# Niche theory for within-host parasite dynamics: Analogies to food web modules via feedback loops

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**ABSTRACT**

Why do parasites exhibit a wide dynamical range within their hosts? For instance, why can a parasite only sometimes successfully infect its host? Why do some parasites exhibit large fluctuations? Why do two parasites coinfect, exclude each other, or win only sometimes over another (via priority effects)? For insights, we turn to food webs. An omnivory model (IGP) blueprints one parasite competing with immune cells for host energy (PIE), and a competition model (keystone predation, KP) mirrors a new coinfection model (2PIE). We then draw analogies between models using feedback loops. We translate those loops into the intraspecific direct (DE) and indirect effects (IE) that create various dynamics. Three points arise. First, a prey or parasite can flip between stable and oscillatory coexistence with their enemy with weakening IE and strengthening DE. Second, even with comparable loop structure, a parasite cannot exhibit priority effects seen in IGP due to constraints imposed by production of immune cells. Third, despite simpler loop structure, KP predicts parallel outcomes in the two-parasite model due to comparable structure of interactions between competing victims and their resources and enemies. Hence, food web models offer powerful if imperfect analogies to feedbacks underlying the dynamical repertoire of parasites within hosts.

## INTRODUCTION

Parasites can show a variety of dynamics within hosts. These within-host dynamics can significantly affect health of individual hosts (Råberg *et al* 2009; Cressler *et al* 2014; Bashey 2015) and alter population-level disease outbreaks (Mideo 2008; Råberg *et al* 2012; Gorisch *et al* 2018). For instance, exposure to parasite propagules often causes infection of some but not all hosts despite seemingly similar starting conditions (Merrill & Cáceres 2018). The success or failure of invasion and persistence of a parasite within a host determines its infection status or even death (Duneau *et al* 2017; Merrill & Cáceres 2018). Once infected, the stability or instability of within-host dynamics can further impact both host health and transmission to others. For instance, periods of high abundance of a cycling gut parasite can both decrease foraging and increase transmission to bee hosts (Otterstatter & Thomson 2006). Similarly, coinfection (*i.e.,* within-host coexistence of parasites) can reduce fecundity of hosts more than single infection (Lohr *et al* 2010). At the between-host scale, coinfection can reduce or increase outbreaks compared to singly infected populations (Clay *et al* 2019; Susi *et al* 2015). Consequently, various dynamics of parasites can arise within hosts, likely mediated by immune systems and nutrient/energy availability (Graham 2008; Cressler *et al* 2014). But which mechanisms determine those dynamics?

To answer this question, two classic food web modules from community ecology provide analogies. In intraguild predation (IGP), an omnivorous predator and its prey compete for a shared resource (Holt & Polis 1997; Verdy & Amarasekare 2010). Similarly, immune cells and a parasite compete for shared energy within a host (Fig. 1A - C; Cressler *et al* 2014). Hence, mechanisms that capture the repertoire of dynamics in IGP (stable coexistence, oscillations, priority effects, exclusion) could also produce those observed in single-parasite studies (Otterstatter & Thomson 2006; Merrill & Cáceres 2018). Additionally, in the diamond-keystone predation (KP) model, two prey species share a resource (exploitative competition) and a predator (apparent competition: Holt *et al.* 1994, Leibold 1996). Similarly, two parasites can compete for a shared resource while facing

68 immune attack (Fig. 1D - F). In such a scenario, the KP model could anticipate the tradeoffs and
69 niche dimensions needed for coexistence, exclusions, and priority effects of coinfecting parasites
70 (Natsopoulou *et al* 2015). The underlying hope, then, is that food web modules might provide apt
71 blueprints, because they share basic consumer-resource structure with their within-host analogues.
72 However, a major complication arises: the enemy is generated differently in food webs vs.
73 within a host (Wodarz 2006). Predators attack and assimilate prey for reproduction into new
74 predators. Immune cells also attack parasites, but they simultaneously require host energy to
75 produce immune cells (Cressler *et al* 2014). These "consumer-resource like" interactions can
76 involve products of immune cells, parasites, and energy. Additionally, hosts can allocate a baseline
77 level of energy straight to immune cells, a pipeline not enjoyed by even omnivorous predators in
78 typical food webs. Therefore, these fundamentals of immune function – even when highly
79 simplified - create more interaction links (Fig. 1). Those additional links might alter feedbacks
80 underpinning the range of stability outcomes (Metcalf *et al* 2020), possibly undermining analogies
81 from food webs or creating new outcomes altogether. Given these issues (Wodarz 2006; Alizon *et*
82 *al* 2008; Fenton & Perkin 2010), how could we usefully compare and contrast stability outcomes
83 in food webs (IGP, KP) to their within-host analogues?
84 We tackle this challenge by using a feedback loop approach. Feedback loops link the
85 strength of consumer-resource interactions to stability (Puccia & Levins 1991). Indeed, feedback
86 loops characterize the biology behind stability and enable comparison of structurally similar but
87 biologically distinct systems. Every $n$-dimensional system consists of $n$ levels of feedback ($F_n$).
88 The simplest level of feedback, level 1 ($F_1$), involves intraspecific direct effects (DE). Here, a
89 small increase of a species impacts its own growth rate – positively or negatively - via interaction
90 with itself and from those directly consuming it. Then, longer loops (from 2 through $n$ dimensions)
91 involve combinations of intra- and inter-specific direct effects (calculated from Jacobian matrices).
92 For instance, in a two-species loop, an increase in a resource's density could increase growth rate

93 of its consumer. Increased density of its consumer, in turn, could then depress growth rate of that
94 resource (hence, binary consumer-resource interactions create negative $F_2$). With more
95 dimensions, the connections between interactors become more complex and varied, potentially
96 introducing both positive and negative feedbacks. The sign and strength of feedback at all relevant
97 levels, then, governs stability. Additionally, key ratios of those longer loops determine
98 intraspecific indirect effects (IE; developed in Box 1). As we then show, feedback at certain levels,
99 translated into intraspecific direct and indirect effects, determines stability of the interactions.

100 Using intraspecific direct and indirect feedback loops, we first revisit the foundational IGP
101 and KP models. We then apply these loop-based lessons to analogous parasite-immune-energy
102 models (PIE and 2PIE; Fig. 1). To study these analogues, we assume that parasite(s) respond to
103 attack by a common immune system. That assumption surely oversimplifies some examples (*e.g.,*
104 in vertebrates: Ezenwa & Jolles 2011), but it seems like a reasonable place to start for others
105 (Graham 2008; Griffits *et al* 2015; Rynkiewicz *et al* 2015). Additionally, we assume that immune
106 cells and parasites share host energy (a resource, following Griffits *et al* 2015). We then evaluate
107 how host energy and immune system interact to mediate parasite dynamics within hosts (De Roode
108 *et al* 2005; Ezenwa & Jolles 2011; Doublet *et al* 2015).

109 The analysis involves three parts. First, we translate loops into a scheme framed as
110 intraspecific direct and indirect effects (DE and IE). This interpretation works most thoroughly for
111 3D systems (IGP and PIE models), but we extended key ideas to 4D systems (KP and 2PIE
112 models). Second, using these tools, we analyzed stability outcomes for IGP vs. PIE. We find that
113 IGP and PIE share some dynamics (coexistence, stably or via oscillations) due to similar loop
114 structure. However, the nature of the generation of immune cells prevents some outcomes present
115 in IGP (involving two variations on alternate stable states). Third, we find that despite having
116 simpler feedback links, KP anticipates coexistence/coinfection vs. priority effects (or alternate
117 stable states) of competing parasites in 2PIE models. Furthermore, these outcomes arise for

118 conceptually similar reasons. Specifically, depending on their traits, competing prey or parasites
119 exhibit symmetries (coexistence/coinfection) or asymmetries (priority effects) in ratios describing
120 '*effects on'* their enemies and resources vs. how they are '*affected by*' them. Those (a)symmetries
121 determine the strength of tradeoffs and competitive hierarchies among competitors. They also
122 underpin the sign of feedback at a key level, hence they govern whether parasites experience
123 negative or positive indirect effects. Furthermore, allocation of energy to constitutive immunity
124 enhances negative feedback, thereby shrinking regions of within-host oscillations, coinfection, and
125 parasite burden. Thus, feedback loops, guided by our interpretation schemes, show when and why
126 comparable dynamics arise in these food webs and their within-host analogues. However, we
127 highlight why differences in production of enemies constrain some outcomes within hosts.
128

129 **METHODS AND RESULTS**

130 *Overview of the models*

131 We compare and contrast modules of food web and within-host dynamics. The model with
132 one prey, predator, and resources (intraguild predation, IGP; Holt & Polis 1997; Verdy &
133 Amarasekare 2010) parallels a within-host model of one parasite species, immune cells, and host
134 energy (PIE; modified from Hite & Cressler 2018). Similar, a two prey, predator, resource model
135 (keystone predation, KP; Leibold 1996) parallels one with the new two parasite species, immune
136 cells, and host energy model (2PIE). However, while the food web and within-host modules share
137 similar structure, they create enemies differently. Specifically, predators proliferate via direct
138 consumption of their prey, while immune cells jointly require both parasites and a shared energy.
139 Additionally, the within-host modules include two variants that commonly arise in invertebrate
140 host-parasite systems. In one, only parasites activate production of immune cells (PIE and 2PIE
141 models). In the other, energy is continuously allocated to maintain baseline immune function, even
142 without parasites (PIEc and 2PIEc, constitutive immunity). Despite their differences, we compare

143 across food web and within-host modules using feedback loops. Feedback loops provide a
144 common metric to unpack the biology underlying stability. Jacobian matrices provide the starting
145 point (Box 1, Appendix Section 1). Each of Jacobian terms represents the direct effect of species
146 $j$ on growth rate of species $i$ ($J_{ij}$), yielding (hereafter) interspecific *positive effects* (black arrow)
147 and *negative effects* (red arrow) and intraspecific *self-limitation* (red curve) or *self-facilitation*
148 (black curve; Box 1, Fig. 1 [not seen here]). As shown below, these terms combine into loops at
149 various levels.
150
151 ***One prey - predator - resource (IGP) | One parasite - immune cells - host energy (PIE & PIEc)***
152 At their heart, both IGP and PIE models hinge on binary consumer-resource like
153 interactions (Fig.2, Table 1). In these interactions, consumers directly benefit while resources
154 suffer direct costs. In IGP, omnivorous predators ($P$) can consume prey ($N_1$) and resources ($R$).
155 An interior equilibrium becomes feasible when each species can maintain positive density ($P^* >$
156 $0$, $N_1^* > 0$, $R^* > 0$). At IGP's interior, these consumer-resource interactions exert positive effects
157 on the predator but negative ones on prey and resource. Then, prey also indirectly compete with
158 predators for the shared resource. Consumption of resources benefits the prey and harms resources.
159 Finally, chemostat-like renewal imposes self-limitation on resources (Fig. 1A). Similarly, in the
160 within-host models, immune cells ($I$) "consume" two items, simultaneously killing parasites ($N_1$)
161 while taking up host energy ($E$). At PIE's interior, these consumer-resource-like interactions have
162 a positive effect on $I$ and negative on $N_1$ and $E$. The parasite competes for this shared energy;
163 consumption of host energy positively effects parasites and negatively effects energy.
164 Additionally, the donor-controlled renewal of host energy imposes self-limitation on energy
165 without baseline allocation ($a_b = 0$; Fig. 1B). Fixed energy allocated to immune cells ($a_b > 0$)
166 creates additional self-limitation on the immune cells in PIEc (Fig. 1C).
167

168

169 *Intraspecific direct and indirect effects: an approach using feedback (Box 1 and Fig. 2).*

170 To compare stability of these models, we used feedback loops (Box 1). Any *n*-dimensional
171 system can be decomposed into *n* levels of feedback that determine stability of an equilibrium
172 (Box 1, Top Panel). An interior equilibrium can allow stable or unstable coexistence (oscillations)
173 or produce, potentially, alternate stable states (if it is a saddle). As illustrated by and applied to
174 IGP and PIE, the three-dimensional system creates three levels of feedback (Box 1, Fig. 2). For
175 example, level 1 feedback ($F_1$) is the sum of intraspecific direct effects (Box 1) and is the
176 Jacobian's trace (Appendix Section 1). At the interior of IGP and PIE, the basal resource / energy
177 contributes to the direct effects at the feasible interior (Fig. 2, Appendix Section 2). Self-limitation
178 comes from the chemostat-supplied resource and its consumption; in PIEc, baseline allocation to
179 immunity adds self-limitation (hence negative level 1 feedback [see below but also Appendix
180 Section 1]). Level 2 ($F_2$) feedback sums up two-species loops (Box 1). In PIE models (Fig. 2), this
181 sum of pairwise consumer resource come from energy-parasite ($E$-$N_1$), energy-immune cells ($E$-
182 $I$), and parasite-immune cells ($N_1$-$I$, with $R$-$N_1$, $R$-$P$, and $N_1$-$P$ analogies in IGP, respectively). At
183 the interior, all of these loops contribute to negative feedback. That negative feedback intensifies
184 in PIEc from the product of energy and immune self-limitation. In all 3D models considered here,
185 $F_2$ is negative at the interior equilibrium (based just on signs alone): level 2 feedback stabilizes.

