Current Opinion in Virology 2015, **10**: 1-6

doi: 10.1016/j.coviro.2014.10.006

Emerging viruses: why they are not jacks of all trades?

Stéphanie Bedhomme[1,3,4,7], Julia Hillung[1,5], Santiago F. Elena[1,2,6].

[1]Instituto de Biología Molecular y Celular de Plantas, Consejo Superior de Investigaciones Científicas-UPV, 46022 Valencia, Spain

[2]The Santa Fe Institute, Santa Fe, NM 87501, USA

[3]Present address: Centre d'Ecologie Fonctionnelle et Evolutive, CNRS – UMR 5175, Montpellier, France

[4]stebed@googlemail.upv.es – Tel: +33 04 67 61 32 01

[5]juhil1@ibmcp.upv.es – Tel: +34 963 879 930

[6]sfelena@ibmcp.upv.es - Tel: +34 963 877 895

[7]Corresponding author.

Abstract

In order to limit the impact of the recent pandemics ignited by viral host jumps, it is necessary to better understand the ecological and evolutionary factors influencing the early steps of emergence and the interactions between them. Antagonistic pleiotropy, i.e. the negative fitness effect in the primary host of mutations allowing the infection of and the multiplication in a new host, has long been thought to be the main limitation to the evolution of generalist viruses and thus to emergence. However, the accumulation of experimental examples contradicting the hypothesis of antagonistic pleiotropy has highlighted the importance of other factors such as the epistasis between mutations increasing the adaptation to a new host. Epistasis is pervasive in viruses, affects the shape of the adaptive landscape and consequently the accessibility of evolutionary pathways. Finally, recent studies have gone steps further in the complexity of viral fitness determinism and stressed the potential importance of the epistatic pleiotropy and of the impact of host living conditions.

Introduction

Many emerging viral diseases are caused by viruses that acquired the capacity to infect a previously non-susceptible host population [1, 2]. The newly accessed population can be constituted of host individuals of a new genotype, ecotype, variety, or species that now becomes part of the virus' host range. Such recent emergences have had tremendous repercussions for human and animal health and agricultural production. Approaches identifying emerging viruses before they become pandemic are thus needed [3]. This requires a better understanding of the independent and concomitant effects of the evolutionary and ecological factors influencing the early steps of emergence, in order to tentatively ameliorate our ability to predict the emerging potential of viral genotypes or isolates [3, 4]. In this review, we use examples from DNA and RNA viruses infecting animal, plant, or bacteria. Host type and genetic material are associated with specific constrains (e.g. mutation rate is higher in RNA virus; the animal immune system is much more specific than the plant one), but we want to give a broad panorama of the factors affecting viral emergence and hopefully draw some general mechanisms ruling it.

Generation of genetic diversity as an a priori condition for emergence

A first and necessary condition for emergence is the existence in the viral population replicating within the primary host of standing genetic variation making possible the infection and multiplication in the new host after occasional and often repeated spillovers [2, 5]. Viruses, and in particular RNA viruses, have a strong evolutionary potential as a consequence of their fast and error-prone replication [6] and large population sizes [2, 5]. Consequently, mutant generation should not be a limitation to their emergence. The only studies systematically investigating the rate of spontaneous host range mutations [7, 8] did so for the

phage Φ6 and its ability to infect new hosts closely related to the ancestral one. In this system, the equilibrium frequency of mutations that enable infection of a novel host was high (3×10^{-4}) [7] and likely higher than in other systems including more distantly related hosts. The strong potential of viruses to generate host range mutants is also supported by the very rapid generation of viral escape mutants breaking RNAi mediated resistance in a plant RNA virus [9, 10].

The antagonistic pleiotropic effect of adaptive mutations

A second condition for emergence is that the host range mutant should be able to replicate sufficiently well both in the primary and the novel hosts. Indeed, it is assumed that the mutant is initially poorly adapted to the new host and its adaptation requires that it persists long enough in the new hosts to allow for evolutionary rescue and/or repeated spillovers from the ancestral host, acting as a source, to the new host, that acts as a temporary sink [11, 12]. It has long been thought that it is difficult to meet this second condition, because of fitness trade-offs between hosts, i.e. because mutants performing well in one host will perform badly in another host (Figure 1). This phenomenon is usually referred to the "jack of all trade" hypothesis [13], or to $G\times E$ interaction (where G designs the virus genotype and E designs the environment in which the virus replicates, otherwise said, the host). More recently, this same phenomenon was also renamed "sign pleiotropy" [14] in the conceptual framework of $G\times G\times E$ interactions (see below). At the mechanistic level, it can be due to the antagonistic pleiotropy of host-range mutations [15] or to the accumulation of mutations neutral in one host, because they are in a gene whose product is not required in the new host, and detrimental in the other host [16]. This second mechanism is, however, unlikely in viruses with small genomes, overlapping genes, and encoding for multifunctional proteins.

