

Defective subviral particles modify ecological equilibria and enhance viral coexistence

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2 ABSTRACT

3 Cooperation is a main driver of biological complexity at all levels. In the viral world, gene sharing
4 among viral genomes, complementation between genomes or interactions within quasispecies
5 are frequently observed. In this contribution, we explore the advantages that flexible associations
6 between fully fledged viruses and subviral entities, such as virus satellites, might yield. We devise
7 a mathematical model to compare different situations of competition between two viruses and
8 to quantify how the association with a satellite qualitatively modifies dynamical equilibria. The
9 relevant parameter is the invasion fitness of each virus or of the virus-satellite tandem, which
10 in the model depends on the transmission rate of viruses and on their effect on host survival.
11 While in a virus-virus competition one of the viruses becomes eventually extinct, an association
12 with a satellite might change the outcome of the competition to favor the less competitive virus
13 (regardless of whether it is the helper virus or not) or to allow for the stable coexistence of the
14 two viruses and the satellite. We hypothesize that the latter scenario, in particular, constitutes
15 a parsimonious evolutionary pathway towards more stable cooperative associations, such as
16 bipartite viral forms.

17 **Keywords:** viral dynamics model, cooperation, ecological competition, subviral agents, viral coexistence

1 INTRODUCTION

18 There are many instances in the Virosphere of associations of viruses with kin or with subviral entities (Elena
19 et al., 2014). The involved agents propagate independently, and engage in transient associations that can
20 be contingent or necessary regarding successful completion of the replication cycle. Virus satellites, for
21 instance, are subviral particles that require the assistance of a specific helper virus for its replication and/or
22 encapsidation (Kassanis, 1962), see Fig. 1. Their association with the helper virus is therefore necessary

23 for the satellite, but contingent in principle for the virus (though some viruses also require the satellite for
24 encapsidation). Bipartite viruses, in turn, have their genome fragmented into two pieces that encapsidate
25 separately but are essential in the viral cycle, so their mutual cooperation is necessary Sicard et al. (2016);
26 Lucía-Sanz and Manrubia (2017).

27 Virus-satellite associations are ubiquitous in plants, and less frequent in other hosts. Examples infecting
28 animals are the *Hepatitis δ virus* (HDV) (Makino et al., 1987), the genus *Dependoparvovirus* (Cotmore
29 et al., 2014; Krupovic et al., 2016) that infects vertebrates, and virus-satellite associations that have
30 bees (Ribi re et al., 2010) and planthoppers (Nakashima et al., 2006) as hosts. There are also two cases
31 of dsRNA satellites associated to the *Totiviridae* family that infect unicellular eukaryotes (Khoshnan
32 and Alderete, 1995; Schmitt and Breining, 2002). In several cases, co-infection of animal hosts with the
33 corresponding satellite results in an attenuation of viral symptoms (Nakashima et al., 2006; King et al.,
34 2012; Yau et al., 2011).

35 Infections by multiple viruses and a variety of subviral entities are common in wild plants (Roossinck,
36 2005), opening up a high potential for mutual interaction. It has been observed that unrelated viruses within
37 these mixtures do not seem to compete, but rather to cooperate, a fact that might explain their ubiquity
38 (Leeks et al., 2018). Co-infection of a host with subviral particles usually modifies the pathogenicity
39 of the helper virus (Roossinck, 2005; Garc a-Arenal and Fraile, 2017). The spectrum of phenotypic
40 modifications elicited in plants through such interactions is actually remarkably broad. Some viral species
41 within the *Tombusviridae* family, for instance, take part in associations that include a variety of satellites
42 coding for the capsid protein (Syller, 2003). *In vitro*, Tombusviruses spontaneously generate defective
43 interfering particles (DIPs) that systematically lessen the symptoms of the infection by interfering with
44 the replication process Havelda et al. (2005). However, co-infections with heterologous viruses, e.g.
45 that of Potyvirus with Tombusvirus species as *machlomovirus of maize chlorotic mottle*, often increase
46 the virulence of Tombusvirus (Scheets, 1998), as it also happens in other Potyvirus co-infections with
47 heterologous viruses (Pruss et al., 1997). In Bromoviruses, virus-satellite associations can both attenuate or
48 enhance the pathogenicity of the phenotype (Palukaitis and Roossinck, 1996). *Geminiviridae* is the family
49 with the largest number of virus-satellite associations, often modifying the virulence and host-range of the
50 virus (Rehman and Fauquet, 2009). Overall, while short-lived interactions may just involve an increase
51 or decrease in viral accumulation levels (a common effect in infections where DIPs or satellites have
52 spontaneously emerged), long-term interactions correlate with a variety of changes in transmission (Elena,
53 2011), host range (McLeish et al., 2019a), or cell tropism. Sustained interactions are in all likelihood a
54 prerequisite to eventually develop a necessary, mutual interdependence between any two contingently
55 interacting elements.

56 From an ecological perspective, phenotypic changes caused by transient associations with other viral and
57 subviral agents affect viral dynamics, change viral epidemiology (Alcaide et al., 2020), and redefine the
58 overall ecological role of the association (Betancourt et al., 2011; McLeish et al., 2019b; Syller, 2020),
59 as compared to infections caused by a single virus. As such, they have to be subject to strong selection,
60 since they may play a main role in virus survival by varying the cost that infection impinges on the host,
61 changing adaptive strategies or, as we show in this contribution, qualitatively modifying the outcome of
62 competition for hosts with co-circulating viral species. An integration of quantitative epidemiology at
63 various levels, including in-host evolution and diverse adaptive strategies, is essential to better understand
64 molecular associations and their ecological effects (Jeger, 2020).

65 Previous modelling studies have addressed the effect of co-infection by viruses and subviral particles
66 unable to replicate on their own. Specific models have addressed the evolution of virulence in *Cucumber*

67 *mosaic virus* over two hosts (Betancourt et al., 2013) and have shown that highly virulent phenotypes
68 occur in mixed infections, in agreement with field observations. Dynamics of virus-DIPs have been also
69 formally studied based on results of *in vitro* observations, revealing that dynamics in virus cultures can be
70 oscillatory (Frank, 2000) but also intrinsically unpredictable under very general conditions (Kirkwood and
71 Bangham, 1994); among others, DIPs can cause the extinction of the parental virus (Grande-Pérez et al.,
72 2005). General models exploring properties of virus-satellite associations have often focused on conditions
73 for coexistence of the partners, showing that it can be favored under structured demes (Szathmáry, 1992)
74 but is in general difficult under metapopulation dynamics (Nee, 2000). A general result for infections
75 within a single host states that beneficial co-infection suffices to allow for the stable coexistence of different
76 variants (Leeks et al., 2018). Still, the variety of models, and therefore mechanisms, identified for the stable
77 coexistence of heterologous viral associations is reduced, probably as a result of our limited knowledge of
78 the intricacies of such associations in nature, and to the small number of cases described (García-Arenal
79 and Fraile, 2017). The state-of-the-art is similar in the case of necessary associations, such as in multipartite
80 viruses, where specific mechanisms that may counteract the deleterious effects of independent propagation
81 are still unclear (Lucía-Sanz et al., 2018; Zwart et al., 2021).

82 In this work, we present a simple model of virus-satellite association and evaluate its epidemiological
83 effects when two monopartite viruses and a satellite that uses one of them as helper virus co-circulate in a
84 host population. Our main result is that the virus-satellite association changes the possible stable equilibria
85 and, in particular, promotes the long-term stable coexistence of both viruses and the satellite in a host
86 population when, as most natural associations do, the satellite modulates the viral phenotype. In contrast,
87 stable co-circulation of two monopartite viruses is not possible in the studied scenario, since one of the
88 species unavoidable invades the host population in finite time.