186 Level 3 feedback ($F_3$) sums three-species loops. It is also the negative of the determinant
187 of the Jacobian, - |**J**| (Appendix Sections 1, 2). In PIE models, these loops at the interior are (Fig.
188 2, $L$-$R$): (i) "*$N_1$ is eaten*", a negative loop coming from the stabilizing product of the immune-
189 parasite loop and energy self-limitation; (ii) "*starving the enemy*", a positive loop where a small
190 increase in the parasite reduces energy for the immune cells, hence reduces immune attack (i.e.,
191 $\uparrow N_1 \rightarrow \downarrow E \rightarrow \downarrow I \rightarrow \uparrow N_1$); (iii) "*feeding the enemy*", a negative loop where a small increase of the
192 parasite 1 stimulates the immune cells which consume energy that then starves the parasite ($\uparrow N_1 \rightarrow$

193 $\uparrow I \rightarrow \downarrow E \rightarrow \downarrow N_1$). Thus, negative feedback operates when $N_1$ hurts itself by "feeding" the immune
194 cells. Similar loops arise in IGP. Finally, in only PIEc, (iv) a negative "*$N_1$ eats*" loop arises from
195 the stabilizing product of energy consumption by the parasite and immune self-limitation.

196 Combined, these three levels of feedback determine stability of the interior equilibrium.
197 First, stability requires that each level of feedback is negative (so, $F_1 < 0$, $F_2 < 0$, and $F_3 < 0$). When
198 $F_3 < 0$, the interior is stable; when $F_3 > 0$, it is a saddle. Additionally, stability requires that $F_1 F_2$
199 $+ F_3 > 0$, or that upper-level feedbacks ($F_3$) not be too strong relative to lower-level feedback ($F_1$
200 $F_2$). All of these conditions have analogies to the Routh-Hurwitz criteria, differing only in sign
201 (Puccia & Levins 1991). Here, we also reframe stability analysis as sums of intraspecific direct
202 effects ($F_1$, hereafter DE) and of intraspecific indirect effects ($-F_2 / F_3$, the trace of the inverse
203 Jacobian, IE: see Appendix Section 1, Box 1). Written this way, IE is a ratio of the longer loops,
204 where each species interacts with other species in feedback at level 2 ($F_2$) and level 3 ($F_3$). It is
205 also the sum of intraspecific indirect effects of each species $N_i$ (lying on tr[$-\mathbf{J}^{-1}$]; Eq. 5):

206 $$\mathrm{IE} = \mathrm{IE}_{\mathrm{N}_1} + \mathrm{IE}_{\mathrm{N}_2} + \mathrm{IE}_{\mathrm{N}_3} = -F_2/F_3 \qquad \text{(Eq. 5)}$$

207 The numerator of the intraspecific indirect effects of each species ($\mathrm{IE}_{\mathrm{N}_i}$) corresponds to specific
208 combinations of the reciprocal two-species $F_2$ loops; the denominator for each species is $F_3$. For
209 example, in general form, the corresponding indirect effect of $N_1$, $\mathrm{IE}_{\mathrm{N}_1}$, is the sum of (i) the product
210 of self-limitation of $N_2$ and $N_3$ and (ii) pairwise consumer-resource loop of $N_2$ and $N_3$, all divided
211 by $F_3$ (green shading over gray shading, Box 1). Similar expressions can be derived for species 2
212 ($\mathrm{IE}_{\mathrm{N}_2}$, yellow shading) and 3 ($\mathrm{IE}_{\mathrm{N}_3}$, blue shading). With DE and IE in hand, stability then depends
213 on their sign and the strength of their product. Specifically, *stable coexistence* occurs when direct
214 and indirect effects are negative (DE < 0, IE < 0) and jointly strong (DE x IE > 1; bottom of Box
215 1, light orange region; equivalent to $F_1 F_2 > -F_3$). *Oscillations* arise when direct and indirect effects
216 are jointly weak (dark orange, DE x IE < 1 for DE < 0, or DE > 0; equivalent to $F_1 F_2 < -F_3$).
217 Finally, *alternate stable states (aka priority effects)* occur with positive indirect effects (IE > 0,

*i.e.*, when $F_3 > 0$ for IGP and PIE, given that $F_2 < 0$ for both at their interiors; Box 1, gray region). Note: we use the terms alternate stable states and priority effects interchangeably. They both denotes how initial densities, even offset in time (*e.g.,* sequential infection), can determine competitive outcomes (depending on whose domain of attraction they move through).

*Weakening DE x IE generates oscillations in these models (Fig. 3 and Appendix Section 2)*

*Assembly of the interior equilibrium:* To compare stability outcomes across IGP and PIE models, we created parallel 2D bifurcation diagrams (Fig 3). These diagrams spread gradients of parameter space of an environmental factor, supply of resource (*S*), and trait space of the focal prey/parasite, feeding rate of $N_1$ on resource, $f_{N_1}$ (Fig. 3A-C; interpreted with 1D bifurcation diagrams: Fig. 3G-I). The lines within the 2D bifurcation diagram represent shifts in species composition or in dynamics (stable coexistence, oscillations, or alternative stable states; see Appendix Section 2 for full analysis). In IGP (Fig. 3A), when resource supply and feeding rate of prey are too low to meet the minimal resource requirement of either the prey or predator, only *R* is supported in the system (*R*, yellow). Increases in *S* allows *R* to meet the minimum resource requirement ($R^*$) of the predator (hence *P* invades creating the *R-P* region, green). As feeding rate of prey increases along a fixed resource supply ($S = 110$), the prey becomes a better competitor for resources, enabling births, $f_{N_1}R^*$, to exceed deaths, $f_{PN_1}\ P^* + m_N$ at the *R-P* boundary. Hence, the prey can invade; both prey and predator push $R^*$ lower in the $R$-$N_1$-$P$ interior (Fig. 3A, Fig. 3G). In this region, $R$-$N_1$-$P$ are able to coexist either stably (light orange) or via oscillations (dark orange). On the other hand, as the feeding rate of prey increases at low *S* ($S = 5$), prey invade the resource-only boundary (creating the $R$-$N_1$ region, blue). The omnivorous predator can then invade this $R$-$N_1$ boundary when its birth rate, $e_{PN_1} f_{PN_1}\ N_1^* + f_{PR}\ R^*$, exceeds its death rate, $m_P$. Successful invasion creates stable coexistence (orange; Fig. 3A). Thus, *R, R-P,* $R$-$N_1$, and $R$-$N_1$-$P$ equilibria (oscillatory and stable coexistence) are possible.

The within-host PIE model contains some but not all analogous states. The key differences stem from how hosts produce immune cells. In PIE (Fig. 3B), immune cells only generate with parasites. Hence, a host energy-immune (*E-I*) state, analogous to the *R-P* one, is not possible. Similar to IGP, though, low feeding rate can prevent parasite invasion (creating the *E*-only state [yellow]). With increasing feeding rates (illustrated at $S$ = 500), parasites ($N_1$) can eventually invade creating $E$-$N_1$ space (light blue; Fig. 3H). Although parasites depress $E^*$, sufficiently high parasite density enables production of immune cells, when the immune system's minimal $E\ N_1$ requirement is met (Fig. 3H). Hence, at medium to high feeding rates of parasites, $E$-$N_1$-$I$ coexist either stably (light orange) or via oscillations (dark orange). However, at sufficiently high $f_{N_1}$, parasites compete too strongly: they successfully starve out the immune cells, re-establishing a $E$-$N_1$ space (blue). Thus, PIE exhibits only three equilibria: $E$, $E$-$N_1$, and $E$-$N_1$-$I$ (oscillations and stable coexistence; Fig. 3B; see Appendix Section 3B for details).

In PIEc, the host always allocates energy to the immune system ($a_b > 0$). This biology eliminates the *E*-alone and $E$-$N_1$ region. Instead, immune cells prevent infection (*E-I* space; low $f_{N_1}$; green) or hosts become infected ($E$-$N_1$-$I$ space; higher $f_{N_1}$; orange). Parasites successfully infect when their births, $(f_{N_1} / e_{N_1 E})\ E^*$, exceed their deaths at immune-enhanced, $m_I + f_{IN_1}\ I^*$. Like IGP, at high feeding rates of parasites, the $E$-$N_1$-$I$ remains stable (light orange) or oscillates (only at low $a_b$ [Appendix Section 2]). Thus, in PIEc, immune biology eliminates even more states; only *E-I* and $E$-$I$-$N_1$ (oscillations and stable coexistence) remain possible (Fig. 3C).

*Stability outcomes:* Despite these differences, oscillations arise for similar reasons in the food web and within-host models. As noted in Box 1, oscillations require weakening of the joint product of intraspecific direct effects (DE) and indirect effects (IE). In all three cases, stable coexistence (DE x IE > 1) envelopes oscillatory regions (DE x IE < 1; Fig. 3A-B; Appendix Fig. A2). In IGP, weakening of IE at low feeding rate of the prey, $f_{N_1}$, triggered oscillations despite strengthening of DE (Fig. 3D). At high $f_{N_1}$, DE strengthens to regain stability. This general pattern

also arises with increasing feeding rate of parasites in the PIE and PIEc models (Fig. 3E-F). However, DE differed slightly among models (Fig. 3D-F, black, solid lines), where DE is:

IGP: $$-a - (f_{N_1}\, Q_{N_1} N_1^* + f_{PR}\, Q_P P^*) \quad \text{(Eq. 6A)}$$

PIE: $$-r - (f_{N_1}\, N_1^* + e_{IN_1}\, f_{IN_1}\, N_1^* I^*) \quad \text{(Eq. 6B)}$$

PIEc: $$\underbrace{-r - (f_{N_1}\, N_1^* + e_{IN_1}\, f_{IN_1}\, N_1^* I^*) - a_b}_{DE_E} + \underbrace{\frac{-e_I\, m_I + e_{IN_1} f_{IN_1}\, N_1 E}{e_I}}_{DE_I} \quad \text{(Eq. 6C)}$$

Here, either the sum (IGP) or sum and product (PIE) of victim and enemy densities strengthens DE (Eq. 6). Strong enough DE then tips the coexistence equilibrium from oscillations to stability. In IGP the additive increase in predator and prey densities strengthens DE of resources (Eq. 6A). Thus, strengthening of DE restores stability at higher $f_{N_1}$ (Fig. 3D, black, solid line). In the PIE models, however, increase in the (weighted) sum of parasites plus the product of parasite and immune cells strengthens DE of energy at higher $f_{N_1}$ (Eq. 6B-C; Fig. 3E-F, black, solid line).

Constitutive immunity enhanced stability in PIEc models by creating immune self-limitation. This self-limitation generates additional loops featured in both intraspecific direct effects (DE) and indirect (IE; Fig. 2). In PIEc, DE now has two components: DE of energy ($DE_E$) and DE of immune cells ($DE_I$; Eq. 6C). The updated $DE_E$ adds fixed energy allocation towards baseline immunity ($-a_b$; Fig. 3F, orange, solid line [$DE_E$]). $DE_I$ is always negative, too (see Appendix Section 2C). This added immune self-limitation (Fig. 3F, green, solid line [negative $DE_I$]) further strengthens DE (as shown in Fig. 3E: black, solid line), potentially enough to help to eliminate even the possibility of oscillations in PIEc (eliminated in Fig. 3C; see Appendix Section 2C, Fig. A2). Constitutive immunity also elevates density of immune cells ($I^*$), lowering parasite burden ($N_1^*$) while maintaining slightly higher $E^*$ available to hosts for metabolic work (at $rE^*$; compare Figs. 3H vs. 3I). Hence, constitutive immunity both stabilized dynamics via self-limitation in PIEc (Fig. 2) and reduced parasite burden.

At low feeding rate in both IGP and PIE models, weakening of IE of the prey or parasite

292 triggers oscillations. IE is a ratio of shorter, binary loops ($F_2$) and longer, three-species loops ($F_3$)
293 (Fig. 2). In all three models, $F_3$ became more negative with feeding rate of the prey/parasite, $f_{N_1}$,
294 than did $F_2$ (as parameterized). That helps explain why the ratio $-F_2/F_3$ (IE) became less negative
295 with increasing $f_{N_1}$ – and hence why weakening IE triggered oscillations (Figs. 2, 3D-F). However,
296 the precise details varied among the models (so it becomes unfruitful to generalize here).
297
298 *Positive feedback leads to alternate stable states in IGP alone (Fig. 4 and Appendix Section 2)*
299 Despite the parallels described above, IGP model can also produce alterative stable states
300 not found in the with-host analogues. In fact, using different parameter values (Fig. 4A; see
301 Appendix Section 2A), a 2D bifurcation diagram shows two forms of alternate stable states in IGP
302 (Fig. 4A; Alt-SS1 [dark grey] and Alt SS-2 [light grey]; see also Verdy & Amarasekare 2010). In
303 these regions, initial densities of species determine competitive outcomes (Fig. 4C, D). The simpler
304 form of alternative stable states (Alt SS – 1; Fig. 4C) yields just the prey ($R$-$N_1$) or just the predator
305 ($R$-$P$) with the resource. If it held in PIE, analogous outcomes would lead to exclusion of immune
306 cells by parasites (yielding stable infection in the $E$-$N_1$ state) or vice versa (yielding immune
307 clearance, a stable $E$-$I$), depending on initial parasite dose. However, in PIE, the host cannot
308 generate immune cells without parasites. Consequently, since the $E$-$I$ state is both biologically and
309 mathematically not feasible, the analogy breaks (Appendix Section 2A). In the other type of
310 alternative stable states in IGP (Alt SS – 2; Fig. 4D), we find either coexistence ($R$-$N_1$-$P$) or a
311 predator-only ($R$-$P$) equilibrium, depending on initial conditions (due to two feasible interior
312 equilibria, one of which is a saddle). Such outcomes would resemble a host that became infected
313 ($E$-$N_1$-$I$) or cleared infection ($E$-$I$), depending on parasite dose. We could not fine such an outcome
314 in PIEc (see Appendix Section 2C). Hence, despite the qualitatively similar loop structure, IGP
315 offered two scenarios for alternative stable states not present in within-host analogues. Alternative
316 infection states would require some other mechanism to produce positive feedback.

