

¹ Host control and species interactions jointly determine
² microbiome community structure

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⁵ 1 Abstract

⁶ The host microbiome can be considered an ecological community of microbes present inside a
⁷ complex and dynamic host environment. The host is under selective pressure to ensure that
⁸ its microbiome remains beneficial. The host can impose a range of ecological filters including
⁹ the immune response that can influence the assembly and composition of the microbial com-
¹⁰ munity. How the host immune response interacts with the within-microbiome community
¹¹ dynamics to affect the assembly of the microbiome has been largely unexplored. We present
¹² here a mathematical framework to elucidate the role of host immune response and its interac-
¹³ tion with the balance of ecological interactions types within the microbiome community. We
¹⁴ find that highly mutualistic microbial communities characteristic of high community density
¹⁵ are most susceptible to changes in immune control and become invasion prone as host immune
¹⁶ control strength is increased. Whereas highly competitive communities remain relatively sta-
¹⁷ ble in resisting invasion to changing host immune control. Our model reveals that the host
¹⁸ immune control can interact in unexpected ways with a microbial community depending on
¹⁹ the prevalent ecological interactions types for that community. We stress the need to in-
²⁰ corporate the role of host-control mechanisms to better understand microbiome community
²¹ assembly and stability.

²² Keywords: microbiome modeling; species interactions; immune response; community ecology

²³ 2 Introduction

²⁴ One of the fundamental questions concerning ecology is understanding the processes influenc-
²⁵ ing species diversity in communities. The field of theoretical ecology has mainly addressed
²⁶ this question using a resource-centric approach introduced by Lotka and Volterra (Kopf and
²⁷ Lotka, 1925, Volterra, 1926). Later, MacArthur and his colleagues using the Lotka-Volterra
²⁸ framework formulated a model for resource competition where species with overlapping re-
²⁹ source requirements competitively exclude the other based on each species carrying capacity
³⁰ and competition coefficient (MacArthur and Levins, 1967, MacArthur, 1970). More recent
³¹ work, building on May's random matrix approach (May, 1972,9), considered the dynam-
³² ics of complex communities with varying prevalence of interaction type such as mutualism,
³³ exploitation, and competition (Melián et al., 2009, Mougi and Kondoh, 2012, Coyte et al.,
³⁴ 2015, Qian and Akçay, 2020). These studies show that the balance of interaction type influ-
³⁵ ence the community dynamics, species richness and the internal and external stability of the
³⁶ community.

37 Microbial communities can be studied using this community ecology framework (Costello
38 et al., 2012, Gilbert and Lynch, 2019), but with a twist. The community dynamics of the
39 host microbiome are governed not just by how species within the microbiome interact with
40 one another, but also by the interaction with the host organism. The species interactions in
41 the microbiome can range from resource mediated competition to cooperative and exploita-
42 tive interactions (Foster and Bell, 2012, Gralka et al., 2020). Many microbial species are
43 auxotrophic - lack essential genes to produce metabolites including vitamins and proteins for
44 cell growth and survival (Zengler and Zaramela, 2018). These species have to rely on other
45 microbial species to fulfil their nutritional requirements and also engage in the successive di-
46 gestion of large complex molecules provided by the host (Levy and Borenstein, 2013, Zengler
47 and Zaramela, 2018, Gralka et al., 2020). The host can mediate the community structure
48 and assembly of such communities through the supply of these resources. The host can also
49 affect microbiome assembly and stability through its immune response which can be specific
50 or general (Hooper et al., 2012, Stagaman et al., 2017).

51 Microbiome dynamics are under the joint control by both their hosts and within-microbiome
52 ecological interactions. The host in particular is under selective pressure to support a micro-
53 bial community that is compatible with the host, which should select for mechanisms that
54 regulate community assembly, diversity, and stability (Foster et al., 2017). In essence the
55 host-associated microbiome can be considered as an ecosystem held on a leash (Foster et al.,
56 2017), where the leash signifies that the host will attempt to keep microbial communities
57 within certain bounds. The host can tighten or loosen its leash on the microbiome that
58 can consequently affect the microbial species that are able to enter the host and eventually
59 colonize within a region such as the gut.

60 Here, we present a model of the microbiome as an ecosystem on a leash using a gen-
61 eralized Lotka-Volterra framework (Bunin, 2017), with type-II functional responses. The
62 Lotka-Volterra framework has been applied to infer and predict microbial population dy-
63 namics (Foster and Bell, 2012, Stein et al., 2013). However, this framework has mainly been
64 applied to study ecological interactions between microbial species without much consideration
65 of the host control over the microbial community. Specifically, we consider immune responses
66 as the leash that the host holds to control the assembly of microbial communities.

67 How host immune system controls microbiota can be complex and variable across species,
68 and is still not fully understood. Inside the gastrointestinal tract of mammals, the host's
69 epithelial barrier and the mucus serve as the first layer of physical separation between the mi-
70 crobiota and the host tissues (Hooper et al., 2012, Belkaid and Hand, 2014, Stagaman et al.,
71 2017). In the event that microbes translocate beyond the epithelium barrier, the host immune
72 system recognizes microbial-associated molecular structures using toll-like receptors and tar-

73 gets these microbes by releasing inflammatory cytokines, macrophages, and immunoglobulin
74 A (Belkaid and Hand, 2014). Hosts can also vary the environmental pH (Ratzke and Gore,
75 2018) and oxygen levels (Byndloss et al., 2018), restricting the growth and persistence of
76 specific microbial species. These physiological and environmental components are instances
77 of host control that can impose negative selection on microbes. However, how this control
78 varies in response to a beneficial symbiont or a pathogen to the host is unclear. The distinc-
79 tion between a pathogen or a beneficial symbiont to the host can be challenging for the host
80 immune response as pathogenicity is context dependent, and there are known instances where
81 pathogens are able to proliferate even in the presence of an active immune response (Rivera-
82 Chávez and Bäumler, 2015). Moreover, host control over the specific microbial community
83 members is less evident from human fecal microbiota analysis (Tap et al., 2009). Inverte-
84 brate hosts that lack an adaptive immune response are more likely to rely on non-specific
85 host immune responses. Invertebrates such as corals have innate immune responses that can
86 sense microbial molecular patterns and release antimicrobial peptides which regulate micro-
87 bial loads in a non-specific manner (Palmer et al., 2011, Palmer, 2018). These observations
88 suggest that host imposing a generalized, non-specific host immune response is likely to be
89 an important mechanism of regulating microbial community abundance in host-associated
90 microbial ecosystems.

91 Here, we consider host control at the level of the whole microbiome, where the host
92 regulates the microbiome density through resource provisioning and the immune response.
93 Microbial community density is a fundamental ecosystem property that can have implications
94 on the host health. How the microbial community responds to host control relies not just on
95 the type of microbial species present, but also on the abundance of these species. Contijoch
96 et al. (2019) observed a natural variation in the gut microbiome density across a range of
97 mammalian hosts, with each host supporting a specific microbial carrying capacity. There is
98 also variation observed in microbiome density observed across host organs, where in humans
99 the bacterial colony forming units increase from stomach to small and large intestine (DiBaise
100 et al., 2006), indicating differential host control at play at the organ level. Contijoch et al.
101 (2019) report a positive correlation between immune cell population and the microbiome
102 density in specific pathogen free (SPF) mice treated with varying density depleting antibiotics.
103 Therefore it is probable that changes in host control can alter the microbiome density, that
104 can consequently affect the host health.

105 In this paper, we present a mathematical framework to model host-associated microbial
106 community dynamics. Understanding microbial community dynamics is essential as the mi-
107 crobiome harbors a vast diversity of functionally important microorganisms ranging from bac-
108 teria, archaea, and fungi (Huttenhower et al., 2012). These microorganisms play a crucial role
109 in providing host protection against pathogens, aid in immune maturation and metabolism

110 (Lozupone et al., 2012). Changes to the stability and composition of the microbiome compo-
111 sition is associated with pathologies such as inflammatory bowel disease, diabetes (Zaneveld
112 et al., 2017, Lozupone et al., 2012) and more recently cancer (Helmink et al., 2019). Exist-
113 ing genomics sequencing of microbial community provide limited understanding of the forces
114 at play that shape the microbiome. Furthermore, existing experimental and theoretical ap-
115 proaches to study microbial community dynamics are unable to provide an understanding
116 of the implications of the interaction between the host control and the balance of ecological
117 interaction types. To address this gap, we apply and extend the framework by Qian and
118 Akçay (2020) to model a microbial community driven by both within-species ecological in-
119 teractions and host control. The host immune response can serve as an active modulator
120 of the microbiome density that can have an affect on microbial community composition and
121 assembly.

122 We use this framework to help us understand the interplay between host control and the
123 assembly of the microbiome, more specifically what is the role of global density dependence
124 mediated by host immune response on the balance of ecological interactions within the mi-
125 crobiome? Our findings indicate that the type of ecological interaction prevalent within the
126 microbial community can influence how the community responds to host mediated immune
127 control. And elevated host control overrides the effects of the balance of interaction types in
128 determining microbial community characteristics.

129 3 Methods

130 We model the host control and the sequential assembly of the microbial community extending
131 the model by Qian and Akçay (2020). We simulate communities comprised of S microbial
132 species. We initialize the community with S_o species, and the community grows in size through
133 successive invasions, and can also decrease in size as extinctions occur. Microbial species can
134 engage in pairwise interactions with other members in the community. We incorporate all
135 possible pairwise combinations of ecological interactions of which a proportion are mutualism
136 (P_m), exploitation (P_e), and competition (P_c) when constructing the interaction matrix A .
137 We vary the proportion of all ecological interactions in intervals of 0.1, with each microbial
138 community having a unique P_m , P_e and P_c . All communities are exposed to some degree of
139 competition ($P_c \neq 0$). We ensure that P_m , P_e and P_c chosen for each community all sum to
140 one.

141 We choose to model mutualism and exploitation using Holling type II functional response
142 and competition with a linear functional response. In the context of the microbiome, species
143 engaged in mutualistic interactions can benefit from each other through the exchange of spe-

144 cific metabolites hence making their interactions unique and non-interchangeable with other
 145 mutualistic partners. However, exploitation maybe more fluid, the exploitative effect can in
 146 essence be both unique and interchangeable as the role of predator and prey in the micro-
 147 biome is contingent on the surrounding environment and can be interchangeable. Therefore
 148 we present two modelling frameworks, i) Unique interaction model (UIM) where all inter-
 149 action types are unique, and ii) Interchangeable exploitation model (IEM) where we model
 150 competition and mutualism as unique and exploitation saturates with the total density of
 151 interacting partners such that it exerts similar effect on all its interacting partners.