84 The existence of *G*×*E* interactions has been verified in various viral experimental
85 systems by two types of approaches. First, negative correlations between fitness in
86 the primary host and in the new host have been established [e.g. 8]. Second,
87 experimental evolution approaches where the same virus isolate or genotype is
88 passaged in different hosts (either different species of the host range or successive
89 hosts of the life cycle) usually show a pattern of specialization, i.e. virus lineages
90 evolved in one host performed better in this host than lineages evolved in other
91 hosts and this specialisation comes to a cost in terms of fitness in alternative hosts
92 in part of the cases [17-25]. Recently, another approach has brought both
93 confirmation and refinement of the antagonistic pleiotropy hypothesis: Lalić et al.
94 [26] measured a component of fitness, the multiplication rate, for 20 point mutants
95 of *Tobacco etch virus* (TEV) in eight host species. The full factorial design of this
96 experiment allowed to partition the variance in fitness in its different components,
97 showing that most of the observed variation (66.82%) was attributable to the *G*×*E*
98 interaction, whereas 26.13% resulted from differences among host species and only
99 4.29% to genetic differences among mutants. Additionally, it showed that the mode
100 and shape of the distribution of mutational fitness effects (DMFE) varied with the
101 host species: mutations were either neutral or deleterious in hosts that are close
102 relatives to the primary one (*Nicotiana tabacum*), and as hosts' taxonomic
103 relatedness to the primary one decreased, the distribution became flatter with
104 larger expected deleterious fitness effect but also a certain fraction of mutations
105 being beneficial.

106 Along these multiple experimental confirmations of the existence of fitness trade-
107 offs between hosts, there are also a number of examples of adaptation to a new
108 host, or specialisation, without any cost on alternative hosts [24, 27-30]. This has
109 important consequences for the understanding of the host range evolution because

110 if broadening of the host range can occur at no cost, it would mean that the idea
111 that generalists are evolutionary disadvantaged because they are outcompeted by
112 specialists in every hosts is not always true and that no-cost generalist should
113 emerge a lot more often than they do. Probably a first step in understanding better
114 what limits viral emergence is to realize that the antagonistic pleiotropy model is
115 useful but overly simplistic and that more realistic models taking into account the
116 complexity of host-range evolution are needed. A first aspect of this complexity is
117 actually revealed by the effect of host relatedness on variation of the DMFE shape
118 and mode. Indeed the *E* in *G*×*E* interaction designates differences between hosts
119 ranging from different host genotypes, host ecotypes or different host species with
120 various degrees of phylogenetic relatedness. The data from Lalić et al. suggest that
121 the *G*×*E* interactions are more pronounced and frequent when the different hosts
122 are phylogenetically distant, as sketched in Figure 1. This makes sense at the
123 mechanistic level: related host species are more likely to share cell receptors and
124 defence mechanisms, thus the ability to infect and replicate in related species is
125 more likely to be positively correlated. This relationship between host jump ability
126 and host phylogenetic relationship also opens the possibility that a virus initially
127 unable to infect a host becomes able to infect it after adaptation to an intermediate
128 host in terms of phylogenetic distance.

129 **Complex interactions between mutations**

130 Another level of complexity that has to be integrated is what hides behind *G* in
131 *G*×*E* interactions. Again, depending on the experiment, *G* can represent point
132 mutants, isolates or experimentally evolved lineages but in any case, the genotype
133 is considered as a whole. Full genome sequences of experimentally adapted virus
134 lineages showed that they frequently differ from their ancestors by several
135 mutations [e.g. 24, 25, 31], opening the possibility of epistasis between them.

136 Epistasis (or $G\times G$ interaction) designates the fact that effect of mutations is not
137 multiplicative but that there are interactions among them. This definition of $G\times G$
138 interaction is the one classically used in quantitative genetics and it should not be
139 confused with the interaction between host genotype and pathogen genotype that
140 plant pathologist also name "genotype" by "genotype" interaction. Epistasis is
141 known to be a key determinant in adaptive processes as it determines the
142 ruggedness of the adaptive landscape [32, 33], and thus the accessibility of
143 adaptive pathways throughout the landscape [34-36] and the probability of
144 trajectories to end up at suboptimal fitness peaks. A measure of epistasis can be
145 derived from experimental fitness measures of single and double mutants [37] and
146 epistasis can be divided in various types depending on the actual effects of the
147 interaction (Figure 2): magnitude epistasis refers to cases where the magnitude
148 effect of a mutation depends on the background while its sign is constant.
149 Magnitude epistasis is positive when the double mutant is fitter than expected
150 from the multiplicative effect of the individual mutations and negative in the
151 opposite case. Sign epistasis refers to cases where the background affects the sign
152 of the effect of a mutation. Reciprocal sign epistasis is a particular case where the
153 sign of the effect of a mutation depends on the allele present at another locus and
154 reciprocally. Reciprocal sign epistasis is a necessary condition for an adaptive
155 landscape to be rugged [33]. The pervasiveness of epistasis is revealed by studies
156 directly investigating the level of epistasis [references in 38 and, 39-45] as well as
157 by the importance of historical contingency and compensatory evolution in viral
158 evolution [46, 47], compensatory evolution being a special case of reciprocal sign
159 epistasis. Additionally, recent studies in plant viruses [43-45], bacteriophages [39]
160 and human viruses [42] highlighted that sign epistasis, and in particular reciprocal
161 sign epistasis, are more frequent than it was previously thought. This suggests the