***Two prey – predator - resource (KP) | Two parasite - immune cells - host energy (2PIE / 2PIEc)***

*Model Summary* (*Fig. 1, Table 2, Appendix Section 3)*

Both keystone predation (KP) and within-host (2PIE) models feature two competitors engaged indirectly via consumer-resource like interactions. In both, consumers directly benefit (positive, black arrow) with direct costs to resources (negative, red circle). In KP, predators ($P$) can consume two prey ($N_i$), leading to positive interspecific direct effects for the predator and negative effects on prey (Fig. 1D). The two prey themselves compete for a shared resource ($R$), creating similar +/- interactions. Additionally, the resource experiences self-limitation at the interior (four species) equilibrium (Fig. 1D). Unlike in IGP, the predator does not consume the resource (i.e., it is not omnivorous). Hence, competitors engage only in apparent and exploitative competition (with $P$ and $R$, respectively). Similarly, 2PIE and 2PIEc extend the within-host PIE models. Now, two parasites ($N_i$) compete for host energy but are attacked by immune cells (Fig. 1E-F). During these attacks, immune cells use host energy to proliferate (as described in the PIE models). In 2PIEc, hosts also directly allocate energy to production of immune cells ($a_b > 0$), forging new connections and self-limitation of immune cells (Fig. 1F, Appendix Section 2). Further, *E-I* links introduce additional components of loops not found in KP (e.g., in $F_3$; Fig 5). Therefore, it might seem that KP provides too simple of a comparison to 2PIE/2PIEc. In fact, 2PIE models best resemble a combination of KP and IGP. Yet, the feedback loops that determine coexistence versus alternate stable states ($F_4$) of the prey or parasite are qualitatively similar (Fig. 5). The resemblance arises because both the prey and parasite are similarly *effected by* and have *affects on* their resources and their enemy. However, stronger negative feedback at level 3 in 2PIEc will shrink opportunities for coexistence while lowering parasite burden (see below).

*Intraspecific direct and indirect effects in the 4D KP and 2PIE model (Fig. 5)*

342 Similar to 3D systems, the sign of intraspecific indirect effects determines coexistence vs.
343 priority effects in 4D systems. But first, in both KP and 2PIE, only self-limitation of the resource
344 or host energy, respectively, contribute to summed intraspecific direct effects (DE; level 1
345 feedback, $F_1$; Fig. 5). 2PIEc has additional contributions from the immune self-limitation. Then,
346 summed intraspecific indirect effects (IE) involve a ratio of feedback loops with three species ($F_3$)
347 and four ($F_4$; IE = $-F_3/F_4$; Fig 5; Appendix Section 3D). In KP and 2PIE models, $F_3$ sums the
348 negative consumer-resource loop between each victim and its enemy times self-limitation of the
349 resource (analogous to loop [i] in PIE [Fig. 2]). Then, energy-immune interactions add two sets of
350 additional loops, analogous to positive "*starving the enemy*" and negative "*feeding the enemy*"
351 loops in PIE, but for each parasite (loops [ii] and [iii], respectively). Finally, immune self-
352 limitation in 2PIEc adds two more negative feedback loops (involving $N_i - E$ for each parasite;
353 loops [iv]). At the interior, we find negative $F_3$ for the interiors evaluated here (algebraically or
354 numerically). Additionally, the sum of loops involving parasite $N_2$ provide the numerator of the
355 intraspecific indirect effect of $N_1$ ($\mathrm{IE}_{\mathrm{N}_1}$; blue shading), while those involving $N_1$ provide that of $N_2$
356 ($\mathrm{IE}_{\mathrm{N}_2}$: purple shading; Fig. 5). Unlike in IGP/ PIE, the intraspecific indirect effect of the enemy
357 and resource now becomes zero. Hence, only the sum of $\mathrm{IE}_{\mathrm{N}_i}$ determines stability: coexistence
358 occurs when each competitor $N_i$ indirectly decreases its own growth rate.

359 Importantly, level 4 feedback loops are qualitatively similar across the KP, 2PIE, and 2PIEc
360 models. These loops (from *L-R*) are: (i) a positive *"feeding the enemy"* loop, where a small
361 increase in one parasite stimulates the immune cells which attack the competing parasite, freeing
362 up energy for the first parasite. In a second positive loop, (ii) *"starving the enemy",* a small
363 increase in a parasite reduces resources, hence density of the competing parasite, thereby lowering
364 immune activation, ultimately reducing mortality on the first parasite. Those two positive
365 (destabilizing) loops then push against two negative (stabilizing) loops, (iii and iv) "$N_i$ *is eaten,* $N_j$
366 *eats*". These loops therefore add the stabilizing consumer-resource interactions within which each

prey/parasite is enmeshed. For instance, a small increase in parasite *i* creates a negative loop with the immune system while parasite *j* is braked by its loop with the resource. Then, those roles reverse, i.e., parasite *j* is slowed by the immune system and parasite *i* is by the resource. Summed, those two loops (iii and iv) jointly determine the amount of negative feedback in the system at level 4. Combined then, loops (i)-(iv) determine the sign of $F_4$, the sign of the summed intraspecific indirect effects ($-F_3/F_4$; since $F_3 < 0$: see above), and stability of a feasible interior equilibrium.

In these 4D systems, stability of the interior can also be understood via symmetries or asymmetries in two quantities. These quantities emerge upon rearranging the loops comprising the level 4 feedback ($F_4$). They reflect ratios of how each prey or parasite has effects on ($-\varepsilon_i$) and is affected by ($-\alpha_i$) their enemies and resources (Fig 5; Eq. 7):

$$F_4 = -J_{N_1E}\, J_{N_2E}\, J_{EN_1}\, J_{EN_2} x \underbrace{\left(\frac{J_{IN_1}}{J_{EN_1}} - \frac{J_{IN_2}}{J_{EN_2}}\right)}_{effects\ on\ (-\varepsilon_i)} x \underbrace{\left(\frac{J_{N_1I}}{J_{N_1E}} - \frac{J_{N_2I}}{J_{N_2E}}\right)}_{affected\ by\ (-\alpha_i)} \qquad \text{(Eq. 7)}$$

where $J_{ij}$ are interspecific direct effects (Jacobians) of species *j* on species *i*, $\varepsilon_I = -J_{IN_1}/J_{EN_1}$, $\alpha_I = -J_{N_1I}/J_{N_1E}$, *etc.* Stability hinges on (a)symmetry of these ratios. As described elsewhere (Appendix Sections 3A, B), the difference in *affected by* ratios ensures a tradeoff in traits influencing resource and apparent competition that permits coexistence. If $N_1$ is the superior resource competitor without the enemy, then $\alpha_1 > \alpha_2$ ensures $N_2$ is sufficiently resistant to attack. The difference in *effects on* ratios then determines arrangements of competitive hierarchies with enemies (involving exploitative [resource, energy] and apparent [predator, immune] competition). Coexistence occurs with symmetry in these ratios (i.e., if $\alpha_1 > \alpha_2$ if $\varepsilon_1 > \varepsilon_2$), guaranteeing that net negative feedbacks dominate ($F_4 < 0$). In contrast, asymmetry in these ratios, (e.g., $\alpha_1 > \alpha_2$ still but now $\varepsilon_1 < \varepsilon_2$) leads to net positive feedback ($F_4 > 0$), triggering alternate stable states.

*Coexistence (coinfection) and alternate stable states (priority effects) in KP & 2PIE (Fig. 6 and Appendix Section 3)*

Despite differences in biology, KP and 2PIE models share similar four species feedback loops, hence qualitatively similar outcomes for stability of the interior equilibrium. That similarity becomes readily apparent in 2D bifurcation diagrams for each model in parameter space of supply point ($S$) – $N_1$'s feeding rate on resources ($f_{N_1}$). In KP (Fig. 6A), at low $S$-$f_{N_1}$, only the resource is supported in the system ($R$, yellow). Increased feeding rate at low resource supply enables prey $N_1$ to meet its minimum resource requirement ($R$-$N_1$; light blue). As $S$ increases, the minimum prey requirement of the predator is met (its $N_1^*$) allowing predators to invade ($R$-$N_1$-$P$; dark blue). Then, the more resistant $N_2$ can invade when the $R$-$N_1$-$P$ food chain provides enough resources, given predator density (mortality). This invasion enables four species coexistence ($R$-$N_1$-$N_2$-$P$; light orange). Similar assembly rules apply for invasion of $N_2$ when feeding rate of $N_1$ stays low enough to grant $N_2$ competitive superiority ($R_2^* < R_1^*$). With increasing $S$, first $N_2$ invades ($R$-$N_2$ space; light purple), then the predator does ($R$-$N_2$-$P$: dark purple). A less typical assembly arises at lower $S$ ($S = 1$) but with increasing $f_{N_1}$. Here, $N_1$ and $P$ simultaneously invade creating the jump from 2 ($R$-$N_2$) to 4 ($R$-$N_1$-$N_2$-$P$) dimensional stability (see Appendix Section 3C for details). Overall, similar transitions appear in 2PIE models. Like KP, the possible states in 2PIE models are energy alone ($E$), just one parasite ($E$-$N_i$), addition of immune cells ($E$-$N_i$-$I$), or an interior ($E$-$N_1$-$N_2$-I; Fig. 6B). However, since hosts always allocate energy to immune cells, they are always present in 2PIEc. Hence, 2PIEc only has $E$-$I$, $E$-$I$-$N_i$, and $E$-$N_1$-$N_2$-$I$ states (but not $E$ or $E$-$N_i$; Fig. 6C).

In all three models, low or high combinations of supply point ($S$) and feeding rate ($f_{N_1}$), create (a)symmetry in *effects on* and *affected by* ratios that, in turn, generate coexistence or alternate stable states for a feasible interior. We assume $N_1$ competes superiorly for energy without immune cells but is sufficiently more vulnerable to immune attack (enabling $\alpha_1 > \alpha_2$). In the coexistence region (i.e., at lower $f_{N_1}$- $S$), $N_1$ is the superior apparent competitor while more resistant $N_2$ is the superior resource competitor (see Appendix Section 3A,B for details and proof). Such a switch in competitive hierarchy means $N_1$ exerts stronger effects on immune cells relative to energy ($\varepsilon_1 > \varepsilon_2$;

Eq. 7). It also produces a symmetry in ratios that generates net negative feedback ($F_4 < 0$) and negative intraspecific indirect effects of the competitors ($IE_i < 0$) enabling coexistence (coinfection; 6D-F). However, high $f_{N_1}$- $S$ produces an asymmetry: $N_2$ now is the superior apparent competitor, and it has stronger effects on immune cells relative to energy ($\varepsilon_1 < \varepsilon_2$) while $N_1$ is the superior resource competitor. This asymmetry in ratios generates net positive feedback ($F_4 > 0$) triggering alternate stable states (or priority effects; Appendix Section 3A,B). Hence, this interior saddle separates dominance by one or the other parasite (or prey). Furthermore, intraspecific indirect effects are both positive ($IE_{N_i}>0$): each competitor now benefits itself through the feedback loops. With even higher $f_{N_1}$, $N_2$ becomes excluded in all three models (Fig. 6G-I). Notice also how, at the border of that exclusion from the coexistence region, $IE_{N_2}$ becomes extremely strong (infinitely negative, since $F_4 = 0$; Fig. 6D-F). In other words, the excluded species suffers extremely strong negative intraspecific indirect effects (i.e., $IE_{N_2} \rightarrow -\infty$).