152 The mathematical equation for UIM population dynamics of microbial species is:

$$\frac{dX_i}{dt} = X_i \left(r_i + \frac{s_i X_i}{K_i} + \sum_{a_{ij} \in C_i}^S a_{ij} X_j + \sum_{a_{ij} \in M_i, E_i^+}^S \frac{a_{ij} X_j}{h + X_j} + \sum_{a_{ij} \in E_i^-}^S \frac{a_{ij} X_j}{h + X_i} \right) \quad (1)$$

153 The mathematical equation for IEM population dynamics of microbial species is :

$$\frac{dX_i}{dt} = X_i \left(r_i + \frac{s_i X_i}{K_i} + \sum_{a_{ij} \in C_i}^S a_{ij} X_j + \sum_{a_{ij} \in M_i}^S \frac{a_{ij} X_j}{h + X_j} + \sum_{a_{ij} \in E_i^+}^S \frac{a_{ij} X_j}{h + \sum_{a_{ij} \in E_i^+} X_j} + \sum_{a_{ij} \in E_i^-}^S \frac{a_{ij} X_j}{h + \sum_{a_{jk} \in E_j^+} X_k} \right) \quad (2)$$

154 where

$$r_i = 1 - \kappa \left(\frac{\sum_{q=0}^S X_q}{I_m} \right) \quad (3)$$

155 X_i represents the population of species i , and r_i represents the intrinsic growth rate. We mod-
 156 ify the growth rate r_i (Equation 3) of all microbial species as an instance of immune-mediated
 157 host control over the microbial community size. The host immune control is synonymous to
 158 introducing global density dependence which ensures that microbial community abundance
 159 dose not exceed the host specific microbial carrying capacity (I_m). We also introduce κ , which
 160 represents the reduction in all microbe growth rates with the total community abundance and
 161 can be thought of as the inverse of a community-wide carrying capacity. X represents the
 162 species population. When simulating a mammalian gut community we choose $I_m = 10000$,
 163 as the bacterial CFUs per milliliter for the gut are estimated at this magnitude (Miller and
 164 Baumler, 2021). Changes to I_m still preserves the qualitative results of our model.

165 The coefficients a_{ij} characterize interactions between species i and j . For mutualistic and
 166 antagonistic interactions, we use Type II functional responses, with h as the half-saturation
 167 constant. We denote by s_i the self-regulation term and K_i the species-specific carrying capac-

ity. C_i is the set of interactions between the i and its competitors, M_i is the set of interactions between i and its mutualistic partners, E^+ represents the set of interaction between i and the species it exploits, whereas E^- refers to the set of interactions between species i and species that exploits it. These equations correspond to a generalized Lotka-Volterra model (Barbier et al., 2018), but with the crucial difference of non-linear functional responses. The saturating functional responses, coupled with the sequential assembly of the communities (which selects for feasible communities) result in almost all our assembled communities being asymptotically stable (Roberts, 1974, Stone, 2018, Qian and Akçay, 2020, see also SI.12, SI.13).

176 3.0.1 Community simulation

177 Both UIM and IEM follow an identical community simulation, differing only in the population
178 dynamics as mentioned in the equations above. The initial population of each species is set
179 to a constant x_o multiplied by a random number from a uniform distribution $U(0,1)$. For all
180 species we set a constant carrying capacity, $K = 100$, and $r = 1$ at the start for the microbial
181 community. We initialize the interaction matrix A_o with dimensions S_o by S_o . The diagonal
182 values of the interaction matrix are set to $s = -1$. We draw a Bernoulli random variable
183 (with probability of success c) to determine the presence or absence of any interaction between
184 species pair i,j (where $i \neq j$). If no interaction exists then a_{ij} and a_{ji} are assigned a zero value.
185 For interacting species, species i and j can compete with each other with P_c . These species
186 are assigned a_{ij} and a_{ji} values drawn from a negative half normal distribution $-N(0, \sigma/K)$.
187 The species that have a mutualistic interaction with probability P_m , are assigned a_{ij} and
188 a_{ji} values drawn form a half normal distribution $N(0, \sigma=0.5)$. a_{ij} and a_{ji} values are chosen
189 independently. Species can also engage in an exploitation interaction with a probability P_e ,
190 in this scenario, we randomly assign species i and j to be either exploited or to exploit the
191 other species. In the case if species i is being exploited then a_{ij} has a value drawn from an
192 $-N(0, \sigma)$ and j being the exploiter, has a_{ji} from $N(0, \sigma)$.

193 After the initial setup of the interaction matrix A with S_o species, we integrate the micro-
194 bial species population dynamics using the Doprí integrator. We determine if the population
195 has reached equilibrium i) if at a single time step the population fluctuates less than the
196 population change threshold δ , and (ii) if the population has not reached the equilibrium by
197 the specified time limit (t_1), we then use the current population sizes of the species in the
198 community as the equilibrium values. We next introduce an invader into the community. An
199 invader can only colonize the resident community if the growth rate of the invader is positive
200 when a small population of the invader is added into the resident community, accounting for
201 the invader's interactions with the existing resident species. To assess this we first draw a
202 small population of the invader and assign it a random interaction based on the P_c , P_m , and

203 P_e for that community. If the growth rate of the invader is positive we then incorporate the
 204 invader in the community by updating the interaction matrix A , such that it has dimensions
 205 of $S_0 + 1$ by $S_0 + 1$. We ensure that the interactions among the resident species are preserved
 206 after an invader is incorporated in the community. We repeat this process where we simulate
 207 the population until the next equilibrium after which we introduce a new species. In the
 208 event if the invasion fails, we redraw the interaction coefficients until the invader is able to
 209 invade. We impose a failed invasion threshold limit, $\beta = 1000$. If β is reached then we end
 210 the simulation and deem that equilibrium externally stable-uninvadable.

211 We also determine the community's competitive barrier to invasion by summing up the
 212 effect of all the competitive interactions(a) between the invader (i) and the resident species
 213 (j) scaled by the resident species abundances (X) in the community:

$$\sum_{a_{ij} \in C_i}^S a_{ij} X_j$$

214 Species also experience a decrease in their abundance and hence can go extinct. If the
 215 species abundance is lower than the extinction threshold ϵ then the species is deemed extinct
 216 and is removed from the community. Throughout the simulation we keep track of the number
 217 of species that went extinct, the number of invasions and the microbial species richness ob-
 218 served for each microbial community. We then use these values to determine the probability
 219 of extinction (number of extinct species over the number of species observed at that point
 220 of community history) and invasion (number of invasions over all invasion attempts) for the
 221 community.

222 Species richness of the microbial communities can converge, and to assess the presence of a
 223 steady state of species richness we use Dickey-Fuller test, as implemented by (Qian and Akçay,
 224 2020). The Dickey-Fuller test is a unit root test, where the null hypothesis suggests that the
 225 time series of species richness is non-stationary and possesses a time-dependent structure.
 226 The alternative hypothesis, on the other hand, suggests that the species richness displays
 227 stationarity over time. We analyze the most recent 1000 equilibria and determine if the P
 228 value is less than the threshold p value, that indicates that the species richness has entered
 229 the steady state. Once a community enters the steady state we run the community for w_2
 230 more equilibria before we end the simulation. We terminate simulations with communities
 231 that never enter the steady state if the community reaches (i) limit on number of species (n),
 232 (ii)limit on the number of equilibria (τ), or (iii) t_1 .

233 We run five simulations for each microbial community, so we end up in total with $55 \times 5 =$

234 275 microbial communities. The results presented in the paper are an average of 5 simulation
235 runs. Table 1 represents the parameters used in the model.

236 4 Results

237 We simulate the sequential bottom-up assembly of microbial communities with varying frac-
238 tions of all possible interaction types that include competition (at fraction P_c of all species
239 interactions), mutualism (at fraction P_m), and exploitation (at fraction P_e), as in Qian and
240 Akçay (2020). We initialize a microbial community with a S_0 number of species, and let
241 the community grow in size through successive invasions. For each invasion event, we draw
242 interaction coefficients for the invader from a random distribution where the probability of an
243 interaction being of a given type is given by the fractions P_c , P_m , and P_e . If the invader can
244 increase from rare, we numerically evaluate the new community dynamics until it reaches an
245 equilibrium and remove species that fall below an extinction threshold at this equilibrium. If
246 the invader cannot increase from rare, we draw a new invader species. In this way, community
247 size can grow or shrink through invasions and extinctions. We model mutualistic and com-
248 petitive interactions to be unique between partners however we consider the scenario where
249 exploitative interaction can be both unique or interchangeable. We show results for UIM that
250 assumes unique interaction for all interaction types, and the IEM that considers exploitation
251 to be interchangeable and have a similar effect on all its interacting partners (see methods
252 for detailed explanation). We will first discuss the results for the UIM framework followed by
253 the IEM.

254 To simulate community dynamics, we integrate microbial within-species interactions and
255 the host immune control in a Lotka-Volterra framework, where microbial species densities are
256 regulated by a combination of intra-specific density dependence, between species interactions,
257 and host immune control. We model the host immune control as responding to the total
258 microbial community size. Specifically, we assume that all species' growth rates decline as
259 a function of the overall community abundance, amounting to a global negative density-
260 dependence term. The strength of host control strength is given by κ , which represents the
261 reduction in all microbe growth rates with the total community abundance and can be thought
262 of as the inverse of a community-wide carrying capacity. Higher κ corresponds to stronger
263 host control.

264 In absence of host control, we recover the results of Qian and Akçay (2020). The micro-
265 bial community species richness is governed by a balance of interaction types, where more
266 mutualistic and less competitive microbial communities (high P_m and low P_c) harbor the
267 highest number of microbial species (Figure 1a, at $\kappa = 0$). In our model, microbial species

richness emerges as a balance between the number of invasions and extinctions of species in a community. Highly mutualistic microbial communities are colonization resistant with a low probability of invasion (Figure 1b, at $\kappa = 0$). This is because communities with a high proportion of mutualistic/cross-feeding interactions are able to achieve a high community density. Mutualistic interactions positively contribute to the growth rate of the interacting species, building up resident species equilibrium population sizes in the community (Figure SI.2b, at $\kappa = 0$). This also explains why highly mutualistic communities have a shallow rank abundance curve slope when compared to the steep slope which is indicative of low species evenness observed for microbial communities with high P_c (Figure 2b). Communities with high P_m and low P_c are still able to achieve a high competitive barrier to invasion due to the high equilibrium population size of resident species (Figure 1c, at $\kappa = 0$) buffering the resident community from getting out competed by incoming microbial species (Figure SI.2a, at $\kappa = 0$).

Introducing host immune response has non-trivial effects on community dynamics. As we introduce host control ($\kappa > 0$), we observe that microbial communities' species richness generally decrease. This decrease is most marked for communities with high P_m (Figure 1a, at $\kappa > 0$), whereas species richness for communities with high P_c remains relatively unaffected to changes in host control (Figure SI.1b). At very high host control strength, species richness of all communities converges to species richness observed for highly competitive microbial communities (Figure SI.1b). This suggests that elevated host control overrides the effects of the balance of interaction types in determining microbial species richness. This also results in the similar species evenness observed across microbial communities regardless of the interaction type when κ is further increased (Figure 2c-d). In our community simulations we have both strong global density dependence through host immune response and highly mutualistic interactions within a community at the same time. These two forces pull in opposite directions: one working to reduce community size and the other increase community size. As a result, we observe communities with a distinct cyclical pattern of species richness as new species are introduced into the community (Figure 3 at $\kappa = 1$), and the frequency of the cyclical pattern increases as we further increase the host immune response strength (Figure SI.5). The pattern emerges as an invasion event causes the extinction of the resident community (Figure SI.2a, at $\kappa > 0$), lowering the community abundance until the community grows back again and becomes increasingly susceptible to the density-regulating effects of the host immune response. We do not observe this pattern with competition alone (Figure 3). Thus, mathematically the incorporation of the host immune term in our model framework is not equivalent to further increasing the competition among the species.