existence of rugged fitness landscapes in these species and that reciprocal sign epistasis is actually a factor partially limiting their emergence potential.

G×*E* and *G*×*G* interactions are thus probably two evolutionary mechanisms limiting viral emergence, but it is more and more clear that they do not capture all the complexity of viral emergence and of the interactions between ecological and evolutionary factors determining its success.

Higher order interactions

A further source of complexity is the triple way interaction corresponding to the combination of the two previous two-way interactions. Concretely, it means that the type and magnitude of epistatis could depend on the host species (Figure 3). Recently, these *G*×*G*×*E* interactions have been suggested by one study in HIV-1 [42] and directly demonstrated in a plant virus [48]: average epistasis was positive in the primary host, but on average negative in alternative hosts. Furthermore, the number of non-epistatic interactions was significantly larger in more phylogenetically distant hosts. *G*×*G*×*E* interactions are equivalent to the recently introduced notion of epistatic pleiotropy [14] which allows for the evolution of either specialist or no-cost generalist viruses, depending on the host in which the viral population evolves. Consequently, these third order interactions will increase or decrease the probability of host-range expansion depending on the specific host-switch.

So far, we have considered the host species or genotype as a constant environment. This assumption is not necessarily true because individual hosts can live in different conditions and these conditions might interfere with processes of transmission [e.g. 49] or within-host multiplication [e.g. 50] and, as such, affects virus fitness and potentially mutation rates. Integrating such environmental effects on virus emergence is going beyond the ecological considerations that

188 traditionally are used to explain emergence on the basis of changes in the
189 frequency of contacts among different species [51]. In the context of global
190 warming, these effects are likely to be particularly important in poikilothermic
191 species, such as insect vectors. This means that $G\times C$ interactions (C standing for
192 host's environmental conditions) should also be taken into account to obtain a
193 complete picture of factors affecting viral emergence, particularly when exploring
194 its link with global climate change. $G\times C$ interactions could actually be a key
195 determinant of geographic extension of viruses. A recent study suggests the
196 existence of $G\times E\times C$ interactions. The triple interaction was shown in an
197 experimental system with three ranavirus isolates, two frog species raised at two
198 different temperatures [52]. This triple-way interaction is actually what plant
199 pathologists and epidemiologists have dubbed for long time as McNew's disease
200 triangle [53].

201 **Conclusions**

202 Evidences for across-host fitness trade-offs in viruses are abundant, yet examples
203 of the evolution of generalist viruses paying no cost also exist. It is often assumed
204 that fitness trade-offs restrict the size of host species range and thus prevent the
205 transformation of occasional spillovers into successful epidemics. Here, we have
206 reviewed the genetic mechanisms that may cause such fitness trade-offs. First,
207 antagonistic pleiotropy makes valuable mutations in the reservoir host detrimental
208 in alternative ones. Second epistasis among beneficial mutations, in particular of
209 the type showing reciprocal sign epistasis, makes certain evolutionary pathways
210 inaccessible for the viral population. Third, epistatic pleiotropy makes epistasis
211 dependent on the host species and traps viral populations in evolutionary dead-
212 ends in alternative hosts. And, finally, the last level of complexity that has to be
213 included is the disease triangle, in which the effects of all the above factors will

depend upon the host's environment. In conclusion, recent studies reveal that factors impeding and favouring the adaptation of viruses to new hosts are numerous and intimately linked. This means that predicting the emerging potential of viral isolates requires a lot of experimental and environmental data that are not always accessible. In the end, the complexity of the factors determining the emerging potential renders it difficult to predict.