2 MODELS

89 We address the epidemic propagation of viruses in a well-mixed host population through a set of differential
90 equations representing the amount of susceptible hosts, H , of hosts infected by a virus, X , of hosts infected
91 by the helper virus, Y , and of hosts simultaneously infected by the helper virus and the satellite, S (see
92 Fig. 2). Capital letters, therefore, describe the abundance of hosts in each of four states: susceptible H
93 or infected hosts in the infected states X , Y , and S ; where needed, we will use lower-case letters to refer
94 to virus x , helper virus y , and satellite s . The model, therefore, does not explicitly consider free viral
95 populations. In our models, infections are persistent and there is no class of recovered hosts. This is the
96 rule for plant viruses, but not necessarily so for animal viruses. Therefore, and although we generically
97 speak of hosts all through the paper, our scenarios better apply to plant-infecting viruses and, as it has been
98 defined, to any system where infections are persistent. Finally, note that we refer to competition for hosts
99 in all instances, not to within-host competition.

100 We keep the model intendedly simple so as to derive general principles arising from competition for
101 hosts between the association of a helper virus and a satellite and a second monopartite virus. We do so to
102 emphasize that relevant ecological dynamics do depend on the success of a specific strategy in front of
103 alternative others. In order to highlight the main processes involved in such competition, we have made
104 some simplifying assumptions. For instance, we assume superinfection exclusion between the two viruses,
105 such that hosts cannot be simultaneously infected by the two monopartite viruses. This is a convenient
106 simplification to obtain exact results; as a consequence, coexistence in the context of our model means
107 "ecological coexistence", in the sense that the two viral strains and the satellite stably co-circulate in the host
108 population under conditions that will be made explicit later. A second simplification is that of a mean-field

109 approximation (common in paradigmatic epidemic models (Hethcote, 2000)), where the dynamics are
110 described through differential equations and space is not explicitly modeled, therefore assuming that hosts
111 interact homogeneously through averaged values.

112 2.1 Competition between two viruses: Model V

113 The general dynamics of the process are as follows. Healthy hosts appear at a constant rate g and decay or
114 die at a natural rate d . The amount of healthy, susceptible hosts at time t is $H(t)$ and that of hosts infected
115 by either virus is $X(t)$ and $Y(t)$. If no confusion arises, we will obviate the explicit dependence on t .
116 Contacts between susceptible and infected hosts cause infection of susceptible hosts at rates p_x and p_y ,
117 respectively, that stand for the transmission rates of either virus. Infection by x or y increases the death
118 rate of the host in amounts d_x and d_y . This scenario corresponds to a simple situation where two fully
119 competent viruses compete for hosts (see Fig. 2A), and is described by the following equations:

$$\frac{dH}{dt} = g - dH - p_x XH - p_y YH \quad (1)$$

$$\frac{dX}{dt} = p_x XH - (d + d_x)X \quad (2)$$

$$\frac{dY}{dt} = p_y YH - (d + d_y)Y \quad (3)$$

120 In the absence of viruses ($X = 0, Y = 0$), the abundance of hosts stabilizes at $H^* = g/d$, as obtained
121 by solving $dH/dt = 0$. Therefore, Eq. 1 entails a maximum carrying capacity of hosts in the absence of
122 parasites. From now on, and given its relevance in determining the existence and stability of the various
123 solutions, as it will be shown, the quantity d/g will be called host turnover.

124 It is a consequence of the symmetry between eqs. (2) and (3) that one of the viruses always displaces the
125 other —with rare marginal exceptions, as we show in the results. Alternatively, for a small enough host
126 replacement, both viruses become extinct: infected hosts die before new susceptible hosts are available to
127 maintain the epidemic.

128 2.2 Competition between a virus and a helper virus with a satellite: Model S

129 In the former scenario of competition between two viruses, we are now introducing a possible association
130 with a satellite that can only multiply in presence of its helper virus. Due to the symmetry between the
131 equations describing the dynamics of each virus, Eqs. (2) and (3), the choice of the helper virus does not
132 affect the results, so we selected virus y without loss of generality. Class S , corresponding to hosts infected
133 by the tandem $y - s$, is affected by an increase d_s in mortality.

134 Due to the dependence of the satellite on its helper virus for replication, s can only be transmitted (to
135 classes H or Y) through contacts with class S , either to healthy hosts, at rate p_{sy} , or to hosts already
136 infected with y , at rate p_s . In agreement with our superinfection exclusion, hosts in class X cannot be
137 infected by classes Y or S . Finally, hosts in class S can also transmit only the helper virus under contacts
138 with class H , this process occurring at rate p_{-y} . A scheme of the interactions of this model can be seen in
139 Fig. 2B, and the set of equations considering all of the previous processes reads:

$$\frac{dH}{dt} = g - dH - p_x XH - p_y YH - p_{sy} SH - p_{-y} SH \quad (4)$$

$$\frac{dX}{dt} = p_x XH - (d + d_x)X \quad (5)$$

$$\frac{dY}{dt} = p_y YH - (d + d_y)Y - p_s YS + p_{-y} SH \quad (6)$$

$$\frac{dS}{dt} = p_s YS - (d + d_s)S + p_{sy} SH . \quad (7)$$

140 Note that, if we set $S(t = 0) = 0$ as an initial condition, this system is in practice equivalent to Model V.
141 This nonetheless, the formal inclusion of the satellite modifies the study of the fixed points and stability of
142 the system, as we show in the Supplementary Information.

143 The satellite non-trivially breaks the symmetry between the dynamics of hosts in classes X and Y , and
144 therefore between the two corresponding viruses. As we will show through analytical and computational
145 analyses, the satellite can benefit or impair its helper virus (thus impairing or benefiting virus x), or can
146 promote the stable coexistence of all parts.

3 RESULTS

147 In order to clarify the effects of the introduction of a satellite in the outcome of competition between two
148 monopartite viruses infecting the same host (model S), we begin by analyzing the stable solutions of the
149 dynamics in the absence of the satellite (model V). All parameters in the models (death and transmission
150 rates and host growth) are positive defined. The results obtained for model V are not conceptually new, but
151 serve to properly compare the dynamics of the more complex model S with a baseline situation. Fixed points
152 of the dynamics are the solutions to $d\vec{R}/dt = \vec{0}$, where $\vec{R} = (H, X, Y)$ (model V) or $\vec{R} = (H, X, Y, S)$
153 (model S). The values of the variables satisfying the fixed point equations are denoted H^* , X^* , Y^* , and S^*
154 in the following. These values have to be equal to or larger than zero for the solution to have biological
155 meaning: this results into conditions for existence and non-negativity that the model parameters have to
156 fulfill. The study of stability of the solutions has been carried out using standard methodology of dynamical
157 systems, as detailed in the Supplementary Information. Stability of the solutions also yields conditions on
158 formal relationships that the model parameters have to satisfy. In the next two sections we summarize the
159 solutions of models V and S and their stability properties, together with their ecological interpretation.

160 3.1 Coexistence is unstable in a system of two viruses in competition for a host 161 population

162 Depending on model parameters, model V has four different, positive and stable solutions: i) none of the
163 virus is able to invade the population of hosts and both get extinct; ii) and iii) one of the two viruses stably
164 coexists with the host and the other virus becomes extinct; iv) the two viruses coexist in the population.
165 These four solutions map on three main extended regions in the space of parameters.