Host control pushes the intrinsic growth of all microbes to negative levels when the total microbial community abundance is greater than the host target carrying capacity. This

305 reduces overall community sizes relative to no host control, and has the largest effect on the
306 stability of highly mutualistic communities that rely on large community sizes to provide com-
307 petitive exclusion to invading species (Figure SI.1d at $\kappa \geq 1$). The high total abundance that
308 communities with high P_m can reach without host control triggers the host immune response
309 to lower the growth rate of all microbial species in the community (Figure SI.2c at $\kappa \geq 1$).
310 As a result the community population size decreases, consequently lowering the community's
311 competitive barrier to invasion (Figure SI.2b and Figure 1c, at $\kappa \geq 1$). These communi-
312 ties become more vulnerable to extinction, and observe a decrease in species persistence (SI
313 Figure SI.2d at $\kappa \geq 1$) as the probability of invasion for the community increases with an
314 increase in host control strength (Figure 1b at $\kappa \geq 1$, Figure SI.1c). In contrast, host control
315 does not have much of an effect on microbial communities with high P_c (Figure SI.1b-d).
316 Such communities are already subjected to high levels of competition and a lower growth rate
317 such that introducing host control which is analogous to incorporating apparent competition
318 in the community further adds/intensifies the competition in a community that is already
319 highly competitive. Highly competitive microbial communities do not reach elevated levels
320 of microbial community abundance to begin with (Figure SI.2b), hence these communities
321 do not trigger the host immune control response. To check for potential history-dependent
322 effects, we also considered community assembly with time-varying host control strength. We
323 found that past host control strength has minimal role in determining how the community
324 responds to a change in κ once the community has reached a steady state with the new host
325 control strength (Figure SI.8 - SI.11).

326 When we simulate the community dynamics under the IEM framework we observe overall
327 very similar qualitative outcomes to UIM. This similarity is particularly evident upon inte-
328 grating host immune control and increasing immune strength (κ) (Figure 4, Figure SI.4). One
329 notable difference between the two models emerges in the absence of host control ($\kappa = 0$):
330 while community level characteristics (e.g., invasion success) under UIM depend on the bal-
331 ance of all interaction types, outcomes under IEM are primarily shaped by the interplay of
332 competition and mutualism only, with exploitation playing a minimal role. When model-
333 ing exploitative interaction as interchangeable its significance appears to be reduced by the
334 broader dynamics of competition and mutualism within the community. It is important to
335 note, however, this difference is only apparent without host control; with $\kappa > 0$, the patterns
336 under the two models are qualitatively similar.

337 5 Discussion

338 In our model we introduce host immune response as the global density dependence term in-
339 dependent of the balance of interaction types within the community. Incorporating such host
340 control can be simply thought to increase competition among species; however, we emphasize
341 that this parameter has important mathematical and biological implications. In our model we
342 demonstrate that we are able to simultaneously capture the opposing forces of decreasing and
343 increasing community density within the community through the incorporation of immune-
344 mediated global density dependence and highly mutualistic interactions. These conflicting
345 forces lead to complex dynamics such as cyclical patterns of species richness. This cyclical
346 pattern doesn't emerge with competition alone, illustrating the non-trivial effects of incor-
347 porating the host immune term into our model. Despite our model just capturing one type
348 of host immune control, we argue that modeling this nonspecific host immune response cap-
349 tures a biologically significant process observed in both vertebrates and invertebrates. In the
350 context of microbiome we also model exploitation as both unique (UIM) and interchangeable
351 (IEM). In absence of host immune control the IEM further emphasizes the interplay between
352 mutualism and competition in driving the community dynamics, with exploitation playing
353 a minimal role in comparison to the UIM. Nevertheless the balance of interaction types in
354 both models becomes less significant, as they produce similar qualitative results when host
355 immune control is introduced.

356 We extend the community assembly model by (Qian and Akçay, 2020) to capture the
357 assembly dynamics of microbial communities. This model is able to capture the diversity-
358 invasion effect which is a phenomenon also observed in the microbial ecosystems (Mallon
359 et al., 2015). Experimental studies have documented an inverse relationship between the
360 species richness, evenness and invader's ability to successfully colonize the community (Mal-
361 lon et al., 2015). Eisenhauer et al. (2013) experimentally show that taxonomically richer
362 resident microbial communities are better able to resist the invasion, with the caveat that
363 the community is functionally distinct and hence is better at exploiting resources than the
364 invader. Furthermore De Roy et al. (2013) show that invasion success becomes lower for an
365 invader when the resident community has high species evenness. Although these studies do
366 not quantify the ecological interactions among the resident community and its connection
367 to species diversity and evenness, (Qian and Akçay, 2020)'s model shows that communities
368 with high levels of mutualistic interactions have a high species richness and evenness com-
369 pared to species-low and less even communities observed with high levels of competition and
370 exploitation. However in our model once we introduce host immune control we observe that
371 the relationship between species richness and evenness with invasibility is reversed. This
372 highlights how host control of microbiomes can alter expectations from community ecology.

373 One of the main findings of our model is that a strong, generalized host immune control
374 weakens the influence of the balance of interaction types on the community level properties of
375 the microbiome. The host control can alter intrinsic dynamics of the microbiome differentially
376 based on the prevalent ecological interaction types in the community. Microbial communi-
377 ties with high levels of mutualism appear most susceptible to changes in the host immune
378 control and become increasingly susceptible to invasion. The high density of resident species
379 characteristic of mutualistic communities, triggers the host immune control to decrease the
380 overall community density which consequently lowers the community's competitive barrier
381 to invasion. In contrast, competitive communities whose species density is already set lower
382 by within-microbiome competition remain stable to changes in the host immune control.
383 Machado et al. (2021) present empirical evidence for the prediction that microbial commu-
384 nities that cooperate harbor a high community density compared to competitive microbial
385 communities that rely more on the availability of externally supplied resources. Hence both
386 species interactions and host control can collectively determine the composition and external
387 stability in microbial communities. Our results suggest that immune control is more relevant
388 as a host control mechanism to regulate microbial communities that are engaged in more
389 cooperative or cross-feeding interactions.

390 Our model also indicates that hosts can achieve microbiome stability against invasion of
391 new species (such as pathogens) either by hosting competitive microbial communities, irre-
392 spective of host immune control strength, or by hosting highly mutualistic microbial commu-
393 nity with minimal immune control. This poses a trade-off between the degree of host control
394 versus colonization resistance for a mutualistic microbial communities. It is important to note
395 that a colonization resistant microbial community may not necessarily be compatible with
396 the host nutritionally and immunologically. Both host and the microbiome are subjected to
397 distinct selection pressures, where microbial species despite providing benefit to the host can
398 fail to persist if they are unable withstand the interspecies competition (Foster et al., 2017).
399 Therefore a colonization resistant microbial community may not necessarily be beneficial to
400 the host. Colonization resistance then comes at a price to the host, where high competitive
401 barrier to invasion results in the host being unable to control the associated microbial commu-
402 nity. Conversely, elevated host control over the microbial community weakens the competitive
403 barrier to invasion for highly mutualistic microbial communities, lowering the resident micro-
404 bial species richness and persistence. Hence a symbiotic relationship between the host and
405 the microbiome for highly mutualistic microbial communities relies on the balance between
406 the host immune control and the colonization resistance.

407 Changes to the balance between the colonization resistance and the host control over a
408 microbial community can have implications for host health and the associated microbiome.
409 Host control can be impaired by changes to the homeostatic immune state of the host (Miller

and Baumler, 2021). Immunodeficiency – a defect in the immune control over the microbiome – can trigger dysbiosis of the microbial community. Immunodeficiency can result in the expansion of the microbial community in the small intestine more than what is observed at the healthy host state, resulting in hosts suffering from small intestine bacterial overgrowth (SIBO) disorder (Zaidel and Lin, 2003). The overgrowth of microbial population interferes with the nutrient absorption in the small intestine as the microbial community is in competition with the host for the nutritional resources. The microbial community with increased energy demands readily consumes carbohydrates, and lowers the availability and absorption of other nutrients such as fats, fat-soluble vitamins and proteins causing the host to suffer from malnutrition (Zaidel and Lin, 2003, Siniewicz-Luzenczyk et al., 2015, Miller and Baumler, 2021). The weakened host immune control as evident in the Small intestinal bacterial overgrowth metabolic disorder might cause the host to be no longer able to restrict the microbial community density to be under the host-supported carrying capacity. A reduction in the background competition imposed by the host immune control results in an increase in the growth of opportunistic microbial species specifically favorable for those that are engaged in cooperative interactions with other members of the community.

Conversely, an overt inflammatory immune state indicative of an elevated host control results in a decreased microbiome density observed in hosts with an inflammatory bowel disease (IBD) (Kiely et al., 2018). Contijoch et al. (2019) found a decrease in absolute abundance of firmicutes, actinobacteria and bacteroidetes with depleted microbiota density in hosts with IBD, whereas proteobacteria sustained a constant density in individuals with IBD. This suggests that some species may be more resilient to changes in host immune control. In line with our findings, proteobacteria phylum is known to be less abundant , which may cause them to trigger less strong immune responses. Further proteobacteria were also more functionally variable at a gene level compared to other phyla (Bradley and Pollard, 2017) which suggests that these species may share fewer metabolic co-dependencies with other species and engage in more competitive rather than cooperative interactions. These patterns need to be experimentally validated to further our understanding of the host-mediated control on microbiota density on the community composition and assembly of the microbial community.

In addition to host immunity, the amount and type of resources supplied by the host can influence microbial community composition. (Saffouri et al., 2019) found that healthy individuals with no symptoms can also exhibit SIBO, which correlated with high-fiber diets rich in complex carbohydrates. Complex carbohydrates might be a resource with higher opportunities for metabolic interdependencies (Smith et al., 2019) and thus positive interactions in the microbiome. Thus, it is possible that a diet rich in complex carbohydrates can shift the balance of interactions from being more competitive to more mutualistic. In that case, our model predicts an increase in both microbiome density and diversity (Fig SI.1b) even in

447 the absence of a change in host control. This is consistent with the finding that gut-derived
448 microbial communities provided structurally complex carbohydrates maintain higher species
449 richness in lab culture (Yao et al., 2020). Our model suggests that such an increase in mutual-
450 istic interactions can either reduce the external stability of the microbiome (increase invasion
451 probabilities) or leave it unchanged, depending on the strength of host control (FigSI.1c).
452 This points to the need for more work on how metabolic relationships in the microbiome
453 change with host-provided resources and how these interact with immune mechanisms.

454 In our model framework we incorporate host control as a global density dependence term.
455 Where host modulates the entire microbial community, indiscriminately. Other mechanisms
456 of host control include host resource availability which can actively modify the landscape of
457 within-species interactions within the microbial community. Resource-based host control may
458 not just serve as a global ecosystem modulator, but may also impose positive and negative
459 selection on specific microbial species in the residing microbial community. Moreover, the
460 host control can also be modified by the microbial community itself. The microbiome can
461 engineer its micro environment by producing metabolites, which in turn can influence the
462 biotic interactions in the microbial community (Gralka et al., 2020, Marsland et al., 2020,
463 Kurkjian et al., 2021). Microbial community members can also influence host immune home-
464 ostasis, as specific microbial species can induce host immune responses (Atarashi et al., 2013,
465 Ivanov et al., 2009). Microbiome-induced host immune response can consequently affect the
466 strength of host control over the microbial community. The effect of these myriad ways of
467 host control needs to be theoretically and experimentally investigated to truly uncover the
468 effect of host-microbiome feedback on the host control over the microbial community.

469 In conclusion, we present a community dynamics framework, incorporating the role of
470 host immune control in regulating microbial community size. We show that host immune
471 control can interact with the within-microbiome species interactions in unexpected ways in-
472 fluencing the microbial community composition and stability. Host immune control may
473 serve as a more relevant host control instance to keep the size of highly mutualistic microbial
474 communities in check. We stress that understanding microbial community assembly and sta-
475 bility is incomplete without considering the role of host-control mechanisms on the microbial
476 community.