The 2PIEc model modifies the patterns in 2PIE in qualitative and quantitative ways. Qualitatively, the range of outcomes in $S$-$f_{N_1}$ space simplifies (as in PIEc: Fig. 4C). Since baseline allocation guarantees positive density of immune cells, there are no $E$ or $E$-$N_i$ regions like in 2PIE (Fig. 6B vs. 6C). Quantitatively, in the co-infection region, constitutive immunity strengthens intraspecific indirect effects (because of the added negative feedback in the $F_3$ loops, the numerator of IE of each species [Fig. 5]). Stronger IE, in turn, narrows the parameter space permitting coexistence. Constitutive immunity also elevates density of immune cells ($I^*$), lowering parasite burden ($N_1^* + N_2^*$) while maintaining slightly higher $E^*$ (allocated at $rE^*$) for other metabolic work (compare Figs. 6H vs. 6I). Hence, constitutive immunity adds to $F_3$ loop structure of 2PIEc (Fig. 5). That addition squeezes coinfection space while reducing parasite load relative to 2PIE.

## DISCUSSION

What within-host factors determine parasite dynamics? To answer this question, we compare

441 two classic food web modules, intraguild predation (IGP) and keystone predation (KP), to their
442 within-host analogues (PIE and 2PIE). On the one hand, the comparison seems apt. Both prey and
443 parasite consume a shared resource while facing mortality from an enemy (predator or immune
444 cell). On the other hand, predator and immune cells are produced rather differently. For instance,
445 predators can eat only prey or the resource or both (in IGP). In contrast, induced proliferation of
446 immune cells requires both energy and parasites simultaneously. Furthermore, hosts can allocate
447 energy to immunity constitutively (a pipeline uncommon to food webs). Given these similarities
448 and differences, we analyze stability of equilibria produced by each model using feedback loops.
449 In particular, we interpret loops as direct and indirect intraspecific effects, and we show how their
450 sign and strength govern stability outcomes (Box 1). With these tools, we make three points. First,
451 both IGP and PIE systems predict stable coexistence / infection or oscillations due to similar shifts
452 in direct and indirect effects (Fig. 2-3). Second, that enemy-generation difference eliminates
453 alternative stable states (priority effects) seen in IGP – the PIE models cannot produce them
454 without inclusion of some other mechanisms (Fig. 4). Third, despite that KP is structurally simpler
455 than 2PIE models, competing prey and parasites coexist (co-infect) or show priority effects for
456 essentially the same reasons (Fig. 5-6). The outcomes hinge on the sum of similar four-dimensional
457 loops that generate positive and negative feedback. We show how those loops, in turn, translate
458 into parallel symmetries (stabilizing) or asymmetries in *effects on* and *affected by* ratios of the two
459 competitors. Overall, food web models offer powerful if imperfect analogies to feedbacks
460 underlying the dynamical repertoire of parasites within hosts.

461 Feedback loops enabled biologically meaningful comparisons of the stabilizing and
462 destabilizing forces in the models analysed here. Traditionally, one evaluates (local) stability using
463 Routh-Hurwitz criteria (Routh 1877; Hurwitz 1895). By rearranging these criteria, we unpack the
464 biology of the feedback loops underlying stability (Box 1; Puccia & Levins 1991; Novak *et al*
465 2016). These loops can involve shorter, direct effects (DE), where increases in intraspecific density

466 leads to self-limitation (negative feedback) or facilitation (positive). Longer loops involve chains
467 of connected interactions – here, between two (e.g., binary consumer-resource), three, or four
468 species (Puccia & Levins 1991). We show that certain ratios of these loops at different feedback
469 levels, in turn, correspond to intraspecific indirect effects (IE – falling along the trace of the inverse
470 Jacobian matrix evaluated at the equilibrium; Box 1). Furthermore, we illustrate how negative IE
471 leads to coexistence (stable or oscillatory [in 3D systems]), and positive IE can produce alternative
472 stable states. In 3D systems, that transition from stability to oscillations involves weakening of DE
473 x IE. Such weakening occurs when feedback at longer loops becomes too strong relative to those
474 at shorter loops. With that framework in mind, the loops then facilitated comparison between
475 structurally similar but biologically distinct systems (Novak *et al* 2016), *e.g.,* food web and within-
476 host modules. Indeed, loops can reveal the biology obscured or overlooked in stability analysis.

477 This loop-based approach to stability analysis revealed that single prey and parasite can persist
478 – stably or via oscillations – with their resource and enemy for similar reasons. Generally speaking,
479 like in IGP, coexistence in PIE requires summed negative intraspecific indirect effects (IE). Like
480 in IGP, weakening of IE ($-F_2/F_3$) triggers oscillations in PIE (due to weakening of $F_3$ relative to
481 $F_2$; Fig. 3D-E). Yet, either the sum (IGP) or sum and product (PIE) of victim and enemy densities
482 strengthens intraspecific direct effects (DE). Strong enough DE then tips the coexistence
483 equilibrium from oscillations to stability. Those oscillations matter because they create boom-bust
484 cycles of parasite and immune response that can harm hosts (Otterstatter & Thomson 2006; Childs
485 & Buckee 2015). For instance, these oscillations produce rapid ramp up or down of immune
486 function that can stress host physiology (exacting e.g., oxidative damage, cellular senescence),
487 making them sicker (Costantini & Mølle 2009). However, in hosts with high constitutive immunity
488 (PIEc), the strengthening of DE by immune-self limitation can prevent oscillations, potentially
489 reducing immune damage to host. Additionally, constitutive immunity can improve host health by
490 lowering parasite burden while maintaining higher energy for other metabolic work.

Despite similarities in loop structure, alternate stable states emerge in IGP but not PIE models. The reason for this discrepancy hinges on production of the enemies. In principle, when each prey / parasite *"starves the enemy"* enough, the resulting positive feedback through the three species might trigger alternative stable states (alt SS; Fig. 2). In fact, IGP with a semi-chemostat like resource produces two types of them (Verdy & Amarasekare 2010). In the simpler, more typical one, either the prey or the predator dominates. In the other less common one, predator and prey coexist or the prey is excluded (Fig. 4A). If they existed, such alt SS in PIE models might explain why large infectious doses overwhelm immune clearance, leading to infection (yielding stable $E$-$N_1$ or $E$-$N_1$-$I$ states), while small doses can be cleared by the immune system (in a stable $E$-$I$ state; as seen in experiments, e.g., Merrill & Cáceres 2018). Yet, we found no such alt SS in PIE or PIEc as formulated (nor did it arise in a similar model with another representation of immune functioning: Greenspoon *et al.* 2018). Hence, some other mechanism is needed to generate alt SS within hosts (e.g., effects of parasites on within-host resource supply points: van Leeuwan *et al.* 2019). In the future, such mechanisms could be added to the PIE/PIEc framework. However, they would likely break the straightforward food web analogues that we strove for here.

In contrast, KP and 2PIE models produced either coexistence or priority effects of competitors for similar reasons. At first glance, such parallels might seem surprising since KP more simply connects species engaged in resource and apparent competition. In contrast, 2PIE has more complex loop structure (created by those omnivory-like $I$-$E$ connections). Despite these structural differences, both models share qualitatively identical four species loops that govern stability (Fig. 5). We translated the net sum of those positive and negative loops into differences in *effects on* and *affected by* ratios for each competitor. Those ratios then lay out conditions for successful coinfection *vs.* alternative stable states (priority effects). First, either case requires a sufficient tradeoff. If one species competes superiorly for host energy, the other must better resist immune attack. Such a tradeoff anchors a directionality of the *affected by* ratio (immune to energy) between

516 competing parasites. Coinfection (and coexistence more broadly), then, requires a symmetry: the
517 parasite with greater *affected by* ratio must also have the greater *effects on* ratio (Fig. 5). Those
518 conditions arise when the superior energy competitor without immune cells (i.e., the one with
519 lower minimal energy needs) becomes the superior apparent competitor with them (i.e., the one
520 that supports and withstands the highest immune density). Meanwhile, the more resistant parasite
521 becomes the best energy competitor. If true, each parasite indirectly inhibits its own growth and
522 facilitates its competitor. Coinfection ensues due to net negative feedback. In contrast, if one
523 parasite always competes superiorly for energy while the superior apparent competitor enjoys
524 resistance, asymmetry in these ratios ensues. That asymmetry means each competitor indirectly
525 facilitates its own growth and slows its competitor, either by *"feeding the immune cells"* that attack
526 the competitor (freeing up energy), or by *"starving the immune cells"* via starving the competitor
527 (Fig. 5). When strong enough, such interactions ensure priority effects via net positive feedbacks.
528 These new within-host competition models can also guide future coinfection experiments.
529 First, the competition models focus attention on traits and mechanism. Traditional coinfection
530 experiments alter initial densities / order of arrival of parasites within a host (Lohr *et al* 2010;
531 Natsopoulou *et al* 2015; *reviewed in* Karvonen *et al* 2019). Then, mechanism is inferred from
532 pattern. Alternatively, with 2PIE-like models in hand now, experimenters can directly measure
533 and/or fit key host-parasite traits that produce within-host dynamics. Second, they highlight how
534 multiple niche dimensions govern competitive outcomes within hosts. Some recent empirical
535 studies emphasized immune- (Ezenwa *et al* 2010; Halliday *et al* 2018) or resource-mediated
536 (Budischak *et al* 2018) competition within hosts. Yet, competition along a single niche dimension
537 predicts only competitive exclusion (*sensu stricto*). Instead, measurements of both immune and
538 energetic niche dimensions together (like in Budischak *et al* 2015) could evaluate the entire range
539 of outcomes anticipated by 2PIE. Third, the bifurcation maps here suggest joint manipulation of
540 resource supply to hosts and parasite traits, perhaps leveraging genetic variation in traits among

541 parasite strains. Such manipulations could then capture a whole array of within-host competitive
542 outcomes (Budischak *et al* 2018) or explain increasing parasite burden along a resource gradient
543 (Wale *et al* 2017). Finally, our model predicts that allocation to constitutive immunity strengthens
544 indirect effects, squeezing parameter space allowing coinfection and reducing parasite burden. One
545 could test such predictions using strains with immune knockouts (like in Chen *et al* 2020) or host
546 genotypes differing in allocation (Fuess *et al* 2020).

547 This within-host parasite framework could become expanded in the future. First, models could
548 add niche dimensions. For instance, parasites might compete for multiple within-host resources
549 (Budishack *et al* 2015; Ezenwa 2021) and/or face multiple immune defenses (Jolles *et al* 2008;
550 Ezenwa & Jolles 2011). These additional dimensions parallel food webs with multiple resources
551 and predators (necessitating statements of clear assumptions about specialist vs. generalist
552 consumption, different possible tradeoffs, etc.: Hulot & Loreau 2006). These niche dimensions
553 might expand conditions promoting coinfection or priority effects (Graham 2008; Rynkiewicz *et*
554 *al* 2015). Second, other mechanisms like relative non-linearities (Armstrong & McGehee 1980),
555 competitive intransitivity (May & Leonard 1975), or other variation-based mechanisms (Chesson
556 2000) may predict successful coexistence in our within-host framework. For example, since PIE
557 can oscillate, two parasites might coexist via oscillations (relative non-linearities). Similarly,
558 multiple parasites competing intransitively for two or more resources might coexist (Huisman &
559 Weissing 2001). Finally, environmental variation could alter key within-host traits (*e.g.,*
560 temperature fluctuations can modulate host immunity and parasite attack rates [Scharsack *et al*
561 2016]). Such intersections of environment with trait plasticity might then alter or enhance
562 opportunities for parasite coexistence (Chesson 2000). Finally, the direct (DE) vs. indirect effect
563 (IE) approach to predicting oscillations may have limits. Perhaps theoreticians can extend it
564 beyond three to four or more dimensions. Together, these expansions would extend mechanistic
565 models of within-host dynamics and produce insight into disease and coexistence alike.

In this study, we gleaned insights for within-host parasite dynamics using food web modules and feedback loops. Feedback loops enabled comparison of stability outcomes in structurally similar but biological distinct systems. For instance, similarity in loop structure in IGP and PIE successfully predicted single prey / parasite persistence either stably or via oscillations. Yet, despite these structural similarities, differences in generation of enemies (predator vs. immune cells) prevented IGP's two alternate stable states from arising in PIE. In contrast, despite omnivory-like *I-E* connections in 2PIE, competing prey or parasites coexist (coinfect) or show priority effects like in KP. Those outcomes arose because competitors within hosts or in food webs engage in structurally similar resource and apparent competition. Such comparable structure meant that symmetries in *effects on* and *affected by* ratios (involving the enemy and resource) determined stability of competition. Hence, dynamical forces governing stability in food-webs can mirror those within hosts. Such insights can guide more predictive experiments at the within-host scale but also better population-level models. For instance, fluctuation in food supply could shift competitive outcomes within hosts that then shifts multi-parasite outbreaks at the population scale. Hence, further development of resource and immune-explicit frameworks can only enhance predictive insight into host health and disease outbreaks alike.