166 An important quantity arising in the formal analysis of the model is the ratio between the transmission
167 rate of a virus, p_i , and its overall effect on host death rate, $d + d_i$, where $i = x, y$. This ratio is an instance of
168 the *invasion fitness* $F_i = p_i/(d + d_i)$ of each virus, and determines which strategy is uninventable (Lehmann

169 et al., 2016). The ratio d/g is a measure of the replacement of healthy hosts. Smaller d/g means shorter
170 times are needed for the appearance of susceptible healthy hosts.

171 Invasion fitness F_i and host turnover d/g are the two main quantities determining the relevant equilibria
172 of the system. A summary of such solutions and their stability is reported in Table 1 (see Supplementary
173 Material for further details). Figure 3 shows a representative example of the localization in parameter space
174 of the four possible solutions for model V. In that particular example, we have fixed $d = 0.05$, $d_y = 0.25$,
175 $p_y = 0.1$, and $p_x = 0.1$ and explored the $\{g, d_x\}$ plane. Changes in parameter values shift the boundaries
176 between different solutions but do not cause qualitative changes. We observe large regions where both
177 viruses become extinct or where either x or y coexist with the host.

178 3.1.1 Extinction of both viral populations

179 If host turnover is larger than invasion fitness for both viruses (solution **V.1**), the viral populations
180 becomes extinct. This region corresponds to the blue area in Fig. 3A, and describes a solution where the
181 rate of appearance of new susceptible hosts is slower than the time needed by any of the viruses to invade
182 the population: in absence of sufficient susceptible hosts, any parasite becomes extinct.

183 3.1.2 Survival of one viral population

184 This situation holds whenever the invasion fitness of the two viruses is different and at least one of them
185 is higher than host turnover: $F_i > F_j$ and $F_i > d/g$ for at least one $i, j \in \{x, y\}$. The solution is symmetric
186 under the exchange $i \leftrightarrow j$. These situations correspond to solutions **V.2** and **V.3**, represented as green and
187 yellow regions in **Figure 3.A**. The abundances of susceptible and infected hosts depends on all model
188 parameters.

189 3.1.3 Coexistence of both viruses

190 This is a marginal solution sitting at the boundary separating the two solutions where one of the viruses
191 invades and the other becomes extinct. Coexistence only occurs when the two viruses have identical
192 invasion fitness, and both are higher than host turnover, $F_y = F_x > d/g$. This condition maps to a single
193 line in parameter space. Further, since the equilibrium values of X^* and Y^* are degenerated, a second
194 condition establishes that none of them be zero (in which case the solution would correspond to cases **V.2**
195 or **V.3**). This means that, at this boundary, the amount of hosts infected by x or y is not unique, as illustrated
196 by the vertical line in Fig. 3B, where the amounts of X and Y appear superimposed. The degeneration of
197 the solution is also reflected in its analytical form **V.4**, since Y^* is given as a function of X^* (see Table 1
198 and Supplementary Information).

199 It is not to be expected that any natural system strictly meets the conditions for coexistence here derived.
200 In the example in Fig. 3, any minor inaccuracy in the value of d_x would kick the system out of coexistence
201 and cause the extinction of one of the viruses. In general, arbitrary changes in d_x , d_y , p_x or p_y would cause
202 the system to depart from the (quasi)stable solution. Therefore, in more realistic situations, stochasticity,
203 noise, or heterogeneity of any kind would push the system away from this marginal solution and into one
204 of the extended regions where either one or both viruses become extinct. Therefore, co-circulating different
205 viral species are, in general, not to be found in a host population under the conditions of model V.

206 3.2 Dynamics with a co-infecting satellite

207 The introduction of the satellite breaks the symmetry of equations describing the dynamics of the two
208 viruses. In this new situation, it is not straightforward to predict which of the viruses or associations is

209 going to succeed in invading the host population. A variety of outcomes is possible depending on the new
210 parameters.

211 We first extend our definition of invasion fitness to the virus-satellite association,

$$F_i = \frac{p_i}{d + d_i}, \quad i \in \{x, y, sy, c\}, \quad (8)$$

212 where for convenience we define $p_c = p_{sy} + p_{-y}$ (with $d_c = d_{sy} = d_s$). Note that, since the likelihood of
213 independent transmission is larger than joint transmission, $F_c > F_{sy}$.

214 The system of equations (4-7) has seven different fixed point solutions (for all parameters taking positive
215 values), summarized in Table 2. Four of them coincide with the solutions for model V, namely: extinction
216 of the two viruses (**S.1**), invasion of virus x (**S.2**) or virus y (**S.3**) and (marginal) coexistence of hosts with
217 viruses x and y (**S.4**). Three new solutions appear where the satellite co-circulates with one or two of the
218 viruses. The first of them (**S.5**) corresponds to the extinction of virus x and the stable coexistence of the
219 tandem virus y -satellite with the host. In two more solutions (embraced under **S.6**) the three agents (virus
220 x , virus y and satellite) stably co-circulate in the population of hosts. In the following, we examine in
221 detail solutions **S.5** and **S.6** to discuss how the introduction of the satellite modifies the different equilibria
222 depending on the phenotypic effects of its association with the helper virus.

223 3.2.1 Neutral association with a satellite does not modify the outcome of competition

224 If the satellite behaves as a commensal parasite, co-infection with its helper virus does neither modify the
225 regions of different equilibria nor their stability. Formally, this occurs when $F_c = F_y$. Fig. 4 depicts the
226 regions for the different equilibria and shows that the region corresponding to solution **V.3** is now split into
227 two subregions embracing solutions **S.3** and **S.5**: in the former, the satellite becomes extinct; in the latter, it
228 co-circulates with virus y .

229 Invasion of virus y without the satellite (**S.3**) holds when $F_y(1 - \gamma) > F_{sy}$, where $\gamma = (g/(d + d_y) -$
230 $d/p_y)p_s/(d + d_s)$. This condition is shown as a vertical, blue dashed line in Fig. 4. As the invasion fitness
231 F_{sy} of the virus-satellite association increases, it becomes harder for the helper virus to survive on its own
232 until, eventually, solution **S.5** becomes stable and substitutes **S.3**: in **S.5**, $Y^* \neq 0$ and, simultaneously,
233 $S^* \neq 0$. In general, this means that satellites are persistent in helper virus populations, but the virus still
234 infects a subpopulation of hosts in the absence of the satellite. The size of this region depends on the ability
235 of virus y to infect susceptible hosts alone when jumping from joint virus-satellite infections. Therefore, it
236 progressively narrows if p_{-y} decreases. A successful strategy from the viewpoint of the satellite, therefore,
237 could be to evolve towards associations that make the y -virus more dependent on s for transmission,
238 progressively selecting increases in p_s that could eventually turn p_{-y} negligible. That is, the association
239 would evolve from commensal to mutualistic.

240 3.2.2 A mutualistic satellite can prevent extinction of the helper virus

241 Consider the situation in model V where $F_x > F_y$, with $F_x > d/g$ (solution **V.2**): virus y is at a
242 disadvantage and therefore unable to invade the population of hosts. In that situation, cooperation with a
243 satellite can prevent its extinction if the satellite provides a sufficiently high increase in invasion fitness to its
244 association with y . This occurs when the invasion fitness of the virus-satellite association is slightly larger
245 than F_x . A region of parameters that was previously occupied only by solution **S.2** becomes now bistable,
246 such that depending on the initial conditions it can lead to the elimination of y (and the concomitant

247 disappearance of the satellite), or to the extinction of x in favor of the virus-satellite association (solution
248 **S.5**), see Fig. 5.