477 6 Figures and Tables

Model Fixed Parameters	
Variable	Definition
$s_i = -1$	self regulation term
$h = 100$	half-saturation constant of type II functional response
$c = 0.5$	connectivity term of the microbial species
$K_i = 100$	species-specific carrying capacity
$\epsilon = 0.001$	failed extinction threshold
$\beta = 1000$	failed invasion threshold
$\tau = 5000$	equilibria limit
$p = 0.01$	p value threshold
$I_m = 10000$	host immune supported carrying capacity
$n = 750$	species number limit
$w_1 = 1000$	number of equilibria analyzed for the Dickey fuller test
$w_2 = 500$	number of equilibria simulated after steady state is reached
$\delta = 0.001$	population change threshold
$t_1 = 10^9$	time limit for simulation
$\sigma = 0.5$	half-normal distribution scale parameter

Table 1: Fixed variables in the model and their definitions.

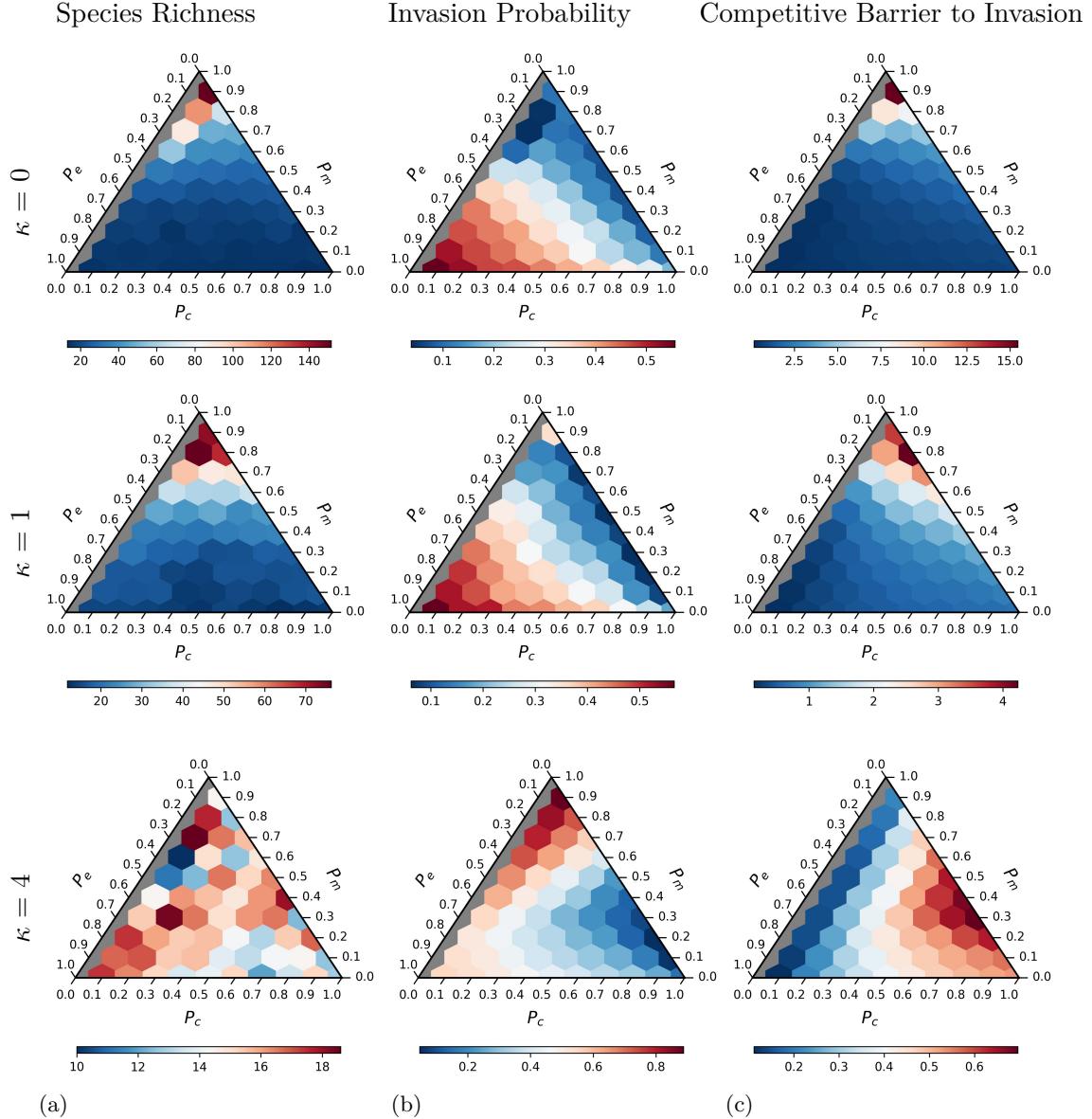


Figure 1: UIM framework - Ternary plots representing the host control on (a) species richness (at steady state), (b) invasion probability at steady state, and (c) competitive barrier to invasion for all possible communities with different balance of interaction types. In each ternary plot, the location of each hexagon corresponds to a particular balance of interaction types, given by probabilities P_c , P_m and P_e for competitive, mutualistic, and exploitative interactions, respectively. Note that scale of each plot shown above has a different range. Each row demonstrates an increasing host control strength (κ) for each community metric, from no host control ($\kappa = 0$) to high host control strength ($\kappa = 4$).

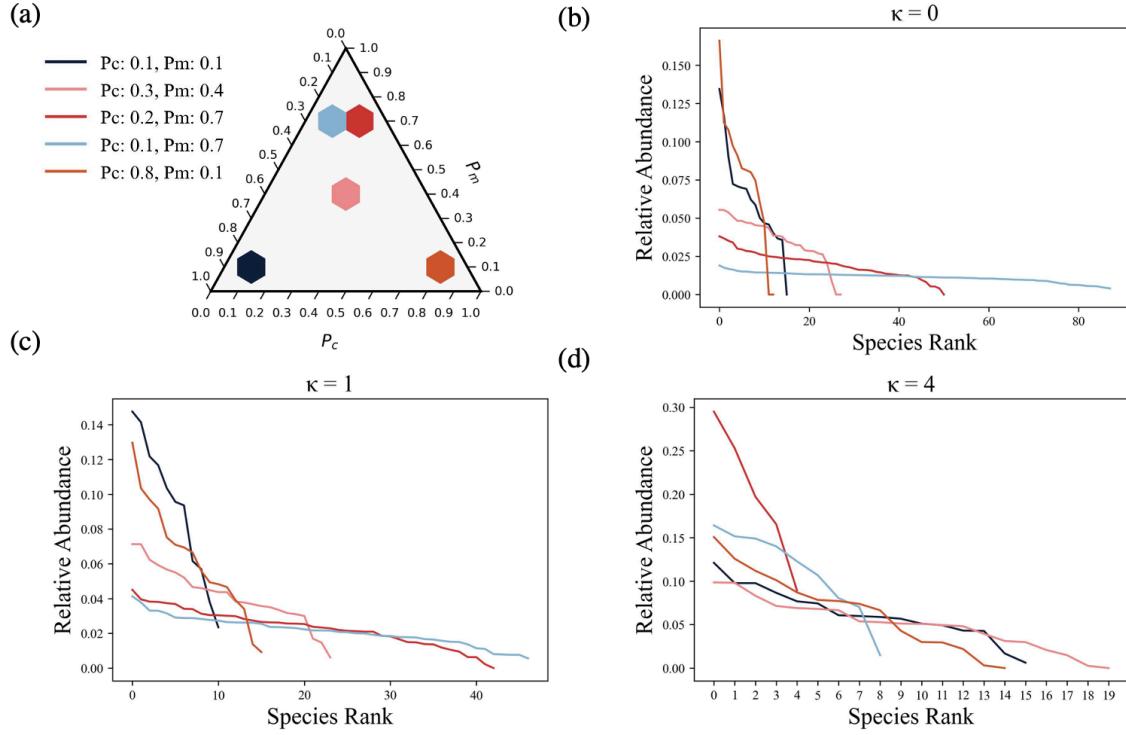


Figure 2: UIM framework (a)Represents a ternary plot with selected microbial communities. The color of each selected community in the ternary plot corresponds to line plots in parts b-d. The line plots represent species rank abundance curves across a range of κ values. Note that scale of each plot shown above has a different range.

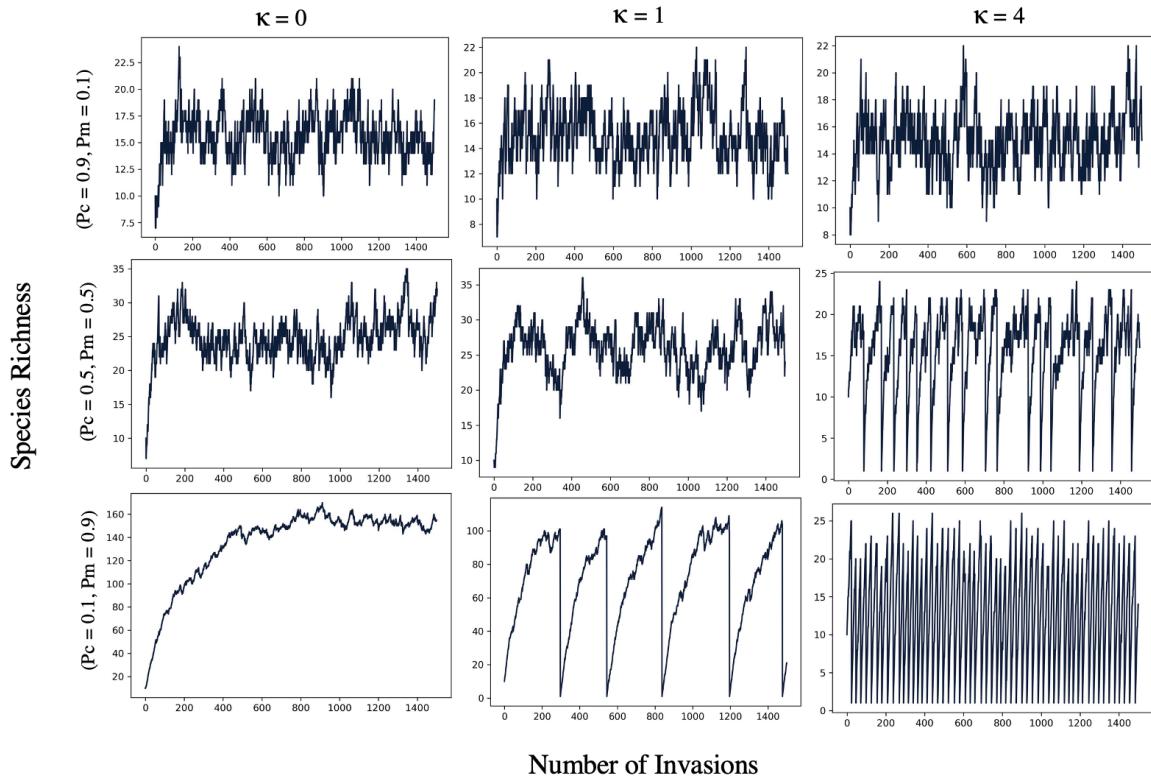


Figure 3: UIM framework - A series of line plots representing species richness for a microbial community as invaders are introduced into the community. Each row of the line plot represents a microbial community with a distinct P_c , P_m , and P_e across a range of κ values. The cooperation (P_m) term increases and the competition (P_c) decreases across rows of the line plots while exploitation $P_e = 0$. Note the y-axis scale of each line plot shown above has a different range.