Acknowledgements

We thank our lab mates for exciting discussions on the topic of this review. This work was supported by the Spanish Secretaría de Estado de Investigación, Desarrollo e Innovación grant BFU2012-30805.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest

** of outstanding interest

1. Woolhouse, M.E., D.T. Haydon, and R. Antia, *Emerging pathogens: the epidemiology and evolution of species jumps.* Trends Ecol Evol, 2005. **20**(5): p. 238-44.
2. Elena, S.F., et al., *The evolutionary genetics of emerging plant RNA viruses.* Mol Plant Microbe Interact, 2011. **24**(3): p. 287-93.
3. Dennehy, J.J., *Bacteriophages as model organisms for virus emergence research.* Trends Microbiol, 2009. **17**(10): p. 450-7.
4. Elena, S.F. and J. Lalic, *Plant RNA virus fitness predictability: contribution of genetic and environmental factors.* Plant Pathology, 2013. **62S1**: p. 10–18.
5. Holmes, E.C., *The evolutionary genetics of emerging viruses.* Annual Review of Ecology, Evolution and Systematics, 2009. **40**: p. 353-372.
6. Sanjuan, R., et al., *Viral mutation rates.* J Virol, 2010. **84**(19): p. 9733-48.
7. Ferris, M.T., P. Joyce, and C.L. Burch, *High frequency of mutations that expand the host range of an RNA virus.* Genetics, 2007. **176**(2): p. 1013-22.
8. Duffy, S., P.E. Turner, and C.L. Burch, *Pleiotropic costs of niche expansion in the RNA bacteriophage phi 6.* Genetics, 2006. **172**(2): p. 751-7.
9. Lafforgue, G., et al., *Tempo and mode of plant RNA virus escape from RNA interference-mediated resistance.* J Virol, 2011. **85**(19): p. 9686-95.

10. Martinez, F., et al., *Ultradeep sequencing analysis of population dynamics of virus escape mutants in RNAi-mediated resistant plants.* Mol Biol Evol, 2012. **29**(11): p. 3297-307.
11. Dennehy, J.J., et al., *Viral ecology and the maintenance of novel host use.* Am Nat, 2006. **167**(3): p. 429-39.
12. Gandon, S., et al., *What limits the evolutionary emergence of pathogens?* Philos Trans R Soc Lond B Biol Sci, 2013. **368**(1610): p. 20120086.
13. MacArthur, R.H., *Geographical ecology: patterns in the distribution of species.* 1972, New York, NY: Harper & Row.
14. Remold, S., *Understanding specialism when the Jack of all trades can be the master of all.* Proc R Soc B, 2012. **279**(1749): p. 4861-9.
15. Via, S., *Ecological genetics and host adaptation in herbivorous insects: the experimental study of evolution in natural and agricultural systems.* Annu Rev Entomol, 1990. **35**: p. 421-46.
16. Kawecki, T.J., *Accumulation of deleterious mutations and the evolutionary cost of being generalist.* American Naturalist, 1994. **144**: p. 833–838.
17. Turner, P.E. and S.F. Elena, *Cost of host radiation in an RNA virus.* Genetics, 2000. **156**(4): p. 1465-70.
18. Wallis, C.M., et al., *Adaptation of plum pox virus to a herbaceous host (Pisum sativum) following serial passages.* J Gen Virol, 2007. **88**(Pt 10): p. 2839-45.
19. Agudelo-Romero, P., F. de la Iglesia, and S.F. Elena, *The pleiotropic cost of host-specialization in Tobacco etch potyvirus.* Infect Genet Evol, 2008. **8**(6): p. 806-14.
20. Coffey, L.L., et al., *Arbovirus evolution in vivo is constrained by host alternation.* Proc Natl Acad Sci U S A, 2008. **105**(19): p. 6970-5.
21. Vasilakis, N., et al., *Mosquitoes put the brake on arbovirus evolution: experimental evolution reveals slower mutation accumulation in mosquito than vertebrate cells.* PLoS Pathog, 2009. **5**(6): p. e1000467.
22. Deardorff, E.R., et al., *West Nile virus experimental evolution in vivo and the trade-off hypothesis.* PLoS Pathog, 2011. **7**(11): p. e1002335.
23. Weaver, S.C., et al., *Genetic and fitness changes accompanying adaptation of an arbovirus to vertebrate and invertebrate cells.* J Virol, 1999. **73**(5): p. 4316-26.
24. Bedhomme, S., G. Lafforgue, and S.F. Elena, *Multihost experimental evolution of a plant RNA virus reveals local adaptation and host-specific mutations.* Mol Biol Evol, 2012. **29**(5): p. 1481-92.
25. Hillung, J., et al., *Experimental evolution of an emerging plant virus in host genotypes that differ in their susceptibility to infection.* Evolution, 2014. **in press, doi: 10.1111/evo.12458**.
26. Lalic, J., J.M. Cuevas, and S.F. Elena, *Effect of host species on the distribution of mutational fitness effects for an RNA virus.* PLoS Genet, 2011. **7**(11): p. e1002378.
27. Novella, I.S., et al., *Lack of evolutionary stasis during alternating replication of an arbovirus in insect and mammalian cells.* J Mol Biol, 1999. **287**(3): p. 459-65.
28. Cooper, L.A. and T.W. Scott, *Differential evolution of eastern equine encephalitis virus populations in response to host cell type.* Genetics, 2001. **157**(4): p. 1403-12.
29. Greene, I.P., et al., *Effect of alternating passage on adaptation of sindbis virus to vertebrate and invertebrate cells.* J Virol, 2005. **79**(22): p. 14253-60.
30. Coffey, L.L. and M. Vignuzzi, *Host alternation of chikungunya virus increases fitness while restricting population diversity and adaptability to novel selective pressures.* J Virol, 2011. **85**(2): p. 1025-35.
31. Remold, S.K., A. Rambaut, and P.E. Turner, *Evolutionary genomics of host adaptation in vesicular stomatitis virus.* Mol Biol Evol, 2008. **25**(6): p. 1138-47.
32. Whitlock, M.C., P.C. Phillips, and F.G.B. Moore, *Multiple fitness peaks and epistasis.* Annual Review of Ecology, Evolution and Systematics, 1995. **26**: p. 601-629.