249 At the boundary that separates the region of bistability (where both **S.2** and **S.5** are possible) from solution
250 **S.2** as a unique solution, the values of H^* for each solution coincide and equal $H^* = (d + d_x)/p_x$, as
251 Fig. 5B shows. By using the explicit expression for H^* obtained for **S.5** (see Supplementary Information)
252 one can obtain an implicit analytical expression for the lower bistability boundary.

253 From an evolutionary viewpoint, satellites that confer their helper virus an increase in invasion fitness
254 may be a low-cost solution to guarantee rapid adaptation to new hosts, since such an adaptive strategy, in
255 principle, does not require adaptive mutations.

256 3.2.3 A parasitic satellite can promote viral coexistence

257 Consider now the situation in model V where $F_y > F_x$, with $F_y > d/g$ (solution **V.3**): virus x is at a
258 disadvantage and virus y has invaded the host population. An association of y with a parasitic satellite
259 can be a burden to the helper virus and diminish its relative advantage while, at the same time, it could
260 potentially benefit x , the virus that was initially eliminated in the competition between the two monopartite
261 viruses. It turns out that the association with a satellite under the conditions above does not necessarily
262 entail, in contrast to previous equilibria, the elimination of either x or the y -satellite tandem. Actually,
263 if the invasion fitness of the association virus y -satellite is such that $F_c < F_x < F_y$, then virus x can
264 simultaneously coexist with virus y and the satellite in regions where it became extinct when the satellite
265 was absent. The conditions above correspond to the relevant solution embraced under **S.6**, that we label
266 **S.6.a**, see SI. There is a second degenerate solution that requires $F_c = F_x = F_y$ (solution **S.6.b**) that has
267 not biological relevance, in the same sense as discussed above for other degenerate solutions.

268 Figure 6 illustrates the parameter space for the case of a parasitic satellite and shows the appearance
269 of an extended region of coexistence. The boundary limiting the coexistence region can be analytically
270 calculated by noting that, at that boundary, the values of X^* for solutions **S.5** and **S.6.a** coincide and are
271 equal to zero. See Supplementary Information for an explicit expression of the latter solution.

272 The case of coexistence is an interesting and ecologically relevant situation where the association with
273 a parasitic satellite is only partly detrimental for virus y , while it actually benefits both virus x and the
274 diversity of circulating viral species (and subviral entities).

275 3.3 Increased dependence between helper virus and satellite

276 We have shown in the previous sections how the asymmetric relationship between virus y and the satellite
277 (the virus can propagate and replicate on its own, while the satellite depends on the helper virus) breaks the
278 symmetry of the simple model V in a non-trivial way. This causes in particular the appearance of regions
279 of bistability and coexistence that depend on the phenotype of the association, as compared to that of virus
280 y alone.

281 There are two other situations implicit in model S and in the solutions analyzed so far that are worth
282 discussing: the case where the helper virus cannot propagate if the host is not co-infected with the satellite,
283 and the limit case where the "helper virus" needs the "satellite" both for propagation and replication. The
284 former case (section 3.3.1) still distinguishes between the two categories of helper virus and satellite, while
285 in the latter (section 3.3.2) the association has turned necessary: the two partners that can no longer be
286 identified as helper virus and satellite, since their interdependence is mutual and alike. Actually, these

287 two cases might represent intermediate steps in a possible parsimonious evolutionary pathway towards
288 bipartitism.

289 3.3.1 A satellite virus coding for genes essential in transmission

290 Consider a situation where virus y can replicate but not propagate without the concurrence of the satellite.
291 Formally, this situation is implemented by setting $p_y = 0$, meaning that hosts in class Y are not infective.
292 This scenario agrees with various common natural situations (see Fig. 1) where a satellite virus codes
293 for the capsid needed for the encapsidation of the helper virus or is essential for vector transmission.
294 Examples of the latter are the requirement of *groundnut rosette satellite* for the transmission of *groundnut*
295 *rosette virus*, of RNA4 for transmission of *beet necrotic yellow vein virus* (Palukaitis et al., 2008) or the
296 dependence of umbraviruses on luteoviruses for transmission (Taliensky and Robinson, 2003).

297 In our formal context, this restriction implies that only hosts in class S can generate virions with virus
298 y able to infect other susceptible hosts. This is the only way in which the Y class is fed, since the term
299 $p_y YH$, corresponding to infections caused by contacts between Y and H hosts, is now absent. Taking
300 an evolutionary perspective, the association between a subviral particle with multiplicative ability and a
301 satellite that endows it with propagative ability appears beneficial for the particle. From the viewpoint
302 of the satellite, it might be also convenient, in order to ensure survival, to carry a highly-valued genome
303 piece, as a capsid or others involved in transmission, that can be likely used by a variety of replicative
304 particles. From this perspective, evolutionary associations between replicative entities and satellites coding
305 for essential genes could be highly dynamic, successful adaptive strategies.

306 3.3.2 The helper virus can neither replicate nor propagate without the satellite

307 The subsequent case corresponds to a situation where the partners become mutually dependent both for
308 multiplication and propagation. The formal representation of this situation corresponds to setting $Y = 0$,
309 since the "helper" virus cannot replicate in the absence of the "satellite", and therefore class Y is empty
310—in the same sense that a class infected only by satellites is irrelevant for the dynamics, and therefore
311 dismissed in our models from scratch. When the set of Eqs. (4)-(7) is reduced to this case, one can see
312 that they are equivalent to model V under the correspondence $Y \rightarrow S$, $d_y \rightarrow d_s$, $p_{sy} \rightarrow p_y$, and $p_{-y} = 0$,
313 since class Y is absent by definition. Still, there is an important difference due to the fact that virus y and
314 the satellite do not necessarily propagate as a unit, but as two independent particles. As a result, p_{sy} in
315 the equivalent formulation may take low effective values, meaning that the probability of simultaneous
316 infection by two independently propagating particles is always lower than the probability of infection
317 by a single propagating particle. Therefore, this situation better describes a bipartite virus, where the
318 genome is divided into two segments that are independently transmitted, where both fragments are needed
319 to successfully complete the viral cycle, and where there is a cost due to independent propagation.

4 DISCUSSION

320 We have introduced a simple epidemic model to analyze stable states in a system formed by two fully
321 fledged viruses and an associated satellite. This model contains the minimum set of players with symmetric
322 (between the two viruses) and asymmetric interactions (between a virus and a satellite) of different nature
323 (commensal, parasitic or mutualistic) able to display a range of ecological equilibria when competing
324 for a common host. Note that our results only refer to long-time equilibria (i.e. to stable coexistence in
325 a mathematical sense), and therefore do not apply to transient coexistence. In natural systems, the time
326 needed for one viral species to cause the elimination of a second one (corresponding, for example, to

327 solutions **V.2** or **V.3**) can be so large that transient co-circulation of various viral species could be the most
328 common situation: this transient coexistence should not be mistaken by solution **V.4**, which strictly refers
329 to stable, long-term coexistence. A detailed analysis of how long it takes to attain ecological equilibrium
330 and a quantification of typical evolutionary times for the emergence of new viral species infecting a given
331 host would be needed, among others, to discriminate between transient and actual coexistence. Such an
332 analysis is out of the scope of the present contribution, but it is important to keep in mind that, due to the
333 long times involved in ecological dynamics, natural systems can be out-of-equilibrium most of the time.