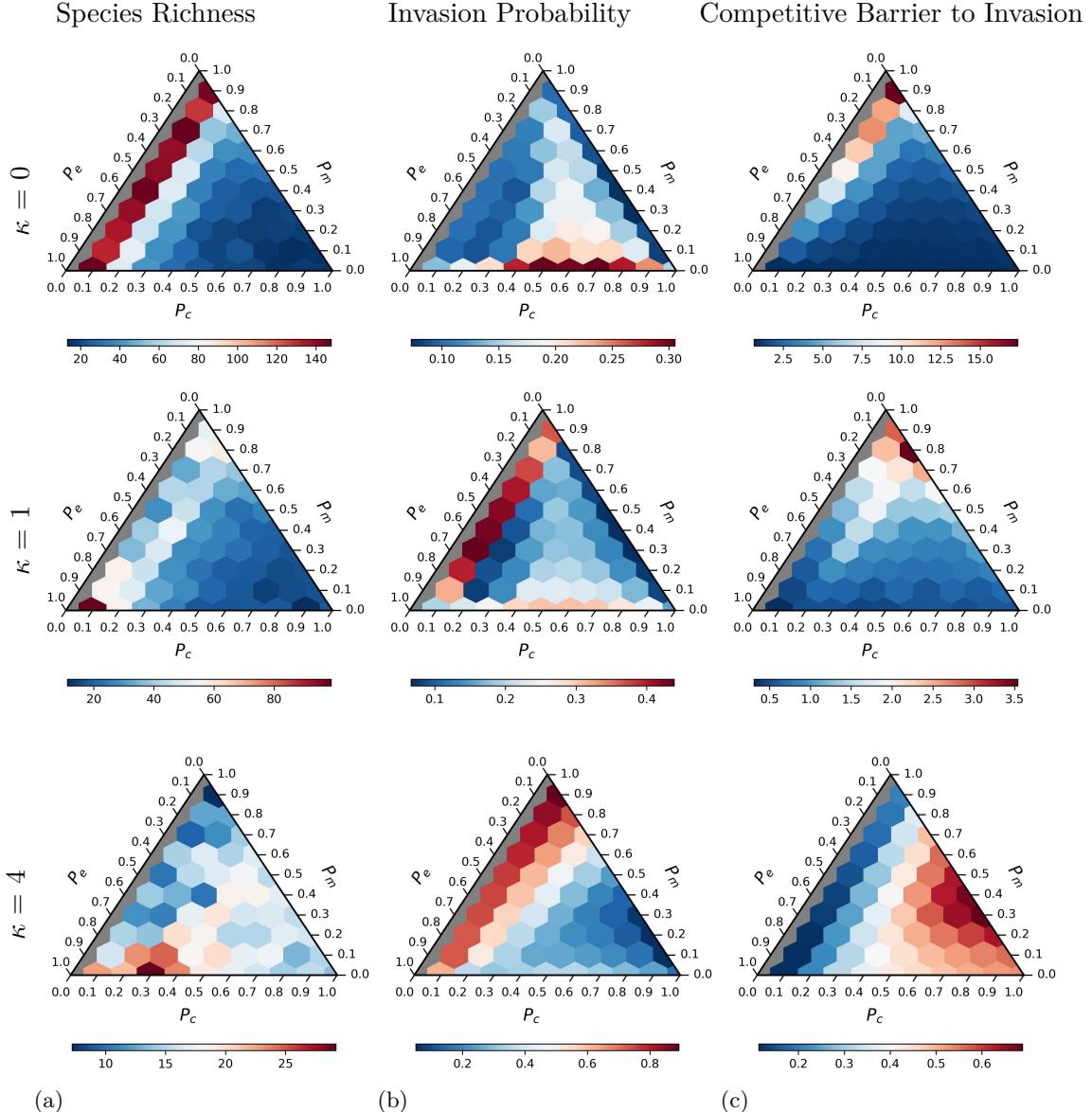


Figure 4: IEM framework - Ternary plots representing the host control on (a) species richness (at steady state), (b) invasion probability at steady state, and (c) competitive barrier to invasion for all possible communities with different balance of interaction types. In each ternary plot, the location of each hexagon corresponds to a particular balance of interaction types, given by probabilities P_c , P_m and P_e for competitive, mutualistic, and exploitative interactions, respectively. Note that scale of each plot shown above has a different range. Each row demonstrates an increasing host control strength (κ) for each community metric, from no host control ($\kappa = 0$) to high host control strength ($\kappa = 4$).

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649 otrophies shape complex communities.

650 7 Code availability

651 The model of microbial community assembly was implemented in Python. The simulation
652 code is available at github: <https://github.com/erolakcay/MicrobiomeCommunityAssembly>

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654 We thank Katie Barott for her helpful comments on the manuscript.

655 9 Competing interests

656 We have no competing interests

657 10 Author Contributions

658 Both authors designed the study, constructed the model, and provided the analysis. Both
659 authors contributed to writing the manuscript. Both authors gave the final approval for
660 publication.

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663 Supplementary Information

664 Host control and species interactions jointly determine microbiome com-
 665 munity structure

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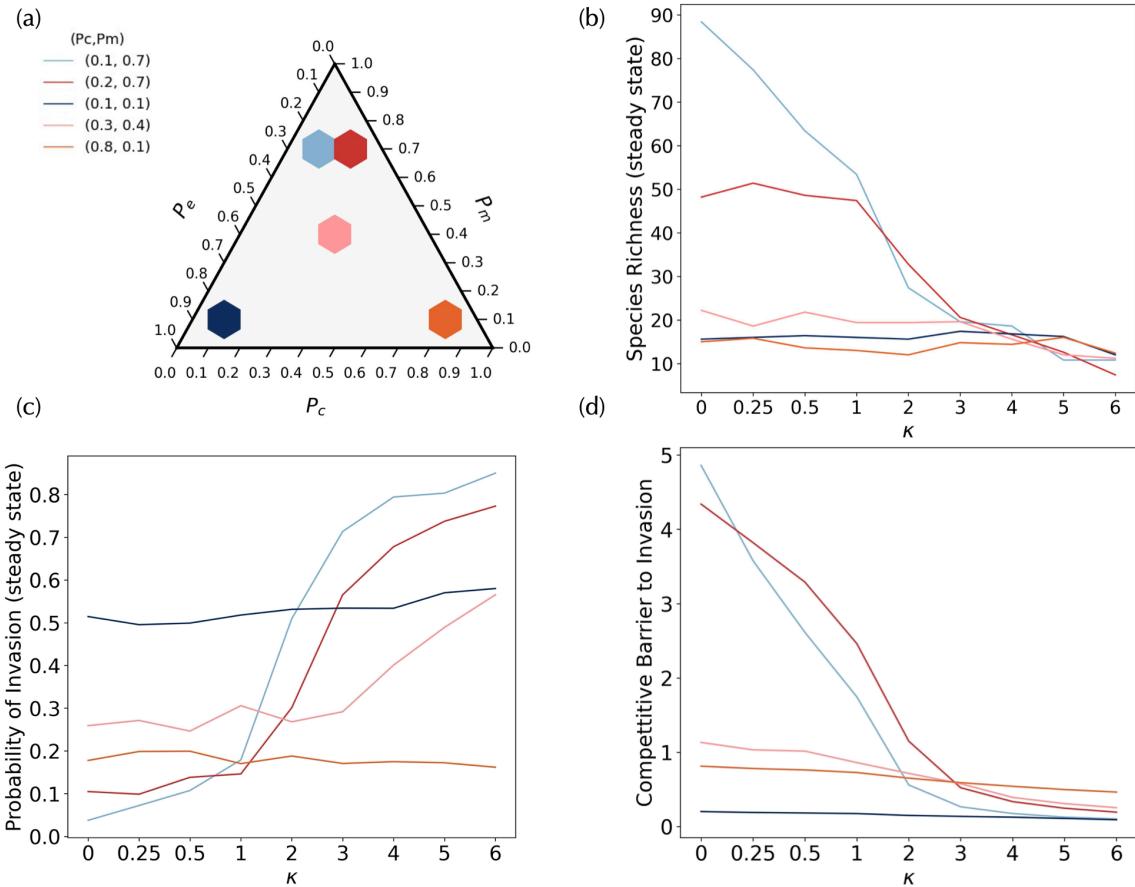


Figure SI.1: UIM framework (a) Represents a ternary plot with selected microbial communities. The color of each selected community in the ternary plot corresponds to line plots in parts b-d, the line plots represent (b) species richness (at steady state), (c) invasion probability (at steady state), and (d) competitive barrier to invasion across a range of κ values.

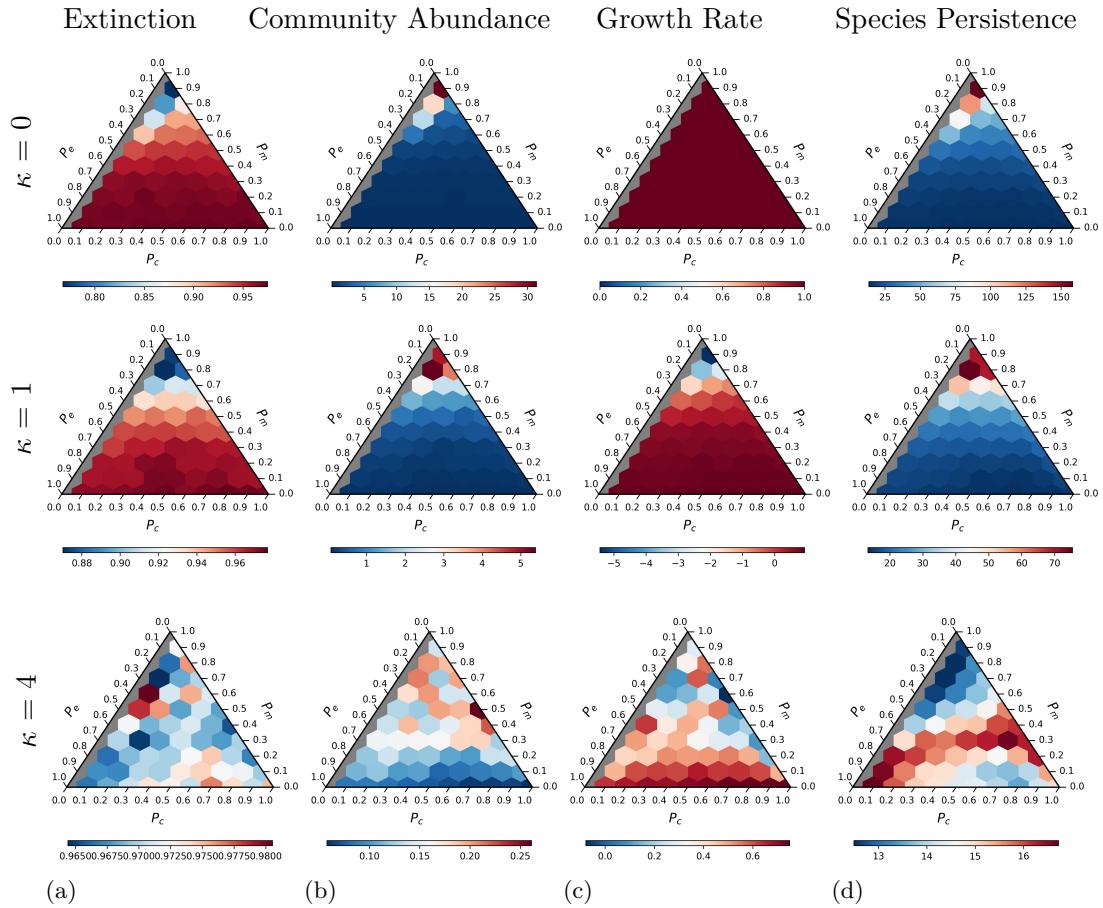


Figure SI.2: UIM framework- Ternary plots representing the host control on (a) probability of extinction (at steady state), (b) community abundance at steady state, and (c) growth rate, (d) mean species persistence for all possible communities with varying P_c , P_m and P_e . Note that scale of each plot shown above has a different range. Each row demonstrates an increasing host control strength (κ) for each community metric, from no host control ($\kappa = 0$) to high host control strength ($\kappa = 4$).