33. Poelwijk, F.J., et al., *Reciprocal sign epistasis is a necessary condition for multi-peaked fitness landscapes.* J Theor Biol, 2011. **272**(1): p. 141-4.
34. Weinreich, D.M., *The rank ordering of genotypic fitness values predicts genetic constraint on natural selection on landscapes lacking sign epistasis.* Genetics, 2005. **171**(3): p. 1397-405.
35. Welch, J.J. and D. Waxman, *The nk model and population genetics.* J Theor Biol, 2005. **234**(3): p. 329-40.
36. Franke, J., et al., *Evolutionary accessibility of mutational pathways.* PLoS Comput Biol, 2011. **7**(8): p. e1002134.
37. Kouyos, R.D., O.K. Silander, and S. Bonhoeffer, *Epistasis between deleterious mutations and the evolution of recombination.* Trends Ecol Evol, 2007. **22**(6): p. 308-15.
38. Elena, S.F., R.V. Sole, and J. Sardanyes, *Simple genomes, complex interactions: epistasis in RNA virus.* Chaos, 2010. **20**(2): p. 026106.
39. Cabanillas, L., M. Arribas, and E. Lazaro, *Evolution at increased error rate leads to the coexistence of multiple adaptive pathways in an RNA virus.* BMC Evol Biol, 2013. **13**: p. 11.
40. Martinez, J.P., et al., *Fitness ranking of individual mutants drives patterns of epistatic interactions in HIV-1.* PLoS One, 2011. **6**(3): p. e18375.
41. Kryazhimskiy, S., et al., *Prevalence of epistasis in the evolution of influenza A surface proteins.* PLoS Genet, 2011. **7**(2): p. e1001301.
42. da Silva, J., et al., *Fitness epistasis and constraints on adaptation in a human immunodeficiency virus type 1 protein region.* Genetics, 2010. **185**(1): p. 293-303.
43. Lalic, J. and S.F. Elena, *Magnitude and sign epistasis among deleterious mutations in a positive-sense plant RNA virus.* Heredity (Edinb), 2012. **109**(2): p. 71-7.
44. Poulicard, N., et al., *Historical contingencies modulate the adaptability of Rice yellow mottle virus.* PLoS Pathog, 2012. **8**(1): p. e1002482.
45. Montarry, J., et al., *Genetic background matters: a plant-virus gene-for-gene interaction is strongly influenced by genetic contexts.* Mol Plant Pathol, 2011. **12**(9): p. 911-20.
46. Bedhomme, S., G. Lafforgue, and S.F. Elena, *Genotypic but not phenotypic historical contingency revealed by viral experimental evolution.* BMC Evol Biol, 2013. **13**: p. 46.
47. Torres-Barcelo, C., J.A. Daros, and S.F. Elena, *Compensatory molecular evolution of HC-Pro, an RNA-silencing suppressor from a plant RNA virus.* Mol Biol Evol, 2010. **27**(3): p. 543-51.
48. Lalic, J. and S.F. Elena, *Epistasis between mutations is host-dependent for an RNA virus.* Biol Lett, 2013. **9**(1): p. 20120396.
49. Zouache, K., et al., *Three-way interactions between mosquito population, viral strain and temperature underlying chikungunya virus transmission potential.* Proc Biol Sci, 2014. **281**(1792).
50. Aliota, M.T. and L.D. Kramer, *Replication of West Nile virus, Rabensburg lineage in mammalian cells is restricted by temperature.* Parasit Vectors, 2012. **5**: p. 293.
51. Gould, E.A. and S. Higgs, *Impact of climate change and other factors on emerging arbovirus diseases.* Trans R Soc Trop Med Hyg, 2009. **103**(2): p. 109-21.
52. Echaubard, P., et al., *Environmental dependency of amphibian–ranavirus genotypic interactions: evolutionary perspectives on infectious diseases.* Evolutionary Applications, 2014. **in press**.
53. McNew, G.L., *The nature, origin, and evolution of parasitism.*, in *Plant Pathology: An Advanced Treatise.*, J.G. Horsfall and A.E. Dimond, Editors. 1960, Academic Press: New York. p. 19-69.