334 In the light of our results, it is worth discussing the major assumption we have made, that is superinfection
335 exclusion. Our second assumption, the use of a deterministic description of the dynamics, mostly affects the
336 stability of marginal solutions (i.e., those solutions demanding a precise coincidence of certain parameters).
337 The incorporation of stochasticity of any kind (in the form of space, which entails probabilistic contagion,
338 finite populations, heterogeneous contacts, noise or any form of disorder), as it would occur in any
339 natural system, turn solutions **V.4**, **S.4**, and **S.6.b** irrelevant, since they become unstable under any minor
340 modification of most parameter values.

341 Assuming superinfection exclusion is useful to obtain exact analytical results, and therefore to gain
342 insight into major ecological effects of virus-satellite associations. If this simplification is lifted, further
343 interaction terms between viruses x and y , between x and the satellite, or even among the three entities,
344 and new equations accounting for different states with various combinations of co-infecting entities have to
345 be considered. Both the number of equations involved and their complexity would increase, preventing the
346 achievement of exact expressions for equilibria and their stability, and therefore masking the interpretation
347 of generic results. This nonetheless, and since we are arguing that coexistence of different viruses and
348 subviral particles in the same host population might be a stepping stone towards stable mutually dependent
349 associations (as bipartitism), let us be more explicit about this point and sketch how the relaxation of
350 that assumption could affect the results here obtained. The simplest scenario corresponds to commensal
351 co-infection, in which case the qualitative results here presented remain unchanged: propagation of different
352 entities in the host population could be independently analyzed, and the state of each individual host at a
353 given time would be the product of probabilities of being infected with any of the viruses or sets of partners
354 considered in the model. If co-infection causes changes in phenotype, however, the nature of the different
355 equilibria might change, but such changes would be qualitatively analogous to these explored here.

356 Take the following example as illustration. Suppose we include in our equations hosts co-infected with
357 viruses x and y , and let us call Z this new class. The dynamical equation for Z would read

$$\frac{dZ}{dt} = p_x XY + p_y YX + p_{-y} XS + p_z HZ - (d + d_z)Z \quad (9)$$

358 The terms in the right-hand side of the equation indicate, from left to right, the rate of infection of hosts
359 in class Y under a contact with class X (virus x is transmitted), of hosts in class X under a contact with
360 Y (virus y is transmitted), of hosts in class X under a contact with S when only y is transmitted, new
361 infections of susceptible hosts under contacts with Z when both viruses are simultaneously transmitted
362 (this introduces the new rate p_z) and, finally, the modification of the death rate due to the co-infection
363 with both viruses (new rate d_z). Equations for dH/dt , dX/dt and dY/dt would also acquire new terms
364 coming from the new transitions to class Z (equation for dS/dt would not be modified since there are
365 no possible transitions between S and Z , since the latter does not contain the satellite). Note that this
366 enlarged model Z would have all fixed points we have described for model S (when $Z^* = 0$) and some new

367 ones corresponding to $Z^* \neq 0$. The analysis would proceed along similar lines, and the actual challenge
368 would then be to characterize the new conditions under which coexistence occurs, since these could take
369 much more involved mathematical expressions. Still, the mechanisms underlying coexistence, in particular,
370 would not differ from the ones identified in this study as long as interaction terms take mathematical forms
371 analogous to those considered here, that is, if interactions occur in pairs. This is not a limiting assumption,
372 since all general contagion processes involve only pair contacts, regardless of whether multiple particles of
373 various types are transmitted through the contact. For example, if another class W infected by x , y and
374 s is considered, it can be easily shown that its dynamical equation only involves pair interactions again,
375 even if the three entities can be simultaneously transmitted (for example through contacts between H and
376 W). We therefore conclude that the basic model explored in this work contains essential mechanisms for
377 coexistence resulting from asymmetrical interactions among the involved partners, and its results can be
378 conceptually extrapolated to scenarios with a larger number of players.

379 This problem of identifying coexistence conditions and the involved partners also admits a complementary
380 viewpoint. Instead of considering an enlarged dynamical system with many interacting viral and subviral
381 entities, and struggle to identify the conditions ensuring coexistence, we could take a more pragmatic
382 approach and ask which is the subset of viruses and subviral agents able to coexist when pooled from a
383 large ensemble of viruses and subviral particles that infect a given host. This subset would be, by definition,
384 an ensemble fulfilling the conditions for coexistence in that host, and it could vary from host to host.
385 From this viewpoint, the result of evolving towards regions of coexistence —should this be a situation
386 under selection— is equivalent to drawing the subset of viral species and subviral entities able to coexist.
387 This latter scenario conceptually agrees with common observations of multiple viral species (and possible
388 subviral particles) persistently co-infecting the same host, especially in plants.

389 Indeed, some of the equilibrium solutions and the overall scenarios we have found in our models and
390 their extensions find their counterpart in natural situations, and do share some of their difficulties. While co-
391 infection by multiple viral species or strains is common, detection and identification of involved parties and
392 the nature of their interactions presents major problems in etiological and epidemiological studies (Jeger,
393 2020). In our modelling approach, we can just describe regions of parameter space where coexistence is
394 or is not possible, but only a quantification of interactions and parameters can allow for a more specific
395 identification of partners and their interactions. For example, in our solution **S.6.a**, we show that due to
396 synergy between virus y and the satellite, x can stably infect the host, while it became extinct in the absence
397 of s . This would be the case of the obligatory mutualism between *Pea enation mosaic virus 1* (PEMV1) and
398 *Pea enation mosaic virus 2* (PEMV2), where PEMV1 provides a capsid required for PEMV2 transmission
399 while PEMV2 provides a movement protein required for systemic movement of PEMV within the infected
400 plant (Doumayrou et al., 2016).

401 Other studies have shown that the level of satellite abundance in virus-satellite associations is highly
402 variable, with up to 100% in some regions for helper virus population in *Rice yellow mottle virus* satRNA
403 (Pinel et al., 2003) to very low, as in *Cucumber mosaic virus* satRNA (Palukaitis and García-Arenal, 2003).
404 These observations are compatible with solutions **S.5** and **S.6.a**, where the level of co-infected hosts in
405 class S depends on several different model parameters. In particular, it grows when the rate of joint y - s
406 transmission, p_s increases, and *vice versa*, reaching 100% in situations where, in the context of our model,
407 both the replication and the propagation of y become fully dependent on the presence of s . Still, we cannot
408 tell the specific mechanism (i.e. parameter value, or set of), allowing for coexistence.

409 Our main qualitative result is that stable coexistence of all players is possible under a broad range of
410 parameters. Though biological and epidemiological outcomes of interactions among co-infecting viruses

411 seem to be hardly predictable (Syller, 2020), long-lived loose interactions as those arising between the
412 agents in our model create favorable circumstances for evolution towards more permanent associations
413 and to promote recombination between dissimilar viral and subviral particles (Elena, 2011; García-Arenal
414 et al., 2003). For example, recombination has led to the emergence of new species, both in DNA viruses as
415 begomoviruses (Chakraborty et al., 2008), and in RNA viruses, as is the case of *Watermelon mosaic virus*,
416 which arose through recombination of two legume-infecting viruses (Desbiez et al., 2011).