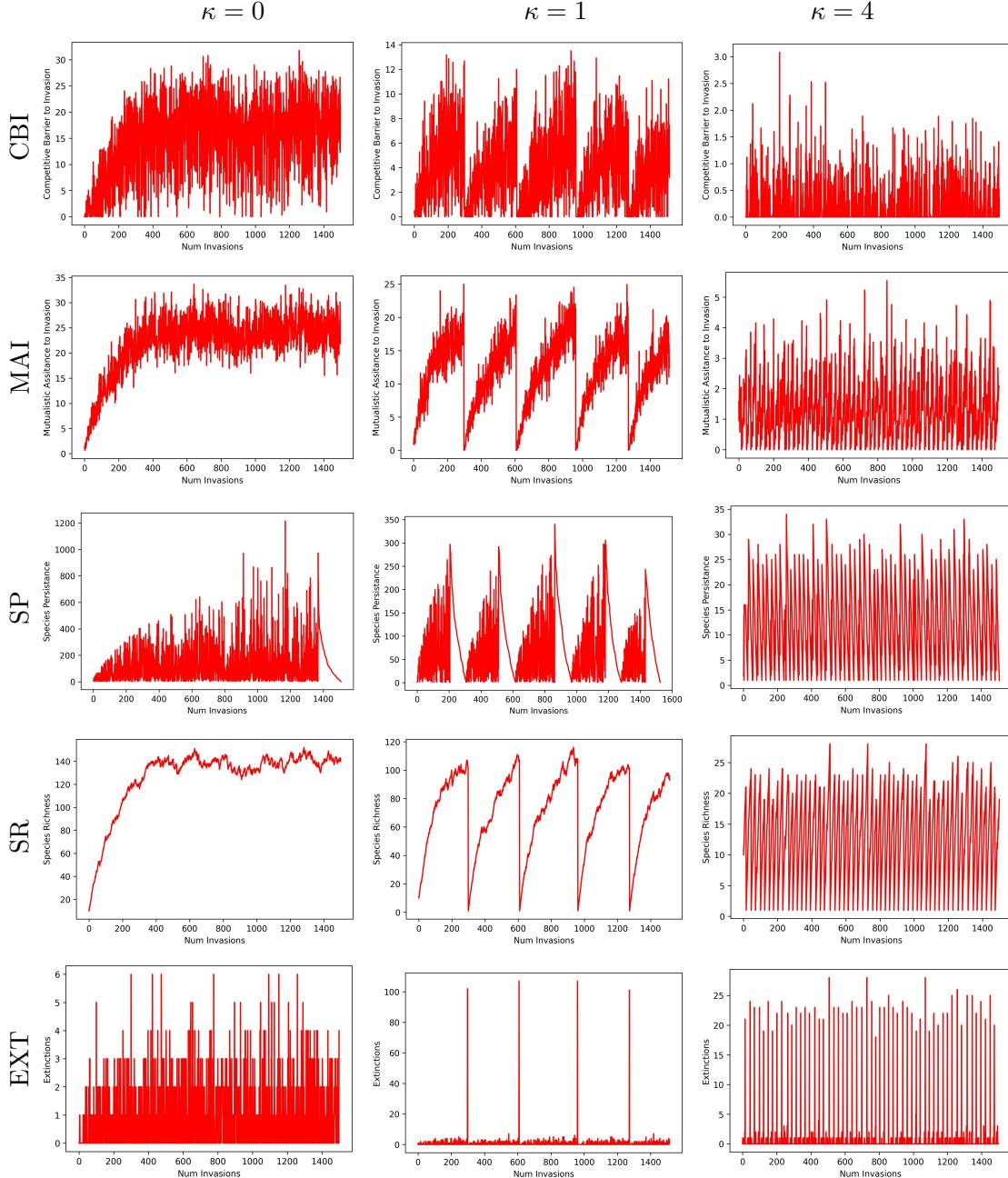


Figure SI.3: UIM framework - A series of line plots for the microbial community with $P_m = 0.9$ and $P_c = 0.1$. The line plots represent how the community level properties, i) competitive barrier to invasion (CBI), ii) mutualistic assistance to invasion (MAI), iii) species persistence (SP), iv) species richness (SR) and v) extinction (EXT) vary across the sequential invasions in the community for a range of host control strength (κ) values.

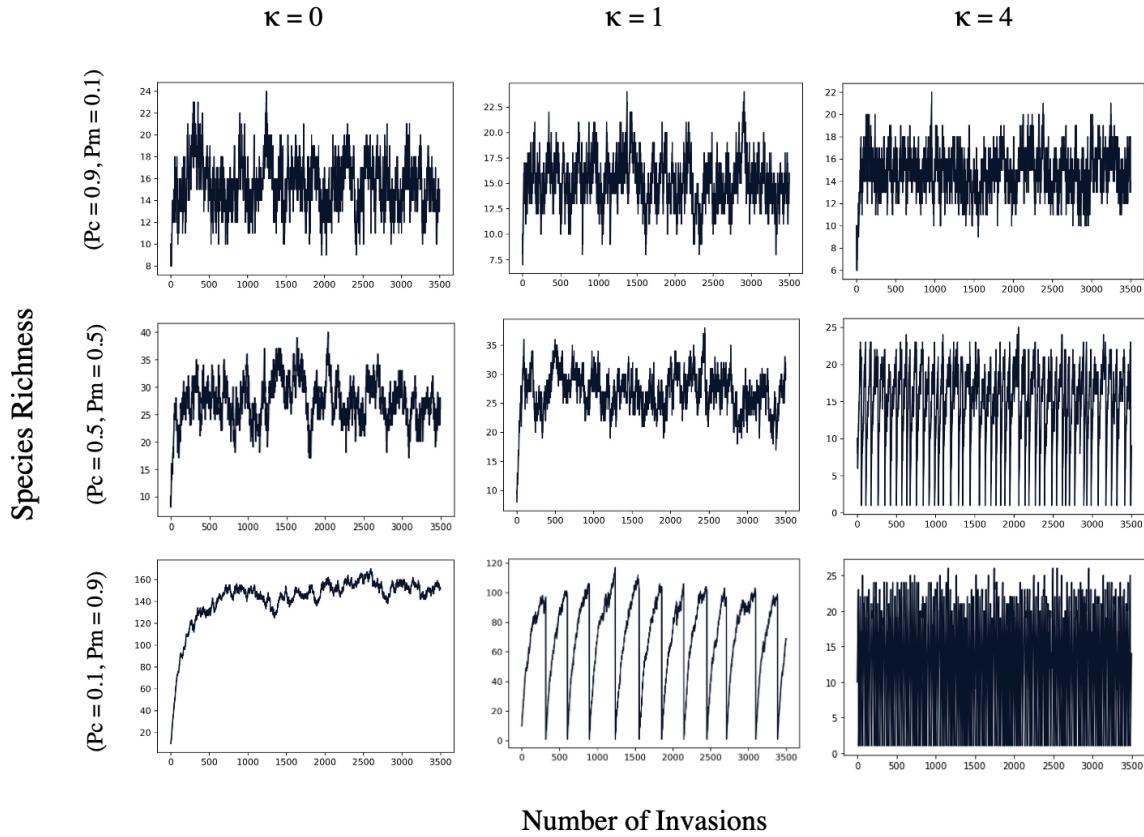


Figure SI.4: IEM framework - A series of line plots representing species richness for a microbial community as invaders are introduced into the community. Each row of the line plot represents a microbial community with a distinct P_c , P_m , and P_e across a range of κ values. The cooperation (P_m) term increases and the competition (P_c) decreases across rows of the line plots while exploitation $P_e = 0$. Note the y-axis scale of each line plot shown above has a different range.

669 .1 Periodicity Analysis

670 We conducted periodicity analysis on the species richness of all microbial communities as a
 671 function of $\kappa(0, 1, 4)$, where we determined the mode frequency and spectral density (ampli-
 672 tude) of species richness time series using the spectrum function in R. We observe frequent
 673 boom and bust cycles in species richness of highly mutualistic microbial communities, at high
 674 κ value.

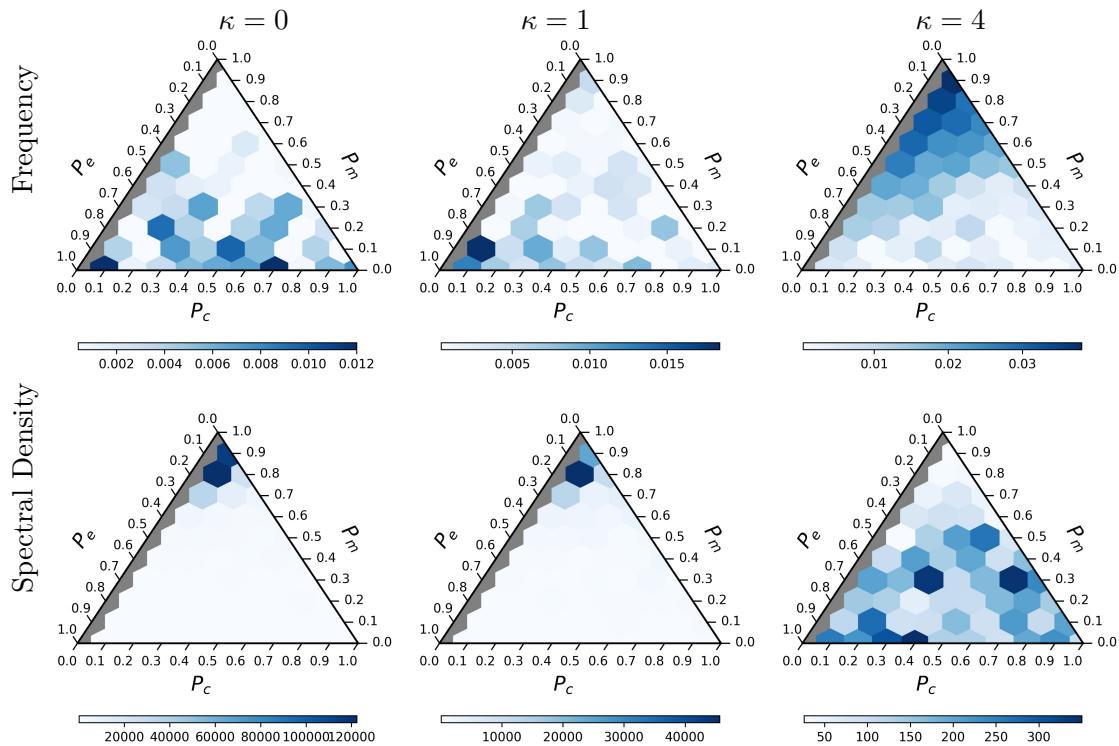


Figure SI.5: UIM framework - Ternary plot representing the frequency and spectral density for species richness time series observed for all possible microbial communities (with varying P_c , P_e , and P_m) at different levels of host control strengths ($\kappa = 0, 1, 4$). Note that scale of each plot shown above has a different range.

675 .1.1 Community Interactions under varying host control strength

676 We counted the number of interactions that were mutualistic, competitive and exploitative at the end of simulation for all communities at varying host control strength (κ).