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## TABLES

**Table 1**. Equations for IGP (Eq. 1) and PIE models (PIE and PIEc constitutive immunity; Eq. 2) with top consumers (predators or immune cells), intermediate consumers (prey or parasite), and basal resource (or host energy). Listed below each model are the variables and parameters, their definition (with units), and corresponding default values used (in Figs. 3,4).

| **IGP** | **PIE and PIEc** |
|---|---|
| $\frac{dP}{dt} = (e_{PN_1} f_{PN_1} N_1 + f_{PR} R - m_P) P$ (Eq. 1A) | $\frac{dI}{dt} = \frac{a_b E + e_{IN_1} f_{IN_1} N_1 EI}{e_I} - m_I I$ (Eq. 2A) |
| $\frac{dN_1}{dt} = (f_{N_1} R - f_{PN_1} P - m_N) N_1$ (Eq. 1B) | $\frac{dN_1}{dt} = \left(\frac{f_{N_1} E}{e_{N_1 E}} - f_{IN_1} I - m_N\right) N_1$ (Eq. 2B) |
| $\frac{dR}{dt} = a(S - R) - (f_{N_1} Q_{N_1} N_1 + f_{PR} Q_P P) R$ (Eq. 1C) | $\frac{dE}{dt} = \frac{f_E S}{h+S} - rE - (f_{N_1} N_1 E + e_{IN_1} f_{IN_1} N_1 I)E - a_b E$ (Eq. 2C) |

| **Var** | **Definition** | **Val. Fig. 3[a]** | **Val. Fig. 4[a]** | **Var** | **Definition** | **Val. Fig. 3** |
|---|---|---|---|---|---|---|
| $P$ | Predator density (#·L$^{-1}$) | | | $I$ | Immune cell density (L$^{-1}$) | |
| $N_1$ | Prey density (#·L$^{-1}$) | | | $N_1$ | Parasite density (L$^{-1}$) | |
| $R$ | Resource density (#·L$^{-1}$) | | | $E$ | Host energy density (L$^{-1}$) | |
| $e_{PN_1}$ | Conversion, prey: predator | 31.61 | 0.75 | $e_{IN_1}$ | Induction of energy per parasite killed by the immune response (L) | 4 |
| $f_{PN_1}$ | Feeding rate, predator on prey, (L·day$^{-1}$) | 0.002 | 0.002 | $f_{IN_1}$ | Killing rate of parasite, per immune cell (L . time$^{-1}$) | 12 |
| $f_{PR}$ | Feeding rate, prey on resource (L . day$^{-1}$) | 0.0005 | 0.01 | $m_I$ | Immune cells background mortality rate (time$^{-1}$) | 24 |
| $m_P$ | Mortality rate, predator (day$^{-1}$) | 0.05 | 0.05 | $e_I$ | Cost of producing immune cell | 3 |

| | | | |
|---|---|---|---|
| $f_{N_1}$ | Feeding rate, prey on resource (L·day$^{-1}$) | var[b] | var[b] |
| $m_N$ | Mortality rate, prey (day$^{-1}$) | 0.05 | 0.05 |
| $a$ | Dilution rate (day$^{-1}$) | 0.1 | 0.1 |
| $S$ | Supply point (L$^{-1}$) | var[b] | var[b] |
| $Q_P$ | Conversion, resource: predator | 1 | 0.5 |
| $Q_{N_1}$ | Conversion resource: prey | 1 | 2 |

| | | |
|---|---|---|
| $e_{N_1E}$ | Cost of producing parasite | 30 |
| $f_{N_1}$ | Feeding rate per parasite on energy (L . time$^{-1}$) | var[b] |
| $m_N$ | Mortality rate, parasite (time$^{-1}$) | 6 |
| $f_E$ | Host resource ingestion rate (L$^{-1}$ . time$^{-1}$) | 44 |
| $S$ | Food supply point, hosts (L$^{-1}$) | var[b] |
| $h$ | Resource ingestion half-saturation constant, host (L$^{-1}$) | 19 |
| $r$ | Rate of host energy use for non-parasite purposes (time$^{-1}$) | 1 |
| $a_b$ | Baseline allocation to immunity (time$^{-1}$) | PIE: 0<br>PIE$_c$: 0.03 |

[a] Values chosen in Fig. 3 such that $Q_{N_1} < e_{PN_1} Q_P$ (ensuring $F_3 < 0$; eqs. A14, 15). In fig. 4, $Q_{N_1} > e_{PN_1} Q_P$, enabling alternative stable states ($F_3 > 0$ for interior). [b] See values on figures.

**Table 2.** Equations for KP (Eq. 3) and 2PIE models (2PIE and 2PIEc constitutive immunity; Eq. 4) with top consumers (predators or immune cells), intermediate consumers (prey or parasites), and basal resource (or host energy). Listed below each model are the variables and parameters, their definition (with units), and corresponding default values used (in Figs. 6).

| **KP** | | | **2PIE and 2PIEc** | | |
|---|---|---|---|---|---|
| $\frac{dP}{dt} = (\Sigma e_{PN_i} f_{PN_i} N_i - m_P) P$ (Eq. 3A)<br>$\frac{dN_i}{dt} = (e_{N_iR} f_{N_i} R - f_{PN_i} P - m_N) N_i$ (Eq. 3B)<br>$\frac{dR}{dt} = a(S - R) - \Sigma(f_{N_i} N_i) Q R$ (Eq. 3C) | | | $\frac{dI}{dt} = \frac{a_b E + \Sigma e_{IN_i} f_{IN_i} N_i E I}{e_I} - m_I I$ (Eq. 4A)<br>$\frac{d N_i}{dt} = \left(\frac{f_{N_i} E}{e_{N_iE}} - f_{IN_i} I - m_N\right) N_i$ (Eq. 4B)<br>$\frac{dE}{dt} = \frac{f_E S}{h+S} - rE - (\Sigma e_{IN_i} f_{IN_i} N_i I + \Sigma f_{N_i} N_i) E - a_b E$ (Eq. 4C) | | |
| **Var** | **Definition** | **Values Fig. 6[a]** | **Var** | **Definition** | **Values Fig. 6[a]** |
| $P$ | Predator density (#·L$^{-1}$) | | $I$ | Immune cells density (L$^{-1}$) | |
| $N_i$ | Prey *i* density (L$^{-1}$) | | $N_i$ | Parasite *i* density (L$^{-1}$) | |
| $R$ | Resource density (L$^{-1}$) | | $E$ | Host energy density (L$^{-1}$) | |
| $e_{PN_i}$ | Conversion, prey i: predator | 2.4, 4.5 | $e_{IN_i}$ | Induced energy allocation rate per parasite *i* killed by the immune response (L) | 3, 4.7 |
| $f_{PN_i}$ | Feeding rate, predator on prey *i*, (L·day$^{-1}$) | 9.8, 2.1 | $f_{IN_i}$ | Killing rate, immune cell on parasite *i* (L . time$^{-1}$) | 0.9, 0.4 |
| $e_{N_iR}$ | Conversion, resource: prey *i* | 2.8, 2.8 | $m_I$ | Immune cells background mortality rate (time$^{-1}$) | 0.4 |
| $m_P$ | Mortality rate, predator (day$^{-1}$) | 0.1 | $e_I$ | Cost of producing immune cell | 2.5 |

| | | |
|---|---|---|
| $f_{N_i}$ | Feeding rate, prey on resource (L·day$^{-1}$) | var[b], 10.4 |
| $m_N$ | Mortality rate, prey (day$^{-1}$)[b] | 0.1 |
| $a$ | Dilution rate (day$^{-1}$) | 7.9 |
| $S$ | Supply point (L$^{-1}$) | var[b] |
| $Q$ | Stoichiometric conversion, resource: prey | 2.8[c] |

| | | |
|---|---|---|
| $e_{N_iE}$ | Cost of producing parasite *i* | 4, 3.4 |
| $f_{N_i}$ | Feeding rate per parasite *i* on energy (L . time$^{-1}$) | var[b], 7.2 |
| $m_N$ | Parasite background mortality rate (time$^{-1}$) | 0.8 |
| $f_E$ | Host resource ingestion rate L$^{-1}$ . time$^{-1}$) | 7.8 |
| $S$ | Food supply point, hosts (L$^{-1}$) | var[a] |
| $h$ | Resource ingestion half-saturation constant (L$^{-1}$) | 3.2 |
| $r$ | Rate of host energy use for non-parasite purposes (time$^{-1}$) | 3.7 |
| $a_b$ | Baseline energy allocation to immunity (time$^{-1}$) | 2PIE: 0<br>2PIEc:0.1 |

[a] Values chosen to ensure $N_1$ is the superior competitor for resources without enemies (prey: $R_1^* < R_2^*$ [eq. A35]; parasite: $E_1^* < E_2^*$ [eq. A47.a]) while $N_2$ is more resistant to attack to enemies (prey: $f_{PN_1} > f_{PN_2}$; parasites: $f_{IN_1} > : f_{IN_2}$). Additionally, they guarantee the *effects on* ratio has structure $\alpha_1 > \alpha_2$ (eqs. A34, A46). [b] See values on figures. [c] Identical between prey i.

## FIGURES AND CAPTIONS

**Figure 1**: *Direct interspecific effects and self-limitation in food web and within-host parasite model*s. *Top row, single prey or parasite models (three-dimension, 3D)*: (A) one prey-predator-resource (intraguild predation, IGP), (B) one parasite-immune cells-host energy (PIE), and (C) PIEc with constitutive immunity (i.e., fixed allocation of energy to production of immune cells). *Bottom row, two prey or two parasite models (four dimension, 4D):* (D) two prey - predator-resource (keystone predation, KP), (E) two parasite - immune cells - host energy (2PIE), and (F) 2PIEc with constitutive immunity. All direct effects evaluated when densities are positive (i.e., at a feasible interior equilibrium). Red (black) arrows: negative (positive) interspecific direct effect; red curve: negative intraspecific specific effect.

**Figure 2:** *Intraspecific direct and indirect effects: an illustration of levels of feedback in IGP, PIE, and PIEc models (Fig. 1A-C).* Evaluated at a feasible interior equilibrium, the IGP and PIE models have similar feedback structure. PIEc adds additional loops involving immune self-limitation. Level 1 feedback ($F_1$) is the sum of the shorter intraspecific direct effects (solid curves): self-limitation (-) of resource/energy and immune cells (PIEc only). In intraspecific indirect effects (dashed curves), each species limits or facilitates itself via interaction with other species in longer loops. The intraspecific indirect effect (IE) sums that of energy, $E$ ($IE_E$; yellow shading), parasite $N_1$ ($IE_{N_1}$; blue), and immune cells $I$ ($IE_I$; green). IE, in turn, is a ratio of two levels of feedback. Level 2 feedback ($F_2$, numerator of IE) sums pairwise consumer-resource loops (-) and the product of energy and immune self-limitation (-; only in PIEc; these are the numerators of the IE components). Level 3 feedback ($F_3$, denominator of IE) sums three-species loops. These loops from *L-R* are: (i) "$N_1$ *is eaten*", the $I$-$N_1$ loop times $E$ self-limitation (-), (ii) "*starving the enemy*" (+), (iii) "*feeding the enemy*" (-), and (iv) "$N_1$ *eats*", the $E$- $N_1$ loop times $I$ self-limitation (- ; PIEc only). This sum of (i)-(iv) determines the sign of $F_3$ and of IE (since IE = $-F_2/F_3$, and $F_2 < 0$ always). The predator ($P$, green), prey ($N_1$, blue), and resources ($R$, yellow) in IGP are analogous

831 to immune cells ($I$), parasite ($N_1$), and host energy ($E$), respectively, in the PIE models.

832 **Figure 3:** *Weakening of the product of intraspecific direct and indirect effects generates*
833 *oscillations in both IGP and PIE / PIEc models (Fig. 1, Box 1).* (A)-(C) *Bifurcation diagrams* over
834 gradients of supply point ($S$) and feeding rate of prey or parasite ($f_{N_1}$): Oscillations (dark orange
835 region) found in (A) IGP also arise in (B) PIE models of within-host dynamics (see Appendix
836 Section 2). These oscillatory regions are enveloped within a region of stable coexistence (light
837 orange). In PIE models, $a_b$ denotes baseline energy allocated to immune cells: $a_b > 0$ in (C) PIEc.
838 (D)-(F) *Direct and indirect effects (after Fig. 2)*: Oscillations occur with weakening of the product
839 of intraspecific direct effects (DE) and intraspecific indirect effects (IE). Weakening of IE
840 primarily triggers oscillations at low $f_{N_1}$ while strengthening of DE restores stability at higher $f_{N_1}$
841 in (D) IGP and (E) PIE. In (F) PIEc, self-limitation comes from energy ($DE_E$, orange) and immune
842 cells ($DE_I$, green). Summed DE eliminates oscillations while lowering parasite burden relative to
843 PIE (see also Fig. A2). (G)-(I) *Equilibrial densities along* $f_{N_1}$: resource, $R^*$ or energy, $E^*$ (orange);
844 prey or parasite, $N_1^*$, (blue); and predator, $P^*$ or immune cells, $I^*$ (green) in (G) IGP, (H) PIE, and
845 (I) PIEc models. Shifts in these densities weakens or strengthens DE and IE (see text and Appendix
846 Section 2 for details; Table 1 for default parameters).