417 All examples of satellite viruses summarized in Fig. 1 represent necessary, asymmetric associations that
418 have likely evolved from more loose interactions between helper viruses and satellites. In a parsimonious
419 evolutionary scenario, it is sensible to assume that a monopartite virus coding for all functions needed
420 to complete the viral cycle modified at some point its genome through the association with a satellite
421 coding for genes providing new or different functions, either improving its packaging efficiency or its
422 transmissibility, or modifying its infecting phenotype. A colonization of a new host where the genes
423 provided by the satellite was instrumental could have also been a plausible evolutionary pathway, followed
424 by the elimination of the old, now useless, equivalent gene in the viral genome. This sort of reasoning
425 agrees with hypotheses relating high viral diversity to advantages at early phases of host colonization
426 (Gonzalez-Jara et al., 2009), where loose associations could quickly modify the viral phenotype without
427 the need of incorporating genetic changes (Lucía-Sanz and Manrubia, 2017).

428 Coexistence of viral and subviral agents in a single host may act as well as stepping stones towards
429 mutually dependent necessary associations, as bipartite viral forms. Symmetric associations characterized
430 by mandatory complementation between the parties could arise through different evolutionary pathways.
431 They could evolve from asymmetric associations, as these described in the previous paragraph, when the
432 survival of the helper virus becomes more dependent on the satellite. Also, they could be generated *de*
433 *novo* through associations between complementary, defective particles. Finally, fully fledged viruses of
434 dissimilar origin could produce a new phenotype and, eventually, streamline their genomes to minimize
435 functional redundancy, in a sort of viral Black Queen association (Morris et al., 2012). The three pathways
436 above could eventually yield what is usually described as a bipartite virus. Further particles could be added
437 to the system through similar processes, causing in a parsimonious way the emergence of multipartite viral
438 forms.

CONFLICT OF INTEREST STATEMENT

439 The authors declare that the research was conducted in the absence of any commercial or financial
440 relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

441 AL, JA and SM participated in the overall conception and design of the study; SM designed the models; AL
442 implemented the models and performed the simulations; AL and JA carried out the analytical calculations.
443 AF and FG made substantial contributions to the discussion and interpretation of the results. AL and SM
444 wrote the manuscript. All authors contributed to manuscript revision, read, and approved the submitted
445 version.

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SUPPLEMENTAL DATA

453 A Supplementary Information text file includes details on calculations retrieving the fixed points of the
454 dynamics and conditions for stability.

DATA AVAILABILITY STATEMENT

455 The computational code required to generate all the results in this study is publicly available at
456 <https://github.com/aluciasanz/satcompet.git>

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FIGURE CAPTIONS

Satellite virus	ssRNA	Tombusviridae, Virgaviridae, Nodaviridae Satellite CBPV, Albetovirus, Aumivirus, Papanivirus, Virtovirus, Macronovirus Nilaparvata lugens commensal X virus		
	dsDNA (Viriophage)	Mimiviridae, Phycodnaviridae Sputnikvirus, Mavirus, Organic lake satellite		
	ssDNA	Adenoviridae Dependoparvovirus Herpesviridae		
Satellite Nucleic Acid	ssDNA	Geminiviridae Alphasatellite		
		Nanoviridae Betasatellite		
		Geminiviridae Deltasatellite		
	dsRNA	Totiviridae M virus satellite, T1 virus satellite		
	ssRNA	Large linear		Secoviridae, Alphaflexiviridae
		Small linear		Tombusviridae, Bromoviridae
		Small circular		Secoviridae, Luteoviridae
Small circular (Virusoid)		Solemoviridae Hepadnaviridae Deltavirus		
DI				

Figure 1. Summary of classes of satellite viruses. There is no straightforward classification of satellites, although distinguishable groups come to light when looking at the genetic material, helper virus family, host, or coded proteins. Here we show a possible classification into two groups, depending on whether they code for a capsid protein (satellite viruses) or not (satellite nucleic acid). Satellite viruses comprise plant satellites with jelly roll capsid proteins, dependoparvovirus and viriophages (Krupovic and Cvirkaite-Krupovic, 2012; Krupovic et al., 2016). Satellite nucleic acids include α/β -satellites and *Secoviridae* satellites coding for a replicase or a replication helper protein; M virus satellite expresses a toxin and HDV codes for an antigen. This group includes non-coding —circular— ssDNAs (Stanley et al., 1997) and RNAs with a compact folded structure with ribozyme activity (Hadid et al., 2017; Roossinck et al., 1992). Colors on the right bars show the protein each satellite codes for: capsid (blue), replicase (green), other (yellow). Grey stands for no coded protein. Helper virus families are shown in bold font; DI stands for defective interfering genomes (e.g., coated like defective interfering particles or uncoated).

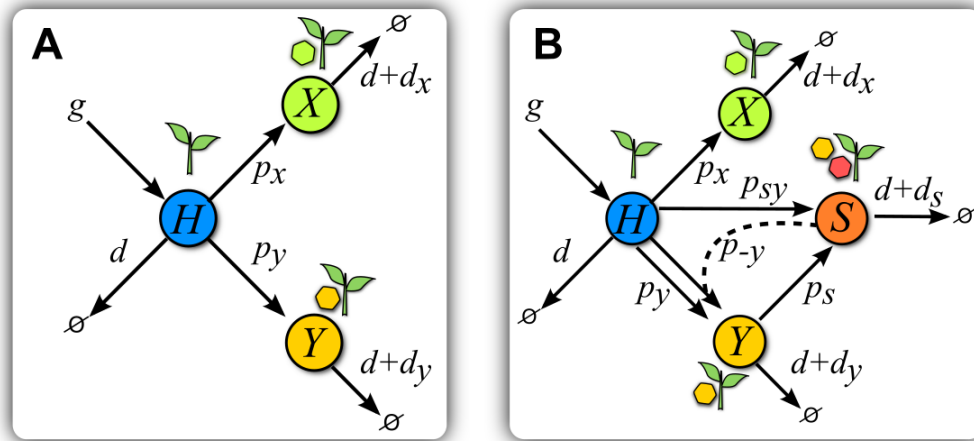


Figure 2. Scheme of models. (A) Scheme of Model V. Healthy hosts H are seeded at a constant rate g and die with basal rate d . Transitions to infected states happen at rates p_x and p_y for each virus. Infected hosts X and Y suffer from an increase d_i in basal mortality. (B) Scheme of Model S. The introduction of a satellite with y as helper virus adds new transitions with respect to (A). Hosts in class Y can get infected at a rate p_s by a satellite upon contact with hosts in class S . Hosts in this latter class are simultaneously infected by virus y and its satellite, and have an increase d_s in their mortality rate. Infection of H plants by the helper virus and the satellite simultaneously occurs at a rate p_{sy} upon contact with class S . A co-infected plant S can also infect H plants only with virus y at a rate p_{-y} . The color code is maintained all through the paper.

