegros et al, 2011 [17]	*The advantage of the bipartite form in [16] is identified and quantified. Shorter genomes independently encapsidated are more stable. No advantages in replication rate or in the effect of mutations are detected* ***foot-and-mouth disease virus***			
Iranzo & Manrubia, 2012 [45]	Multipartite	Higher stability, lower degradation	Combinatorial stochastic model, game theory	Grounded in results by [16, 17], implements frequency-dependent replication and population bottlenecks
Sicard et al, 2013 [6]	*The significant imbalance in the abundances of different fragments in a multipartite virus is hypothesized to stem from a gene-copy number regulation.* ***faba bean necrotic stunt virus***			
Sánchez-Navarro et al, 2013 [13]	*Genome segments appear in different frequencies and lead to differences in the invasion probabilities of each particle. Infection kinetics are delayed for a tripartite virus compared to the monopartite situation (updating results in [12] and subsequent research)* ***alfalfa mosaic virus, nicotiana tabacum***			
Valdano et al, 2018 [9]	Multipartite virus	Higher transmissibility	Epidemic spatial model	Complex network of host contacts. Generalizes [45] to the ecological context

A major leap in the quantitative characterization of multipartitism arrived with a cell culture experiment with an unsegmented animal virus [16]. After a long number of serial passages at high MOI, two defective and complementary viral genomes spontaneously emerged. Competition experiments between the evolved bipartite form and the wild, parental type, demonstrated the superiority of the former under high MOI conditions, while the wild parental type re-emerged through recombination as soon as the population was subjected to bottlenecks. Eventually, it was shown that defective complementary particles were more stable between infection events, this advantage sufficing to displace the parental wild type [17•].

The unequal abundances of fragments qualitatively present in early experiments [4,5] have been recently detected and quantified in other multipartite viruses [6•,7,8]. *Nanoviridae* is a multipartite viral family with species having up to eight independent segments. Though they manage to maintain all those segments *in vivo*, it has been shown that some of the segments are actually dispensable *in vitro* [18]. This is a puzzling observation considering the cost imposed by any