847 **Figure 4***: Positive intraspecific indirect feedback leads to two forms of alternate stable*
848 *states (Alt SS-1 and -2) in the IGP model of prey ($N_1$), predators (P), and resources (R) not found*
849 *in PIE models.* (A) A bifurcation diagram over gradients of resource supply point ($S$) and prey
850 feeding rate ($f_{N_1}$) and species dynamics at the interior equilibrium (see Fig. A2 for more details).
851 (B-D) Sample dynamics. (A,B) Stable coexistence ($R - N_1 - P$, light orange) found in IGP also
852 arises in PIE predicting successful infection (Fig 3; $E - N_1 - I$). (B-D) IGP predicts two forms of
853 alternate stable states, where initial densities (inset) determine competitive outcomes between $N_1$
854 and $P$. (A, C): In more typical alternative stable states (Alt SS-1; dark grey), either prey ($R$-$N_1$) or
855 predator ($R$-$P$) wins. Analogous within-host states would lead to infection ($E$-$N_1$) or not ($E$-$I$). (A,

F) Another example (Alt SS – 2; light grey) predicts either coexistence ($R$-$N_1$-$P$) or an only-predator ($R$-$P$) equilibrium (analogous to infection [$E$-$N_1$-$I$] or clearance [$E$-$I$]). Neither of these types of alternative states emerge in PIE models (see text, Appendix Section 2).

**Figure 5**: *Intraspecific direct and indirect effects in four-dimension models: feedback in KP, PIE, and 2PIEc (Fig 1).* Evaluated at a feasible interior equilibrium, feedbacks for KP and 2PIE are nested within 2PIEc. In 2PIE and 2PIEc, additional loops arise from interactions between immune cells and host energy ("add loop in 2PIE & 2PIEc"), and immune self-limitation loop ("add loop in 2PIEc"). Level 1 feedback ($F_1$) sums intraspecific direct effects (solid curves) from energy and immune self-limitation (- ; only in 2PIEc). The intraspecific indirect effects (dashed curves) involve a ratio of longer loops, where each species, $N_1$ ($\mathrm{IE}_{\mathrm{N}_1}$; blue shading) and $N_2$ ($\mathrm{IE}_{\mathrm{N}_2}$; purple shading), interacts with others in feedback at level 3 ($F_3$) and 4 ($F_4$). $F_3$ sums three species loops in PIE models: (i) "*$N_1$ is eaten*", the $I$-$N_1$ loop times $E$ self-limitation (- ; all models), (ii) "*starving the enemy*" (+ ; from PIE models), (iii) "*feeding the enemy*" (-; from PIE models), and (iv) "*$N_1$ eats*", the $E$-$N_1$ loop times $I$ self-limitation (- ; only from PIEc). $F_4$ sums, from $L$-$R$, two destabilizing (+) loops and stabilizing (-) ones. $N_i$ benefits as it (i) "*feeds*" or (ii) "*starves*" the enemy, but is restrained by (iii) and (iv) "*$N_i$ is eaten, $N_j$ eats*" loops (the product of $I$-$N_i$ and $N_j$-$E$ loops). With some rearrangement, $F_4$ becomes proportional to differences in ratios of how each competitor has *effects on* ($\varepsilon_1 - \varepsilon_2$) and is *affected by* ($\alpha_1 - \alpha_2$) immune cells and host energy (see text). Finally, the sign of $F_4$ determines that of IE (see text). The predator ($P$, green), prey 1 ($N_1$, blue), prey 2 ($N_2$, purple), and resources ($R$, yellow) in KP are analogous to immune cells ($I$), parasites ($N_1$ and $N_2$), and host energy ($E$) in 2PIE models, respectively.

**Figure 6**: *KP anticipates coexistence and alternate stable states in 2PIE models.* (A)-(C). *Bifurcation diagrams* over gradients of resource supply point ($S$) and feeding rate of prey or parasite ($f_{N_1}$): alternative stable states or priority effects (grey region) and stable coexistence (orange) found in (A) KP also arise in (B) 2PIE and (C) 2PIE constitutive immunity (2PIEc)

models of within-host dynamics. In 2PIE, $a_b$ denotes baseline energy allocated to immune cells. Stable coexistence (coinfection) happens at low $f_{N_1}$ and $S$ in all models. (D)-(F) *Indirect effects through coexistence/coinfection regions*: Strong, negative indirect effects (IE; black, short dash) from $N_1$ ($\mathrm{IE}_{\mathrm{N}_1}$; blue, long dash) and $N_2$ ($\mathrm{IE}_{\mathrm{N}_2}$; purple, long dash) shift systems from coexistence to exclusion of $N_1$ or $N_2$ at lower or higher $f_{N_1}$ respectively in (D) KP, (E) 2PIE, and (F) 2PIEc. (F) Immune self-limitation in 2PIEc enhances negative indirect effects and squeezes parameter space enabling coinfection. (G)-(I) *Equilibrial densities along* $f_{N_1}$: Resource, $R$ or energy, $E$ (orange); prey or parasite 1, $N_1$, (blue); prey or parasite 2, $N_2$, (purple); and predator, $P$ or immune cells, $I$ (green) in (G) KP, (H) 2PIE, and (I) 2PIEc models. (See text and Appendix Section 3 for details, Table 2 for default parameters).

**Box 1.** *A feedback loop approach to analyze a general 3-dimensional system of equations*

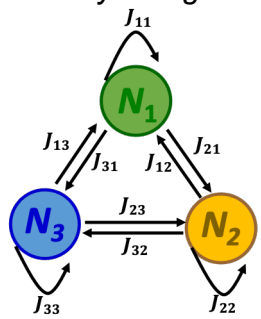
Imagine three species $N_1$, $N_2$ and $N_3$ where the effects of their interactions are captured by a 3D Jacobian matrix ($J_3$):

$$J_3 = \begin{bmatrix} J_{11} & J_{12} & J_{13} \\ J_{21} & J_{22} & J_{23} \\ J_{31} & J_{32} & J_{33} \end{bmatrix}$$

Characteristic polynomial of $J_3$

$$\lambda^3 + \lambda^2 F_1 + \lambda F_2 + F_3$$

$F_i$ is level of feedback




Stability requires that ..

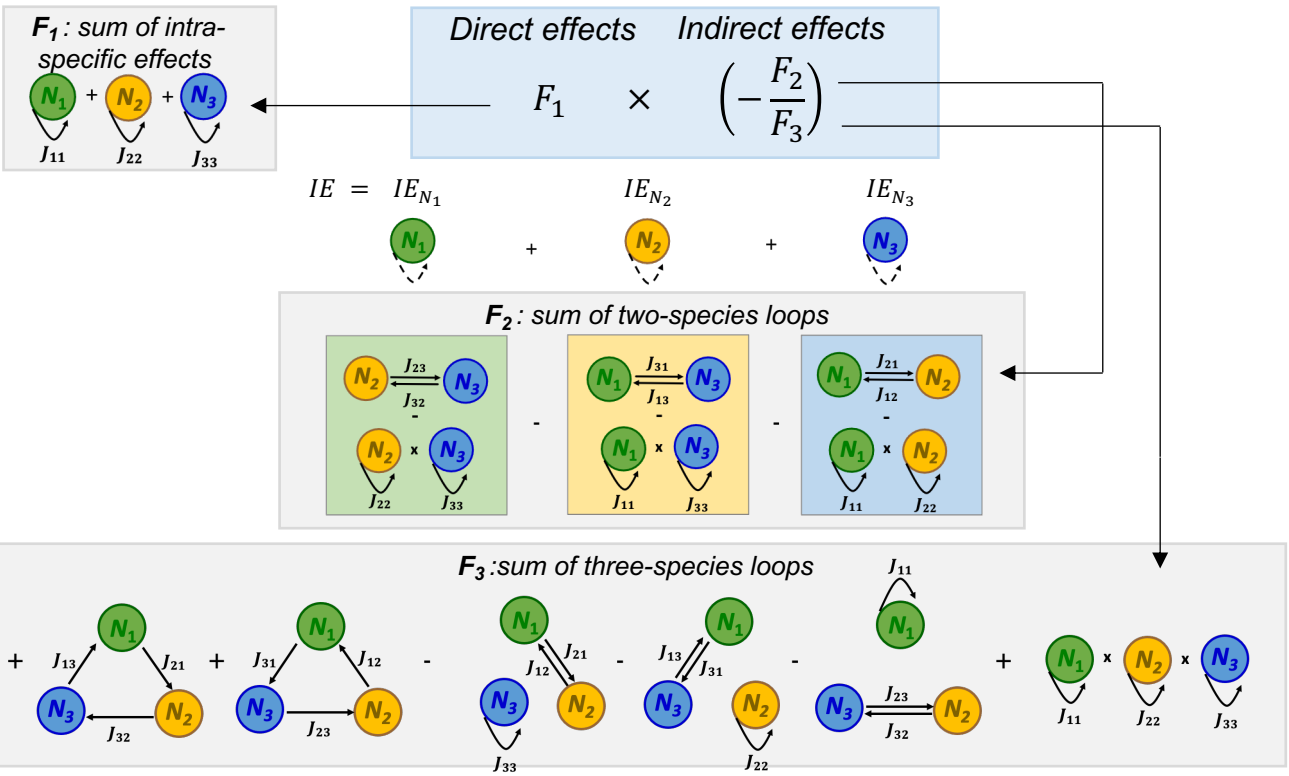
$F_1 < 0$
$F_2 < 0$
$F_3 < 0$

.. each level of feedback is negative*

*and* $F_1 F_2 + F_3 > 0$

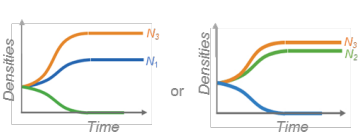
We rewrite this criterion as $F_1 \times \left(-\frac{F_2}{F_3}\right) > 1$ to highlight intraspecific direct and indirect effects

*Stability as a product of intraspecific direct effects (DE) and indirect effects (IE) (Appendix)*

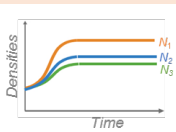


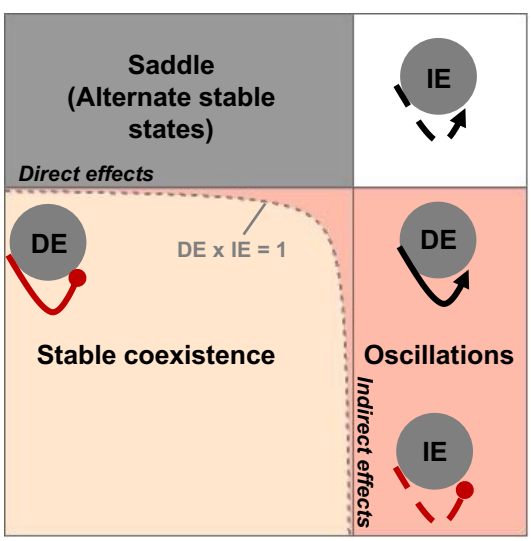

*Stability of an equilibrium depends on the sign and strength of the product of DE and IE*

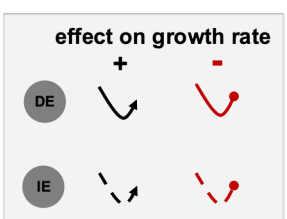
**Alternate stable states:**
Indirect effects are positive (DE < 0, IE > 0)



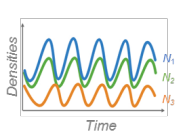

**Stable coexistence**:
Direct and indirect effects are negative (DE < 0, IE < 0) and jointly strong (DE x IE > 1)




**Oscillations:**
Weakening of DE x IE
1.DE < 0 and IE < 0, DE x IE < 1
2.DE > 0 and IE < 0.




*Note: The signs required for stability using Routh Hurwitz criteria (more traditional) are opposite those here for feedback. Thus, $F_1$ is Tr($\mathbf{J_3}$) and $F_3$ is -|$\mathbf{J_3}$|