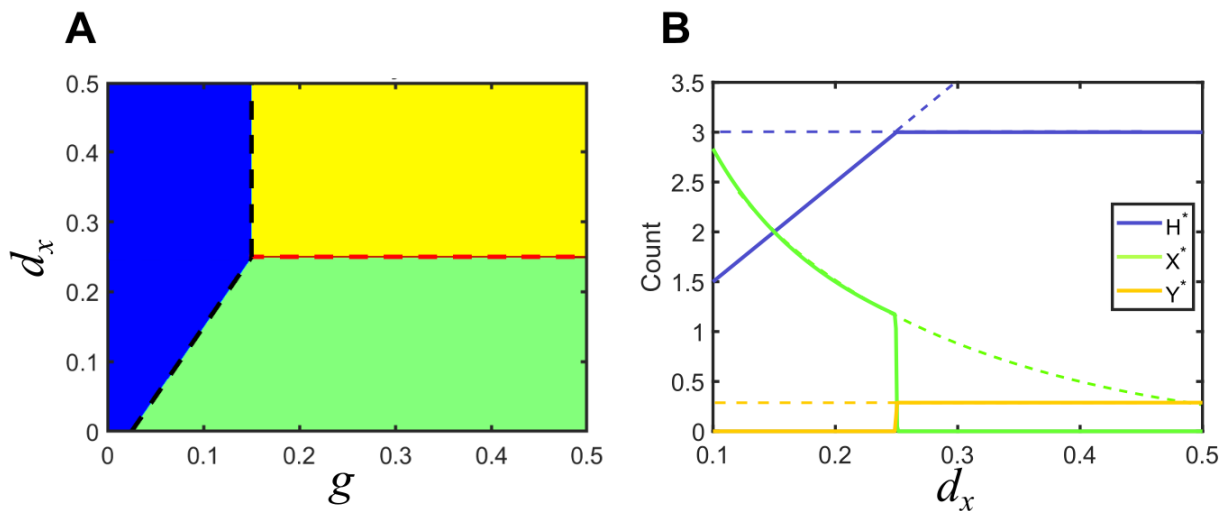


Figure 3. Solutions for Model V in parameter space. (A) Phase space of solutions in the plane $\{g, d_x\}$. In the blue region, none of the viruses can invade the population of hosts, $d/g > F_i$, $i = x, y$. The black dashed line indicates the boundary where $d/g = F_i$. Green and yellow regions correspond to solutions that satisfy $F_x > F_y$ and $F_y > F_x$, respectively, where one of the viruses invades the population of hosts and displaces the other. The red dashed line corresponds to the marginal coexistence solution. (B) Bifurcation diagram for a cross section of the phase space in A corresponding to $g = 0.5$. Lines indicate the amount of each class at the fixed point, as shown in the legend. Dashed lines represent unstable solutions, while solid lines correspond to stable solutions. Green and yellow regions in A correspond to $d_x < 0.25$ and $d_x > 0.25$. Vertical lines show the degenerate solution of coexistence of the two viruses for $d_x = 0.25$. Note that the values of H^* and Y^* become independent of d_x in the region where y is the invading virus (and thus x becomes extinct). Parameters used: $d = 0.05$, $p_x = 0.1$, $p_y = 0.1$, $d_y = 0.25$.

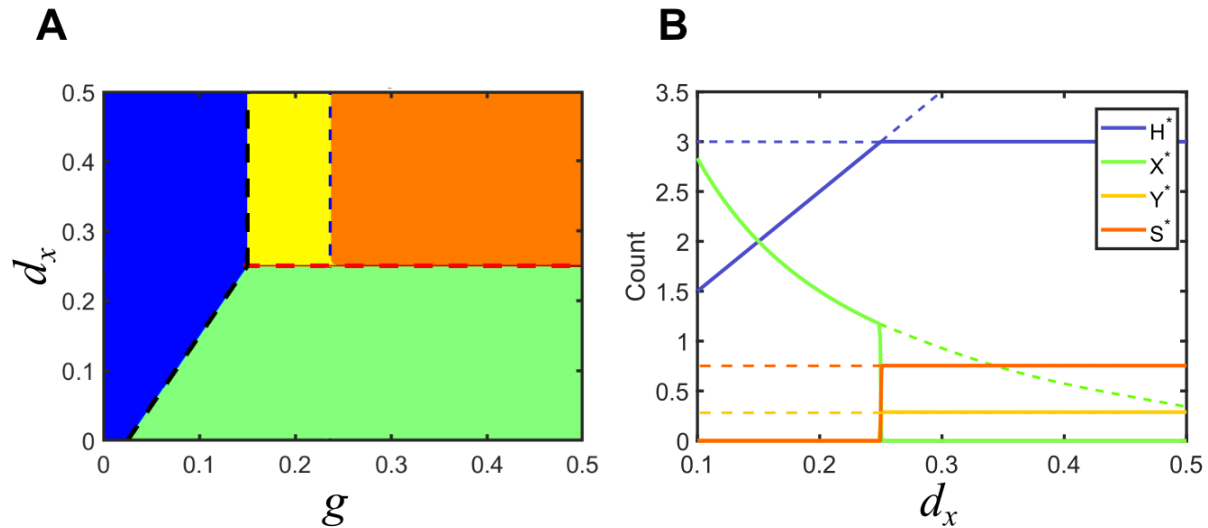


Figure 4. Solutions for model S in parameter space: commensal satellite. (A) Phase space of solutions in the plane $\{g, d_x\}$ for a commensal satellite ($F_c = F_y$). The description of regions corresponding to solutions **S.1** (in blue, viruses cannot infect hosts), **S.2** (in green, virus x invades and virus y becomes extinct) and **S.3** (in yellow, virus y invades and virus x becomes extinct) are analogous to those described for Model V. In the new orange region, the satellite stably coexists with its helper virus, **S.5**. Red and black dashed lines are as in Fig. 3. The blue dashed line signals the boundary separating the regions with and without co-circulating satellite. Note that the absence of virus y prevents the stable circulation of the satellite (below $d_x = 0.25$). (B) Bifurcation diagram of a cross section of A, for $g = 0.5$. As above, lines stand for the amount of each class at equilibrium. Dashed lines correspond to unstable solutions, while solid lines correspond to stable solutions. Solutions collide with the degenerated solution **S.4** at $d_x = 0.25$. Parameters used: $d = 0.05, p_x = 0.1, p_y = 0.1, d_y = 0.25, p_s = 0.8, p_{sy} = 0.04, d_s = 0.3, p_{-y} = 0.0766$.