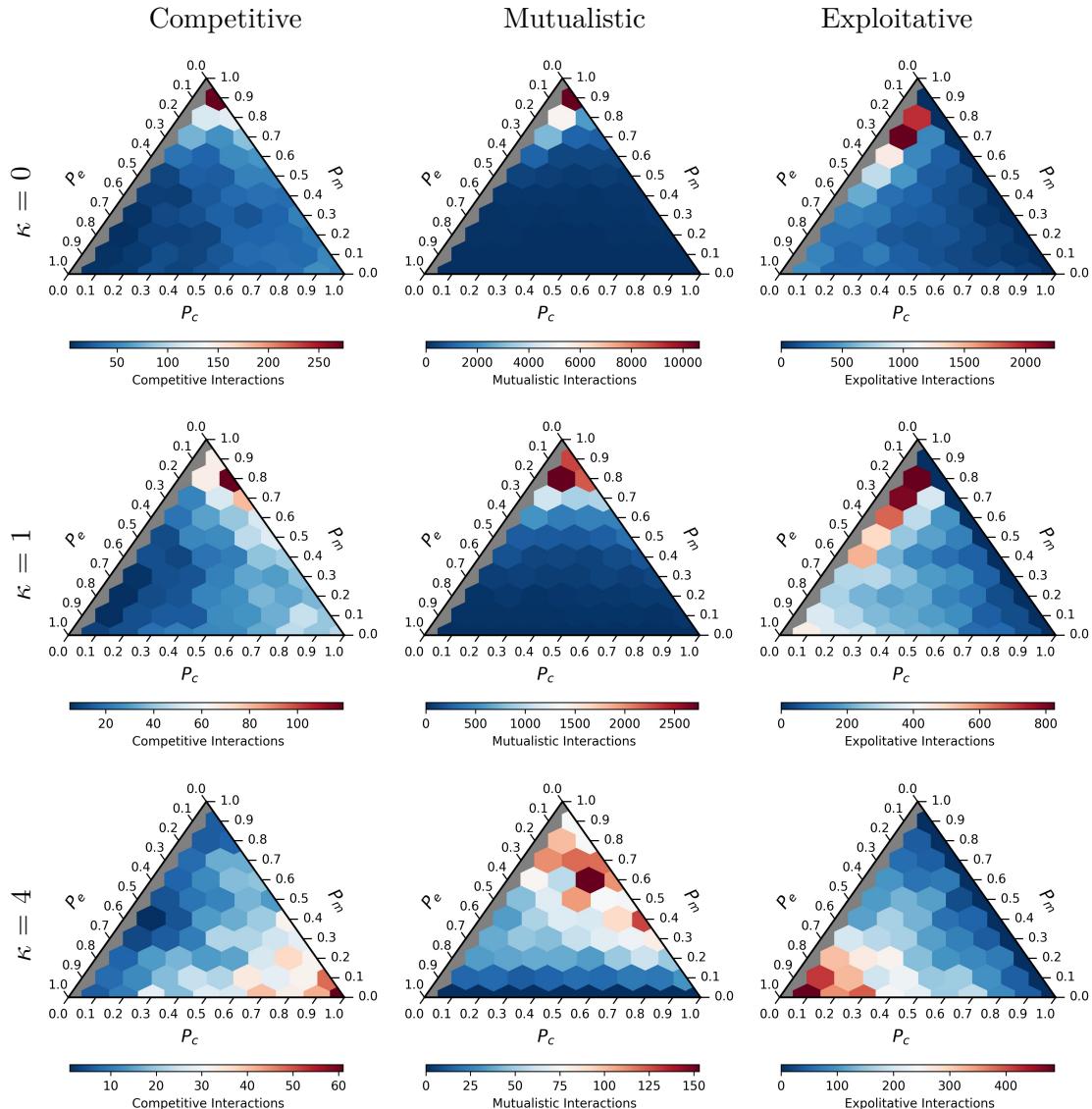


Figure SI.6: UIM framework - Number of competitive, mutualistic and exploitative interactions observed for each microbial community at the end of the community history under varying levels of host control ($\kappa = 0, 1, 4$). Note that scale of each plot shown above has a different range.

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678 We also simulate communities until the species diversity reached a steady state. Once after
679 the community had reached steady state we sampled the community 100 times at an interval
680 of every 10th equilibrium. We used the 100 samples to calculate the average distribution of

interaction types for that community. We plot the distribution of the interaction types that were assigned outside the host (extrinsic), and the actual average interaction type that we calculated using the sampled communities. As explained in our methods for each equilibrium we allow an invasion to take place. The invader interaction type is randomly assigned however the ones that are able to invade a given community may be biased towards a specific interaction type. We show below the change in the direction of the community interaction types with no host control and when host control is incorporated.

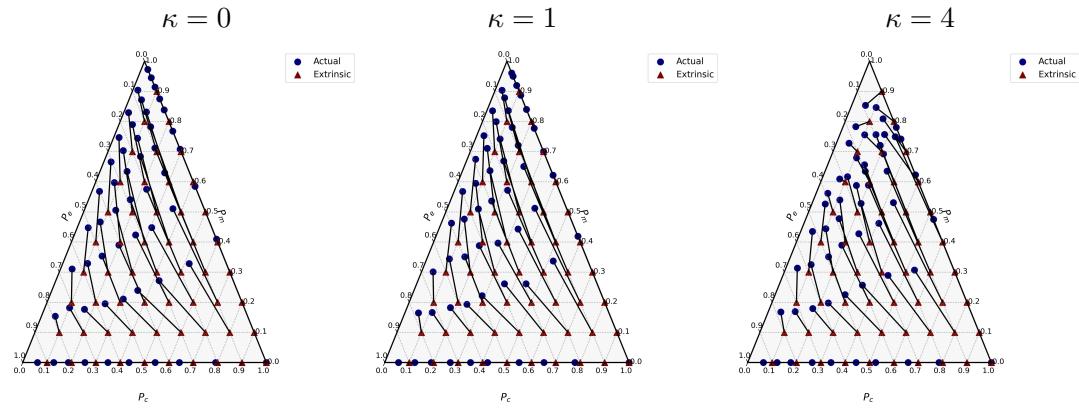


Figure SI.7: UIM framework- Represents ternary plots across varying κ values showing the extrinsic and actual proportion of interactions in the community. The black line connects the extrinsic to the actual interaction types for the same community..

688 .1.2 Changing host leash strength on the microbiome community

A healthy host can be perturbed to a disease like state which is known to shift microbiome community structure, size and diversity. Diseased-state is reflective of a stressed host, which can have an impaired host control on the microbiome. In our model, we varied the host leash (κ) to either a higher or a lower term (0, 1, 4) - encompassing possible variations in the host control, only after the initial community had reached a steady state. We chose the $\kappa = 4$, as the highest host control term, a value higher produces the same qualitative patterns. When changing the (κ), we allowed the community to reach equilibrium and then allowed sequential invasions to occur.

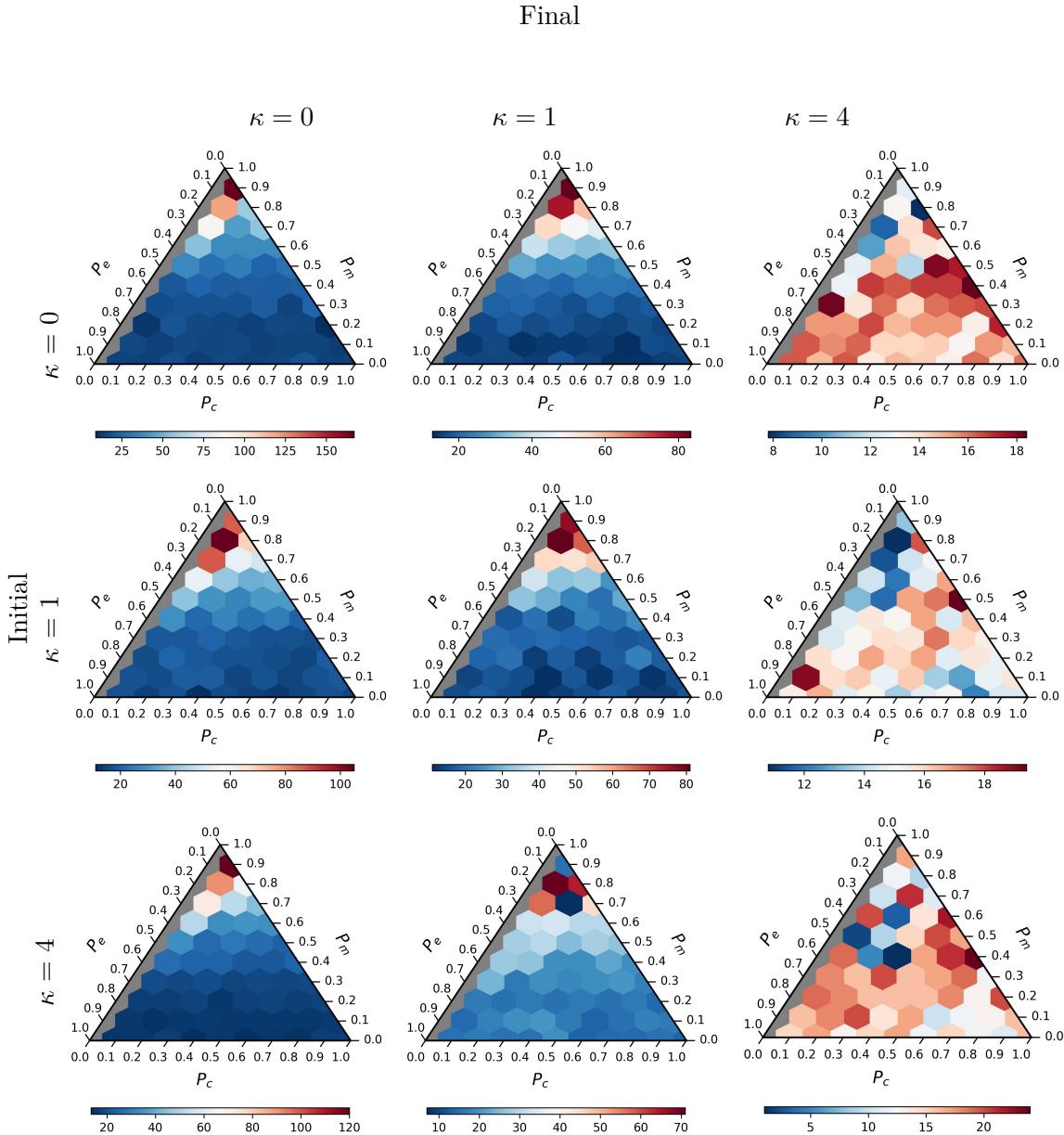


Figure SI.8: UIM framework - Ternary plots representing species richness (at steady state) observed for microbial communities. The κ terms observed on the vertical axis are the initial κ terms observed when the community reaches the steady state and the κ term on the horizontal axis represent the host control enforced on the community once after the the community has reached a steady state. Note that scale of each plot shown above has a different range.