**Figure 1**

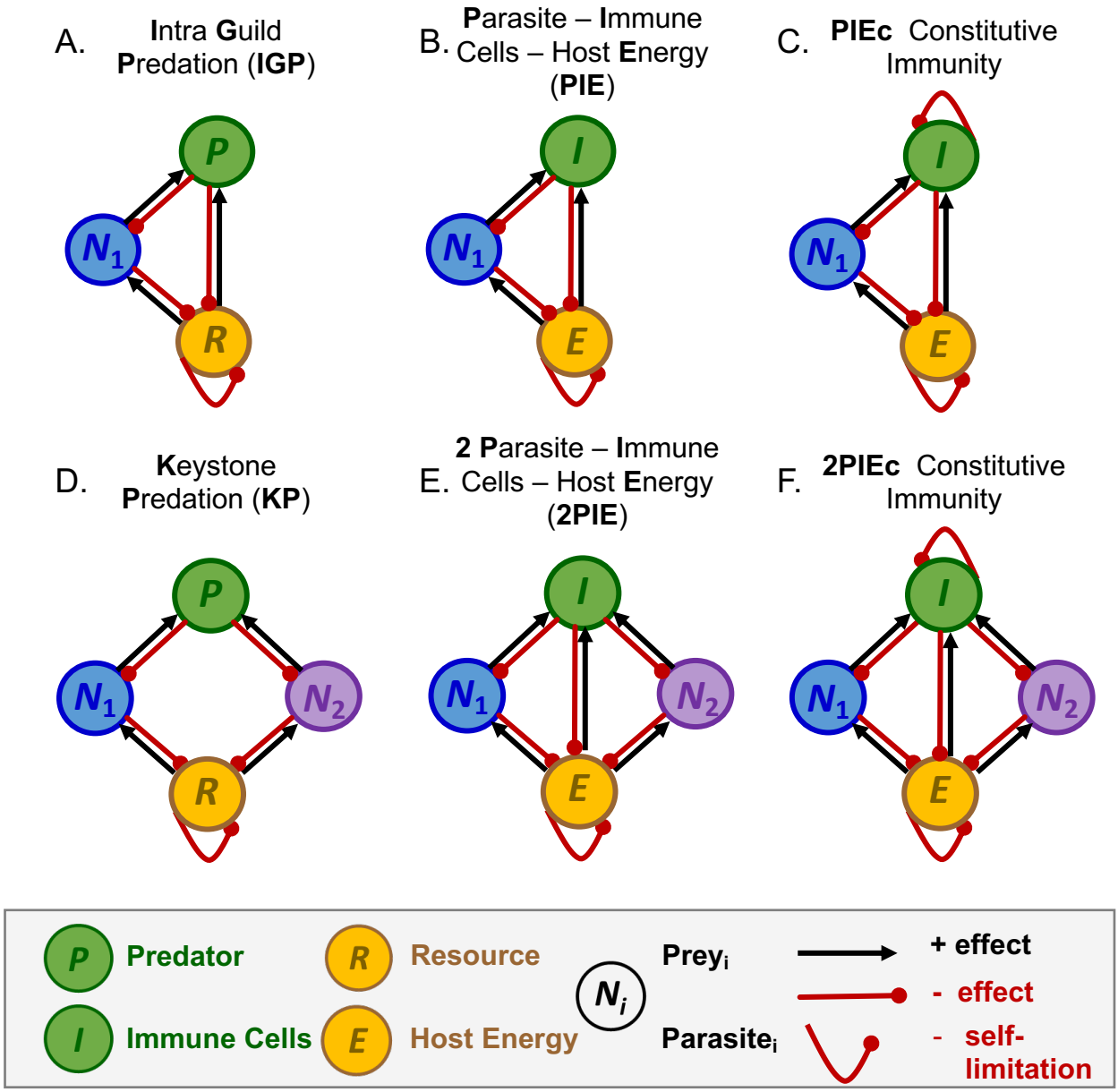

A.
Intra Guild Predation (IGP)
B.
Parasite – Immune Cells – Host Energy (PIE)
C.
PIEc Constitutive Immunity
D.
Keystone Predation (KP)
E.
2 Parasite – Immune Cells – Host Energy (2PIE)
F.
2PIEc Constitutive Immunity
P
I
R
E
N1
N2
Predator
Immune Cells
Resource
Host Energy
Ni
Preyi
Parasitei
+ effect
- effect
- self-limitation

**Figure 2**

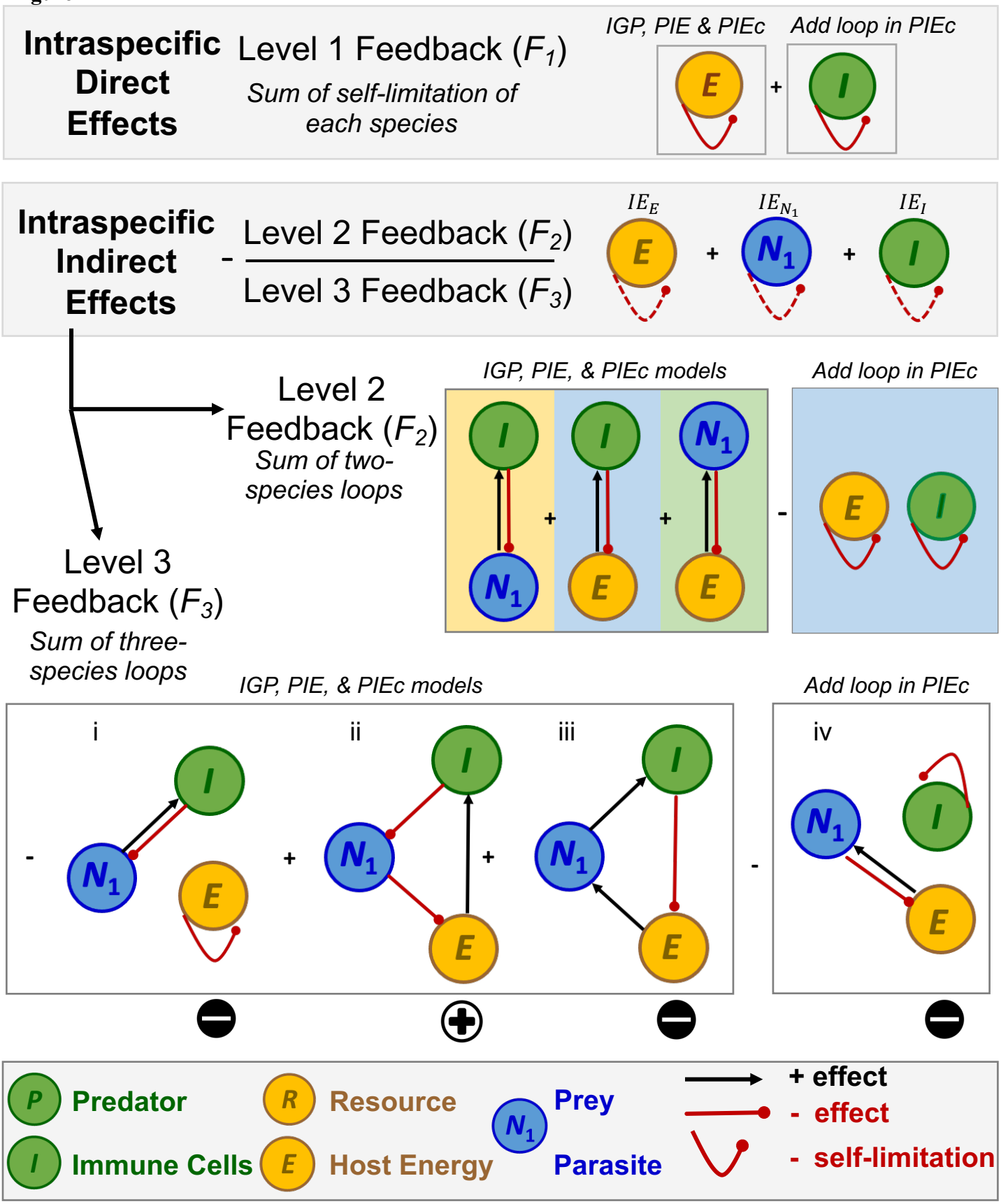

Intraspecific Direct Effects
Level 1 Feedback ($F_1$)
Sum of self-limitation of each species
IGP, PIE & PIEc
Add loop in PIEc
Intraspecific Indirect Effects
Level 2 Feedback ($F_2$)
Level 3 Feedback ($F_3$)
$IE_E$
$IE_{N_1}$
$IE_I$
Level 2 Feedback ($F_2$)
Sum of two-species loops
IGP, PIE, & PIEc models
Add loop in PIEc
Level 3 Feedback ($F_3$)
Sum of three-species loops
IGP, PIE, & PIEc models
Add loop in PIEc
i
ii
iii
iv
Predator
Immune Cells
Resource
Host Energy
Prey
Parasite
+ effect
- effect
- self-limitation

**Figure 3**

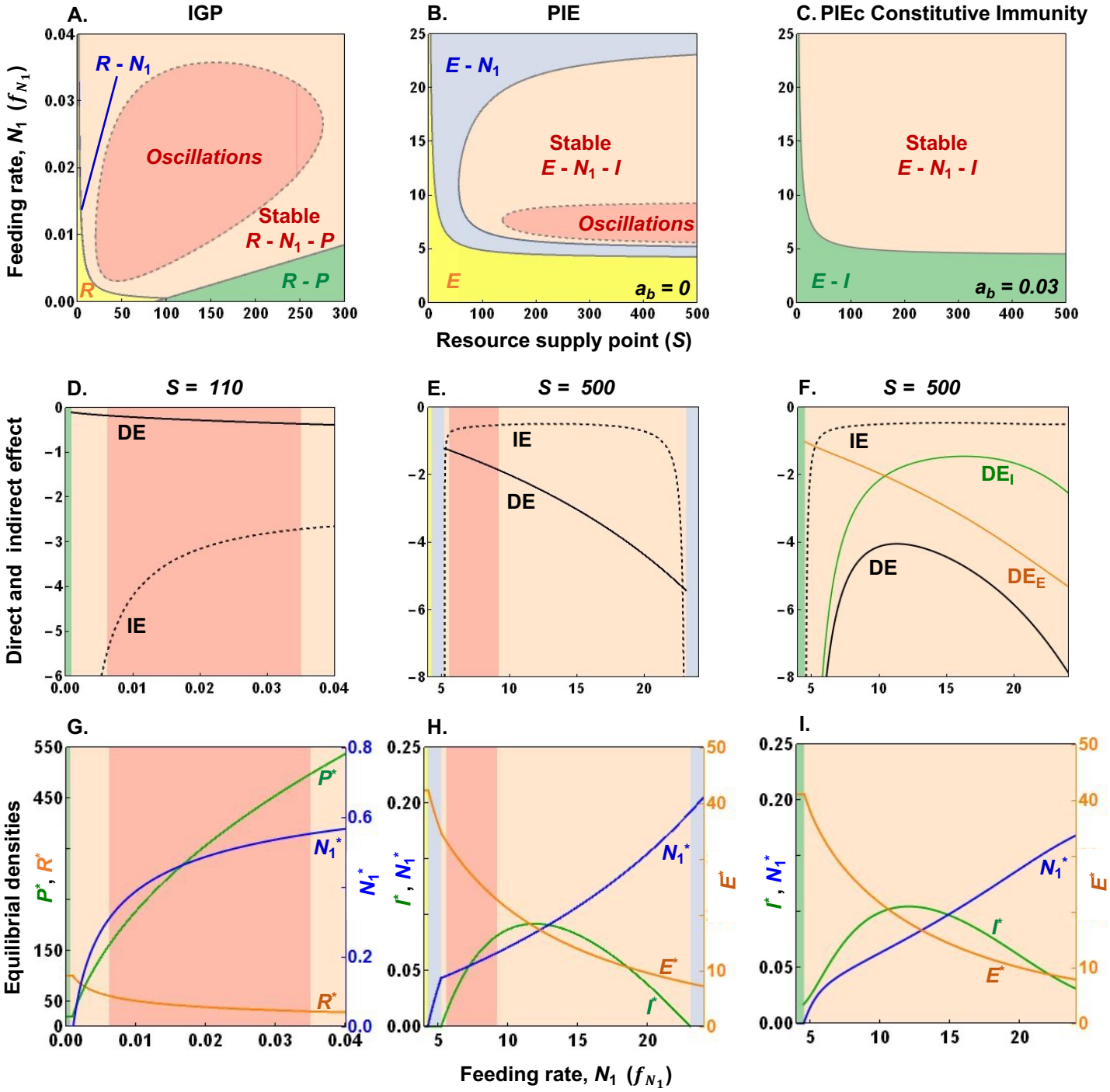

A. IGP
B. PIE
C. PIEc Constitutive Immunity
Feeding rate, $N_1$ ($f_{N_1}$)
R - $N_1$
Oscillations
Stable
R - $N_1$ - P
R - P
R
E - $N_1$
Stable
E - $N_1$ - I
Oscillations
E
$a_b$ = 0
Stable
E - $N_1$ - I
E - I
$a_b$ = 0.03
Resource supply point (S)
D. S = 110
E. S = 500
F. S = 500
Direct and indirect effect
DE
IE
IE
DE
IE
$DE_I$
DE
$DE_E$
G.
H.
I.
Equilibrial densities
$P^*$, $R^*$
$N_1^*$
$P^*$
$N_1^*$
$R^*$
$I^*$, $N_1^*$
$E^*$
$N_1^*$
$E^*$
$I^*$
$I^*$, $N_1^*$
$E^*$
$N_1^*$
$I^*$
$E^*$
Feeding rate, $N_1$ ($f_{N_1}$)