348

Figure 1. *G*×*E* interactions and host phylogenetic relationship. Fitness of three theoretical viral genotypes across a panel of susceptible hosts that differ in their degree of genetic relatedness. The genotype represented by the green line has evolved on and adapted to species 2 (S2) and is a specialist in host species belonging to the "green" clade, but has very low fitness in species belonging to the "blue" clade. Likewise, the genotype represented by the blue line has evolved on and adapted to species 6 (S6) and is a specialist of high fitness in the "blue" clade but pays a fitness cost in host species belonging to the "green" clade. Finally, the brown line illustrates the situation for a generalist virus that is paying a fitness costs in both hosts: on average it performs well across both clades of potential host species but its fitness on each host is always lower than the one shown by the corresponding specialist.

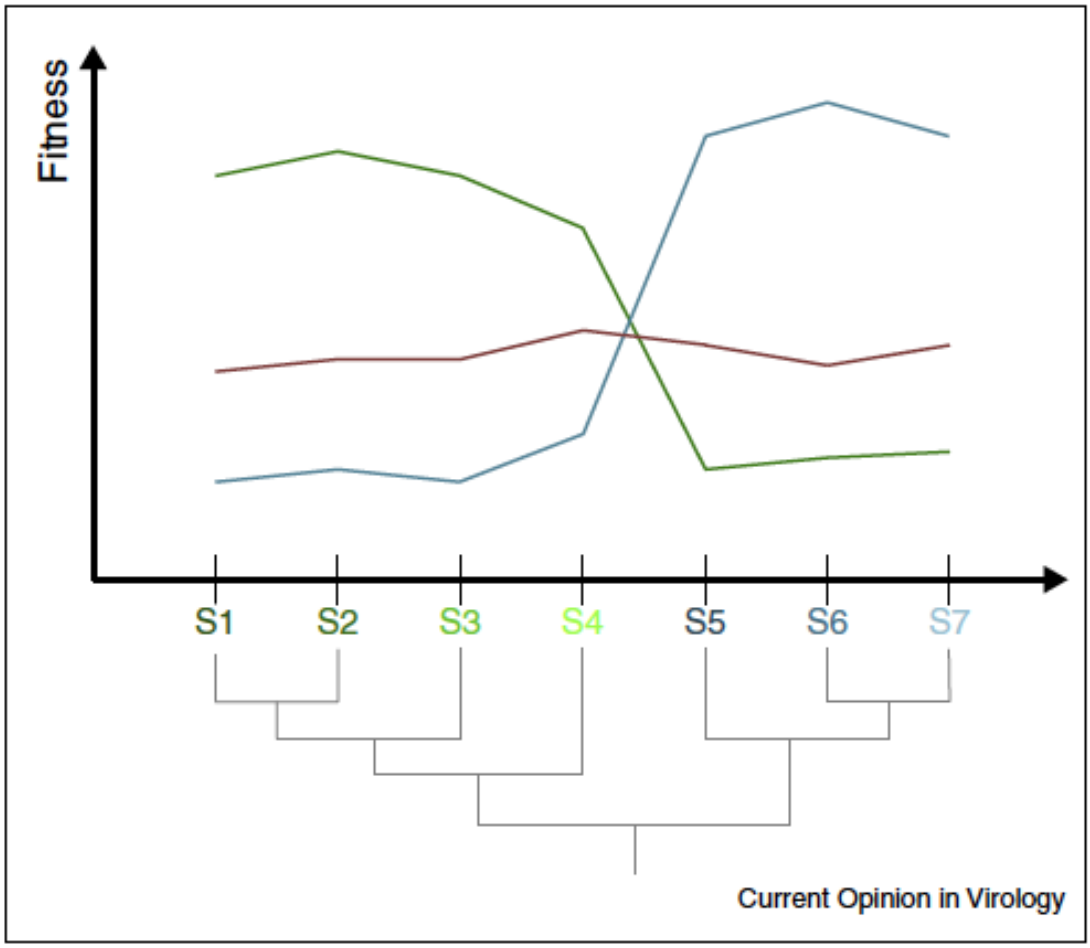
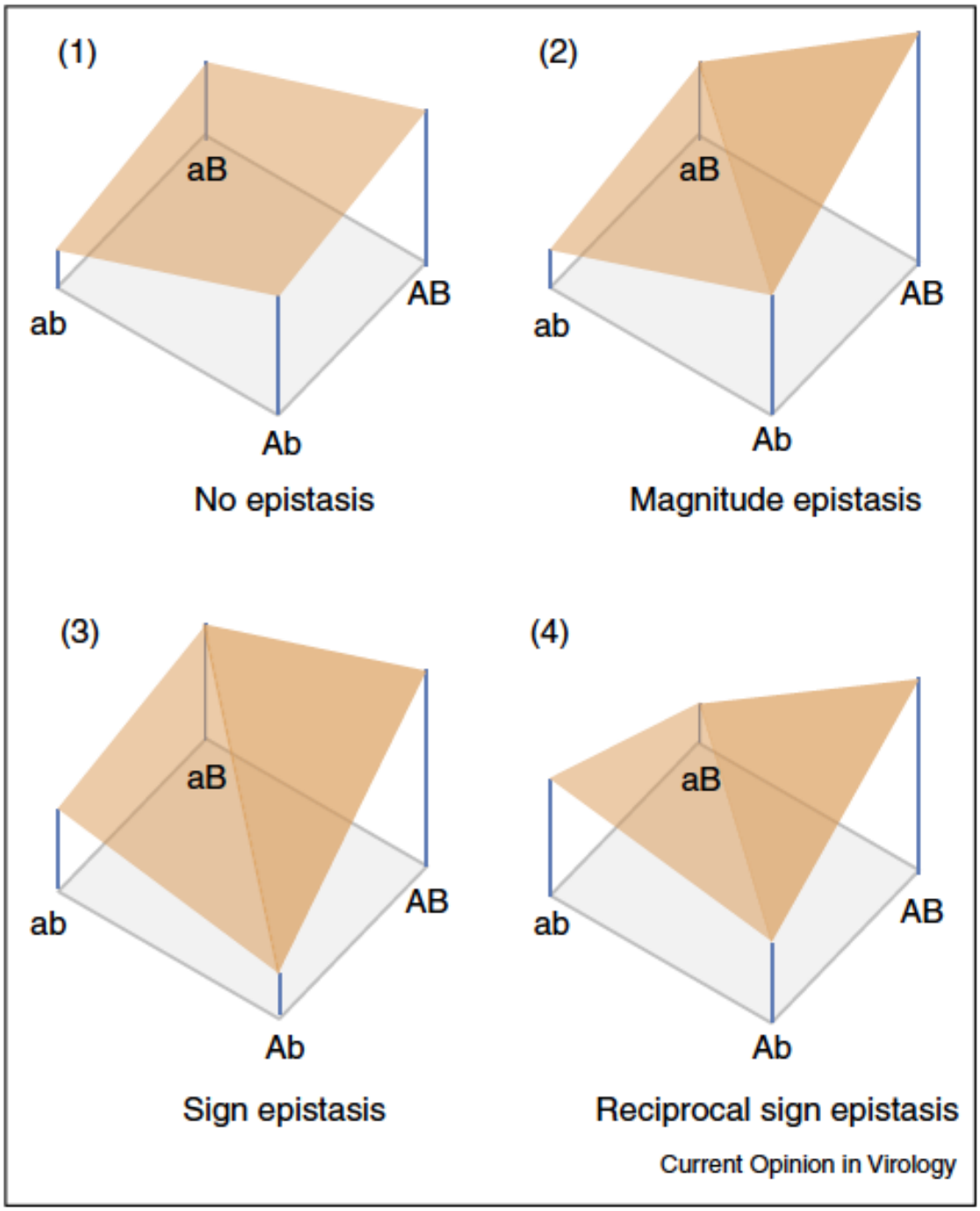