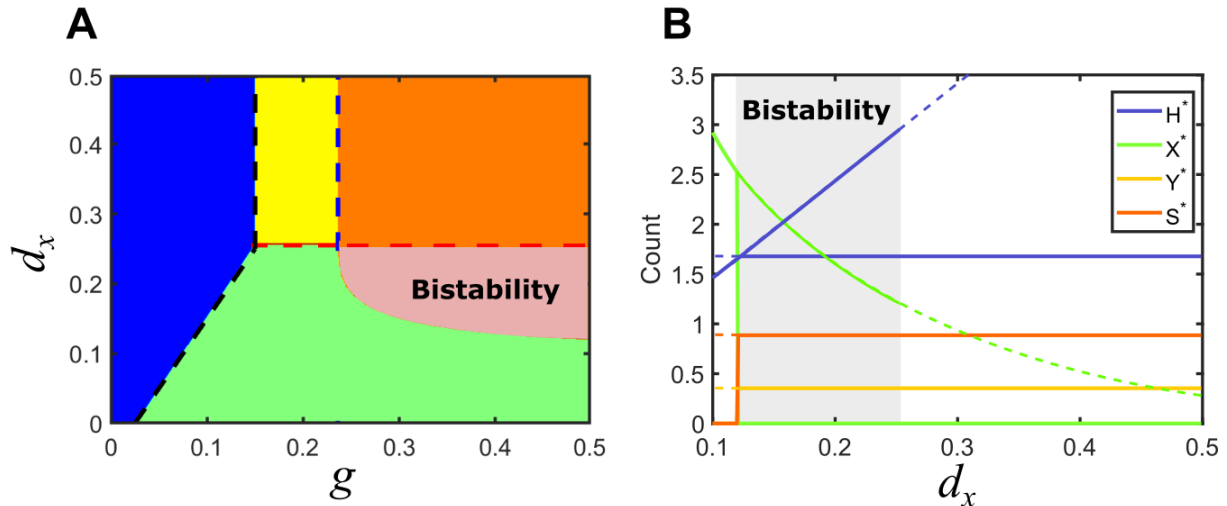


Figure 5. Solutions for model S in parameter space: mutualistic satellite. (A) Phase space of solutions in the plane $\{g, d_x\}$ for a mutualistic satellite. Here, $F_c > F_y$. Some of the previous equilibrium solutions are maintained, as long as the inequalities that define them remain unchanged. However, a region of bistability appears, where solutions **S.2** and **S.5** are possible for the same parameters, depending on the initial conditions. (B) Bifurcation diagram of a cross section of A, for $g = 0.5$. As above, lines stand for the amount of each class at equilibrium. Dashed lines correspond to unstable solutions, while solid lines correspond to stable solutions. A region of bistability for $0.12 < d_x < 0.25$ is shown in gray. A bifurcation where two solutions appear occurs at $d_x = 0.12$; solutions collide with the degenerated solution **S.4** and stability is modified at $d_x = 0.25$. Parameters used: $d = 0.05, p_x = 0.1, p_y = 0.1, d_y = 0.25, p_s = 0.8, p_{sy} = 0.04, d_s = 0.3, p_{-y} = 0.2$.

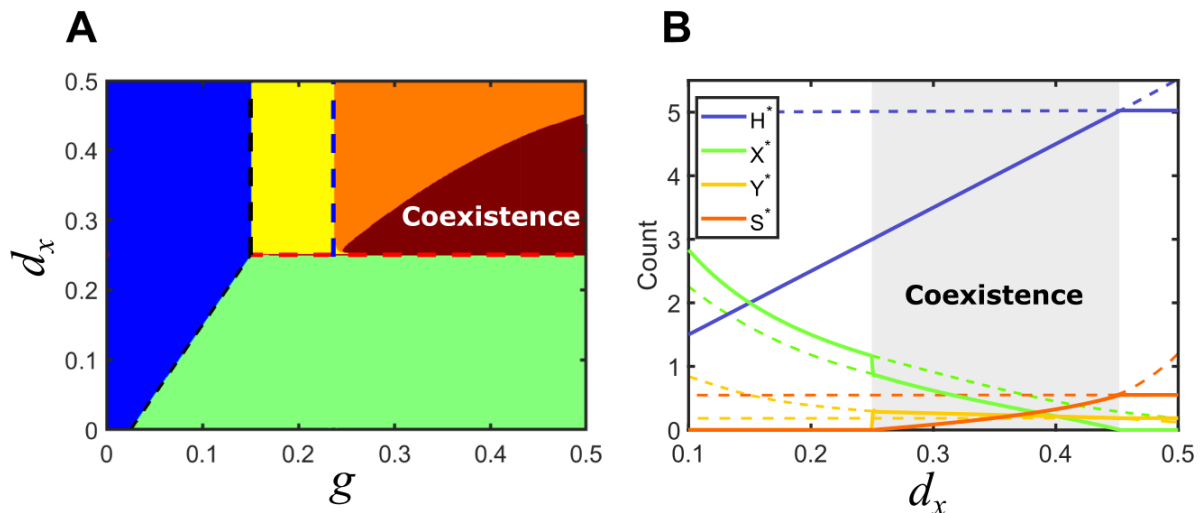


Figure 6. Solutions for model S in parameter space: parasitic satellite. (A) Phase space of solutions in the plane $\{g, d_x\}$ for a parasitic satellite in the particular case $F_c < F_y$. A region of co-existence occupies part of the area where the virus y -satellite eliminated virus x if the satellite was commensal or mutualistic. (B) Bifurcation diagram of a cross-section of A, for $g = 0.5$. A region of co-existence of all the populations is shown in gray for $0.25 < d_x < 0.4529$, corresponding to solution **S.6**. Solutions collide with the degenerated solution **S.4** at $d_x = 0.25$; a bifurcation occurs at $d_x = 0.4529$. Parameters used: $d = 0.05, p_x = 0.1, p_y = 0.1, d_y = 0.25, p_s = 0.8, p_{sy} = 0.04, d_s = 0.3, p_{-y} = 0.016$.













Fixed point	Classes at equilibrium	Existence, non negativity and stability
V.1: $\left(\frac{g}{d}, 0, 0\right)$	  	$F_x < d/g$ and $F_y < d/g$
V.2: $\left(\frac{d+d_x}{p_x}, \frac{g}{d+d_x} - \frac{d}{p_x}, 0\right)$	  	$F_x > d/g$ and $F_x > F_y$
V.3: $\left(\frac{d+d_y}{p_y}, 0, \frac{g}{d+d_y} - \frac{d}{p_y}\right)$	  	$F_y > d/g$ and $F_y > F_x$
V.4: $\left(\frac{d+d_x}{p_x}, X^*, \frac{g}{d+d_y} - \frac{d}{p_y} - \frac{p_x}{p_y} X^*\right)$	  	$F_x = F_y > \frac{d}{g}$ and $\frac{g}{d+d_x} - \frac{d}{p_x} > X^* > 0$

Table 1. Properties of the solutions of model V. The left column shows the analytical solution (fixed point of the dynamics, (H^*, X^*, Y^*)); the central column symbolically illustrates the states with positive population at equilibrium (colored circles), gray circles are for classes with zero population. The right column specifies the conditions for existence, non-negativity and stability of each solution.

TABLES

























Fixed point	Classes at equilibrium	Existence, non negativity and stability
S.1: $\left(\frac{g}{d}, 0, 0, 0\right)$	   	$F_x < d/g$, $F_y < d/g$ and $F_{sy} < d/g$
S.2: $\left(\frac{d+d_x}{p_x}, \frac{g}{d+d_x} - \frac{d}{p_x}, 0, 0\right)$	   	$F_x > d/g$, $F_x > F_y$ and $F_x > F_{sy}$
S.3: $\left(\frac{d+d_y}{p_y}, 0, \frac{g}{d+d_y} - \frac{d}{p_y}, 0\right)$	   	$F_y > d/g$, $F_y > F_x$ and $F_y(1 - \gamma) > F_{sy}$
S.4: $\left(\frac{d+d_x}{p_x}, X^*, \frac{g}{d+d_y} - \frac{d}{p_y} - \frac{p_x}{p_y} X^*, 0\right)$	   	$F_y = F_x > d/g$ and three others, see SI
S.5: $(H^*, 0, Y^*(H^*), S^*(H^*))$	   	See SI
S.6: $\left(\frac{d+d_x}{p_x}, X^*(H^*), Y^*(H^*), S^*(H^*)\right)$	   	See SI

Table 2. Properties of the solutions of model S. The left column shows the analytical solution (fixed point of the dynamics, (H^*, X^*, Y^*, S^*)); the right column summarizes all conditions for existence, non-negativity and stability of that solution. We have defined $\gamma = (g/(d + d_y) - d/p_y)p_s/(d + d_s)$, see main text. Solution **S.4** is degenerate in the same sense than **V.4** was: there is a continuum of values of X^* and Y^* that satisfy the fixed point equations. Further, it is a marginally stable solution, since parameter values have to be fine-tuned for it to persist. This is the reason it requires strict conditions that we detail in the Supplementary Information. Coexistence solution **S.6** takes two different forms, therefore embracing two different fixed points (see main text and SI for further details).