**Figure 4**

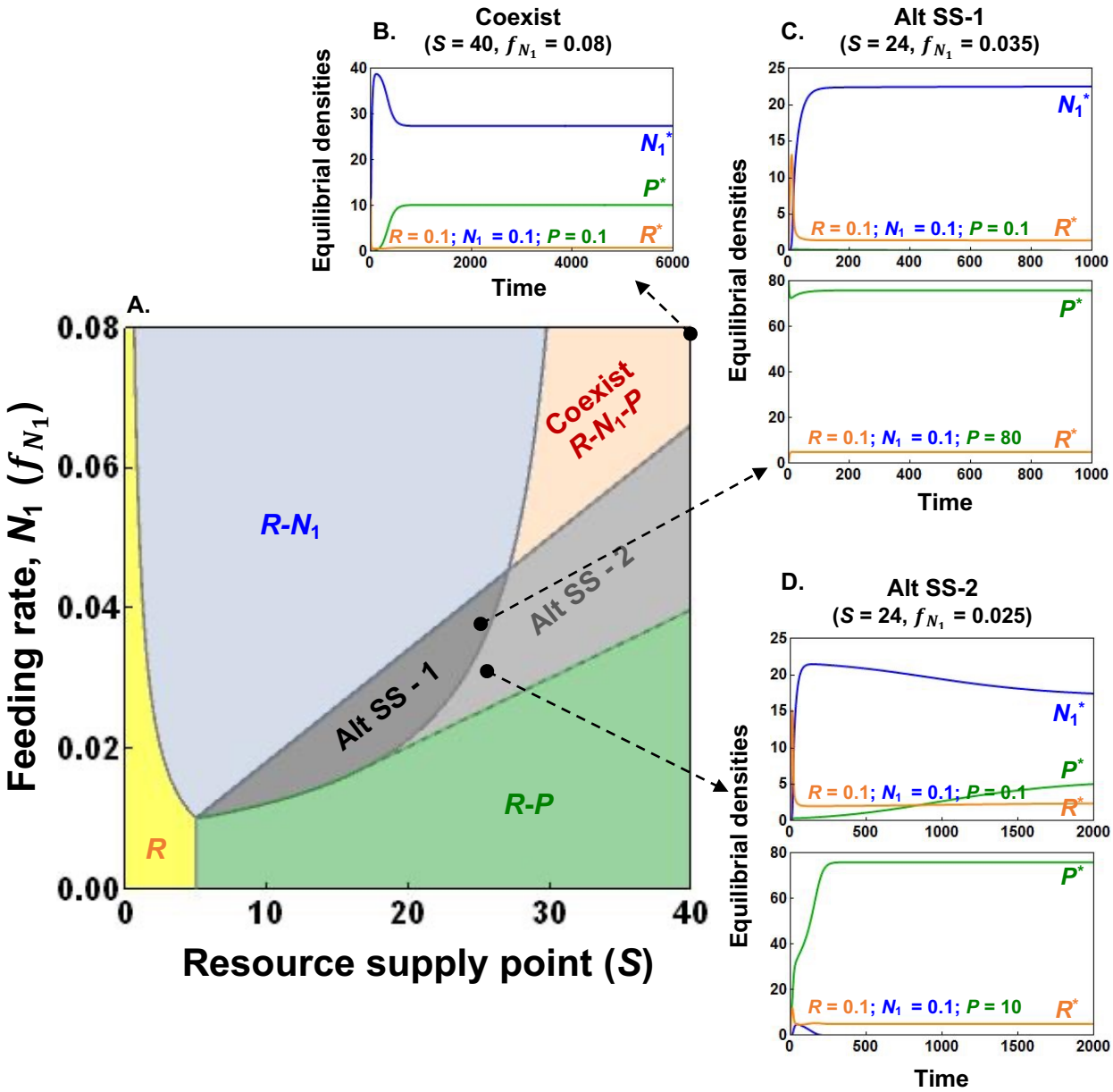

A.
B.
Coexist
(S = 40, $f_{N_1}$ = 0.08)
C.
Alt SS-1
(S = 24, $f_{N_1}$ = 0.035)
D.
Alt SS-2
(S = 24, $f_{N_1}$ = 0.025)
Equilibrial densities
Time
$N_1^*$
$P^*$
$R^*$
R = 0.1; $N_1$ = 0.1; P = 0.1
R = 0.1; $N_1$ = 0.1; P = 80
R = 0.1; $N_1$ = 0.1; P = 10
Feeding rate, $N_1$ ($f_{N_1}$)
Resource supply point (S)
R-$N_1$
Coexist R-$N_1$-P
Alt SS - 1
Alt SS - 2
R-P
R

**Figure 5**

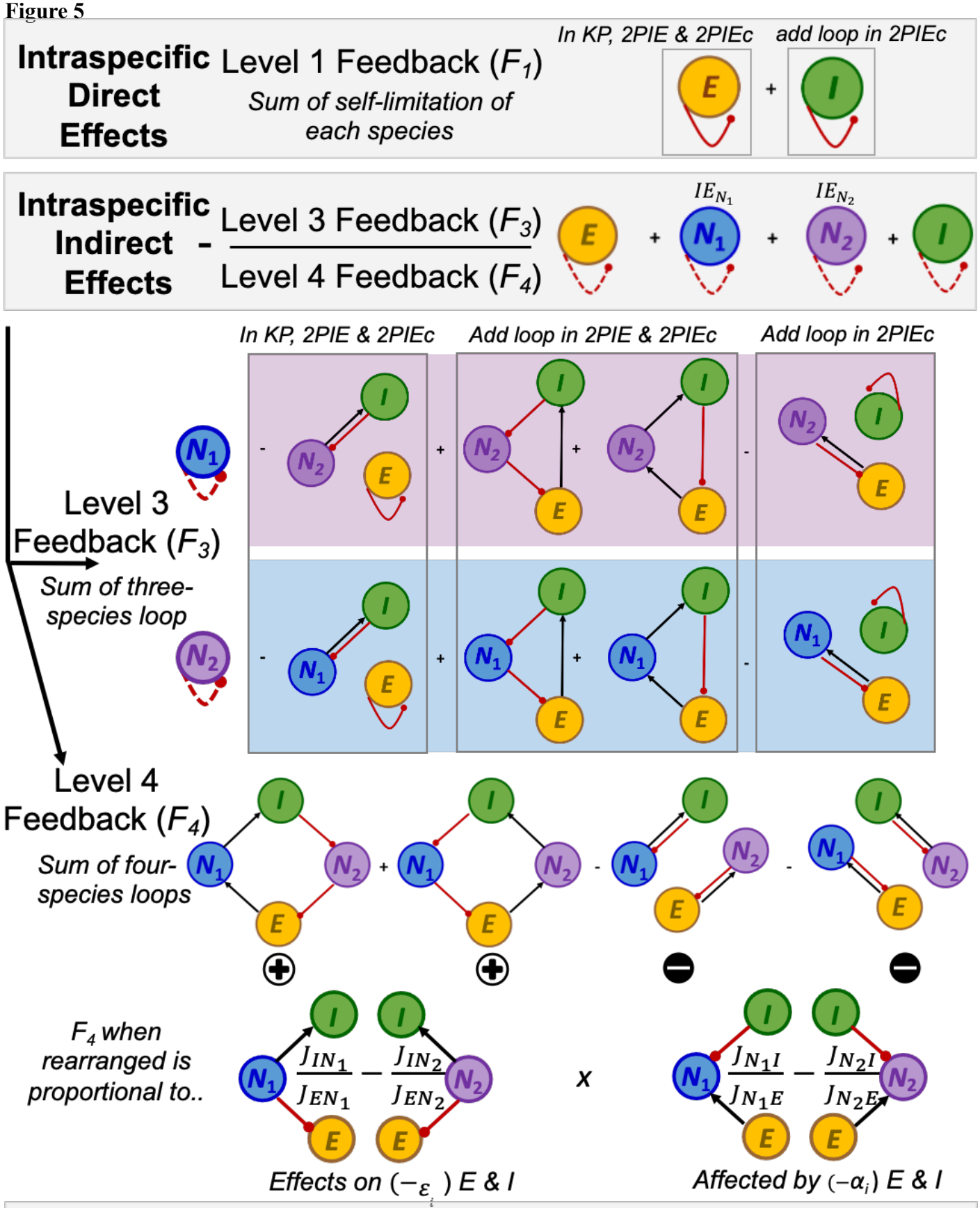
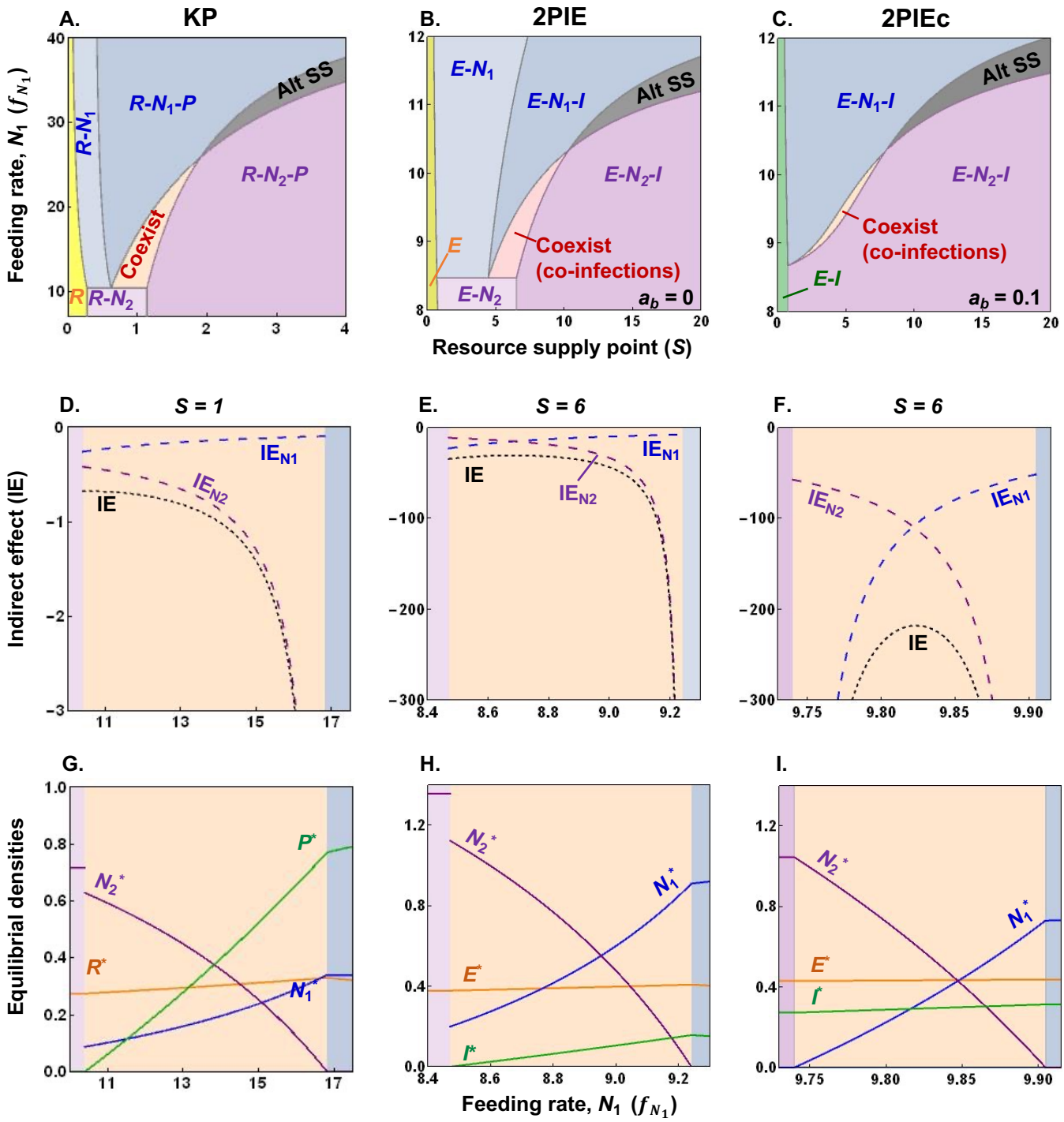

Intraspecific Direct Effects
Level 1 Feedback ($F_1$)
Sum of self-limitation of each species
In KP, 2PIE & 2PIEc
add loop in 2PIEc
Intraspecific Indirect Effects
Level 3 Feedback ($F_3$)
Level 4 Feedback ($F_4$)
$IE_{N_1}$
$IE_{N_2}$
In KP, 2PIE & 2PIEc
Add loop in 2PIE & 2PIEc
Add loop in 2PIEc
Level 3 Feedback ($F_3$)
Sum of three-species loop
Level 4 Feedback ($F_4$)
Sum of four-species loops
$F_4$ when rearranged is proportional to..
$\frac{J_{IN_1}}{J_{EN_1}} - \frac{J_{IN_2}}{J_{EN_2}}$
x
$\frac{J_{N_1I}}{J_{N_1E}} - \frac{J_{N_2I}}{J_{N_2E}}$
Effects on ($-\varepsilon_i$) E & I
Affected by ($-\alpha_i$) E & I
Predator
Resource
Prey$_i$
+ effect
Immune Cells
Host Energy
Parasite$_i$
- effect
- self-limitation

**Figure 6**


A.
KP
B.
2PIE
C.
2PIEc
Feeding rate, $N_1$ ($f_{N_1}$)
R-N1
R-N1-P
Alt SS
R-N2-P
Coexist
R
R-N2
E-N1
E-N1-I
E-N2-I
E
E-N2
Coexist
(co-infections)
$a_b$ = 0
E-I
$a_b$ = 0.1
Resource supply point (S)
D.
S = 1
E.
S = 6
F.
S = 6
Indirect effect (IE)
IEN1
IEN2
IE
G.
H.
I.
Equilibrial densities
$N_2^*$
$P^*$
$R^*$
$N_1^*$
$E^*$
$I^*$
Feeding rate, $N_1$ ($f_{N_1}$)