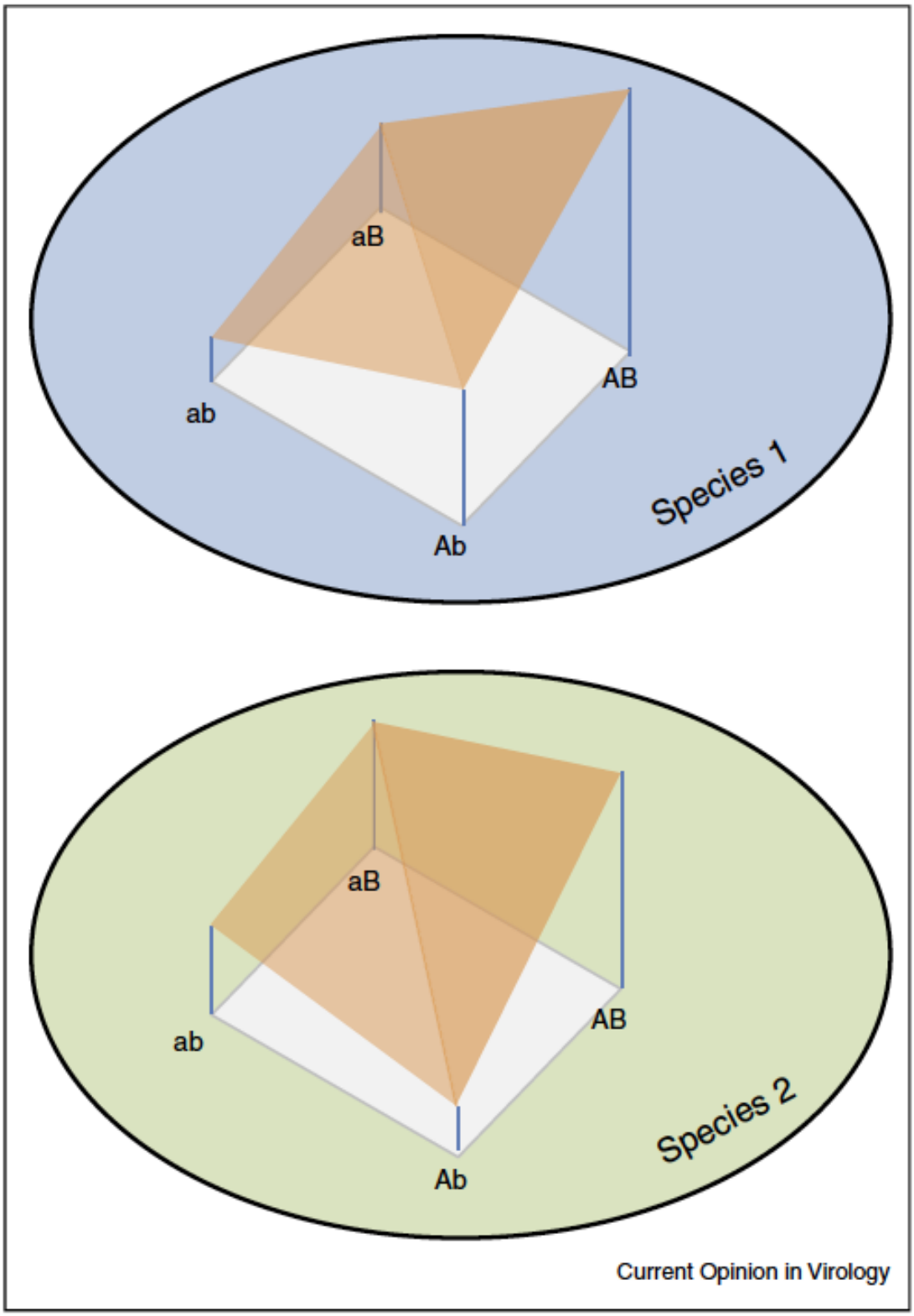
Figure 2. Illustration of the relationship between the type of epistasis among mutations and the ruggedness of the adaptive landscape. Two loci define fitness of a genotype. Small letters indicate the wildtype alleles and capital letters the mutant alleles. (1) In the case of no epistasis the fitness of the double mutant *AB* simply results from multiplying the fitness effects of mutations *A* and *B* on the wildtype genetic background (i.e., the fitnesses of genotypes *Ab* and *aB*). (2) If magnitude epistasis exists, the fitness of the double mutant *AB* is different from the multiplicative expectation. In the example, the observed fitness of *AB* is larger than expected (positive epistasis). Both in the cases of no epistasis or of magnitude epistasis, the effects of mutations *A* and *B* are unconditionally beneficial. If the effect of one of the mutations is conditionally beneficial (i.e., beneficial in one genetic background but deleterious in another), then we are in the situation of sign epistasis (3). Finally, if both mutations *A* and *B* are deleterious by themselves, but beneficial when combined, we are in the situation of reciprocal sign epistasis (4).


(1)
aB
ab
AB
Ab
No epistasis
(2)
aB
ab
AB
Ab
Magnitude epistasis
(3)
aB
ab
AB
Ab
Sign epistasis
(4)
aB
ab
AB
Ab
Reciprocal sign epistasis
Current Opinion in Virology

376

377

Figure 3. The type, strength and sign of epistasis among mutations in a viral genome may depend on the host species wherein fitness is evaluated. In this example, mutations *A* and *B* show positive magnitude epistasis in host species 1 but change to sign epistasis in host species 2 due to the deleterious effect of mutation *A* on the genetic background *Ab* when replicating in this host species.


aB
AB
ab
Ab
Species 1
aB
AB
ab
Ab
Species 2
Current Opinion in Virology

383