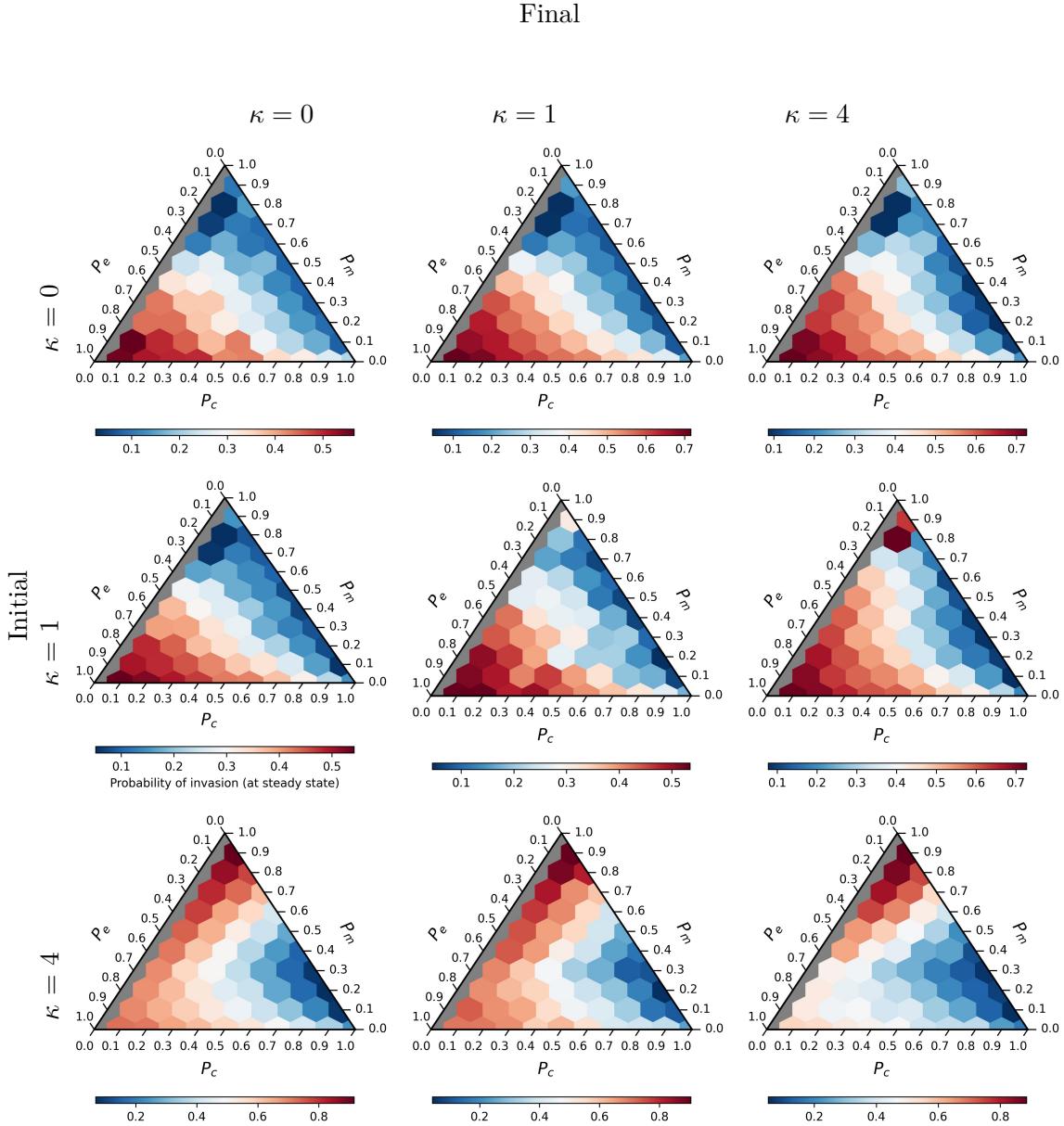


Figure SI.9: UIM framework - Ternary plots representing probability of invasion (at steady state) observed for microbial communities. The κ terms observed on the vertical axis are the initial κ terms observed when the community reaches the steady state and the κ term on the horizontal axis represent the host control enforced on the community once after the the community has reached a steady state. Note that scale of each plot shown above has a different range.

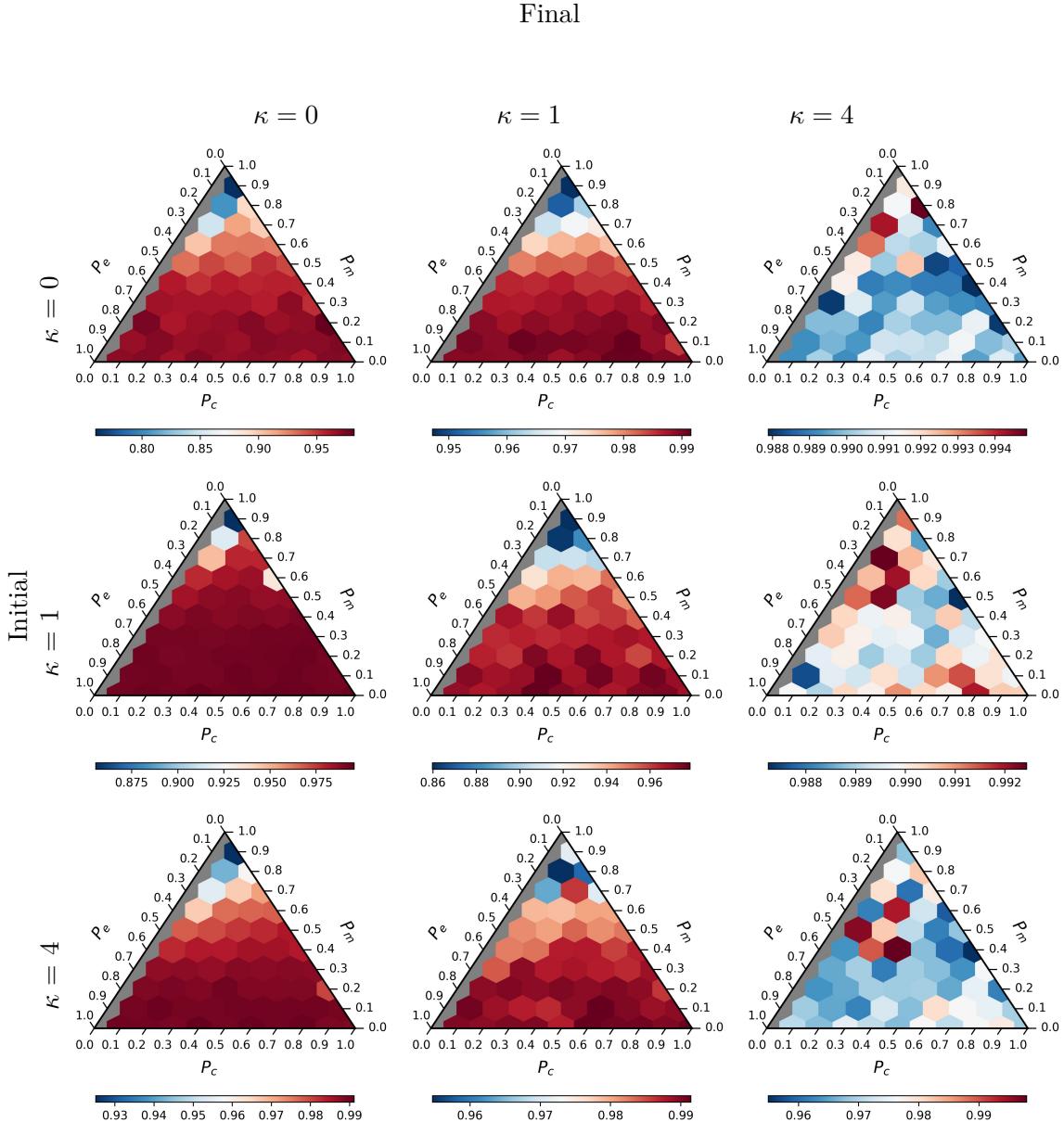


Figure SI.10: UIM framework - Ternary plots representing probability of extinction (at steady state) observed for microbial communities. The κ terms observed on the vertical axis are the initial κ terms observed when the community reaches the steady state and the κ term on the horizontal axis represent the host control enforced on the community once after the the community has reached a steady state. Note that scale of each plot shown above has a different range.

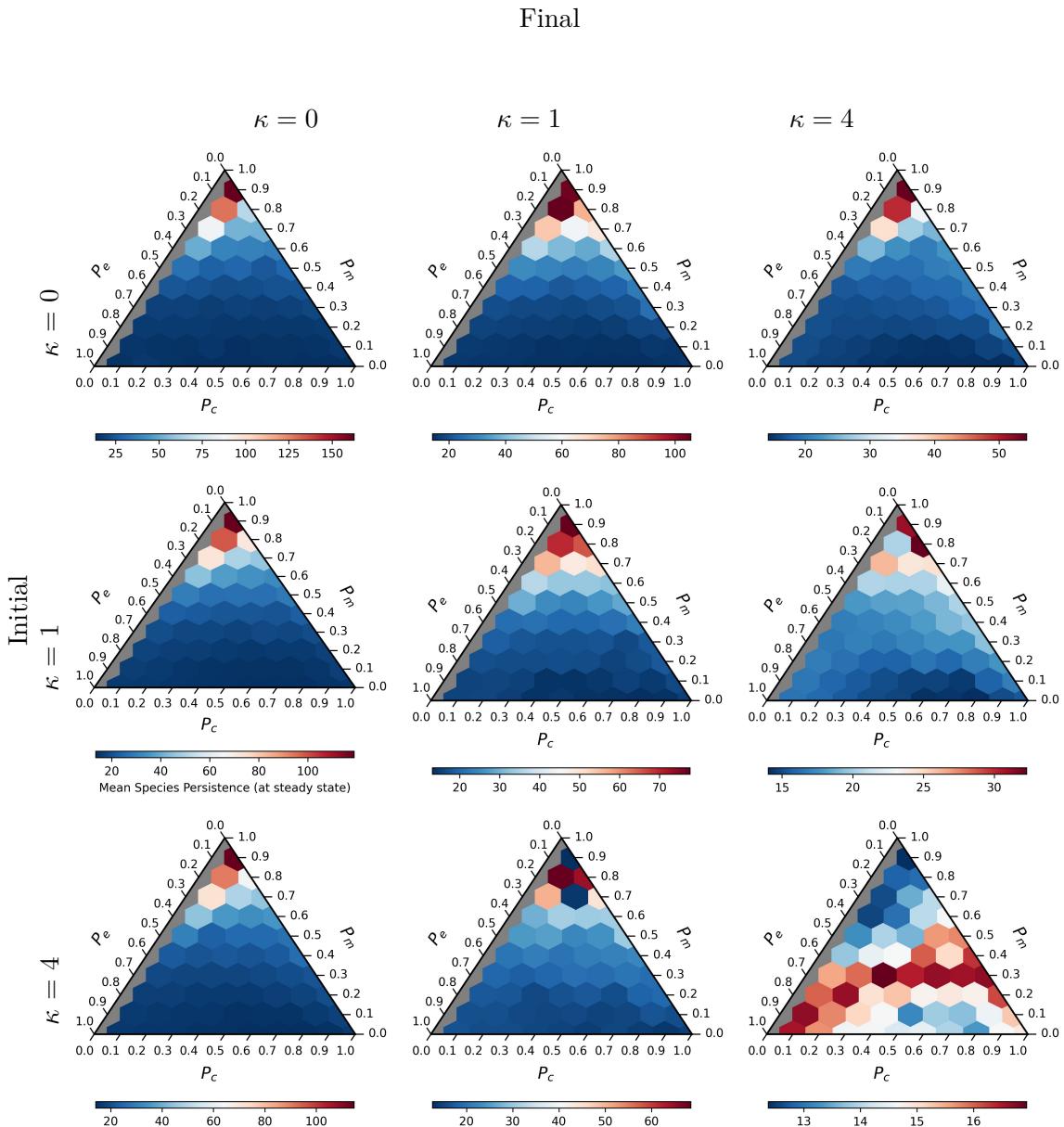


Figure SI.11: UIM framework - Ternary plots representing mean species persistence (at steady state) observed for microbial communities. The κ terms observed on the vertical axis are the initial κ terms observed when the community reaches the steady state and the κ term on the horizontal axis represent the host control enforced on the community once after the the community has reached a steady state. Note that scale of each plot shown above has a different range.

697 .1.3 Multi-stability Analysis

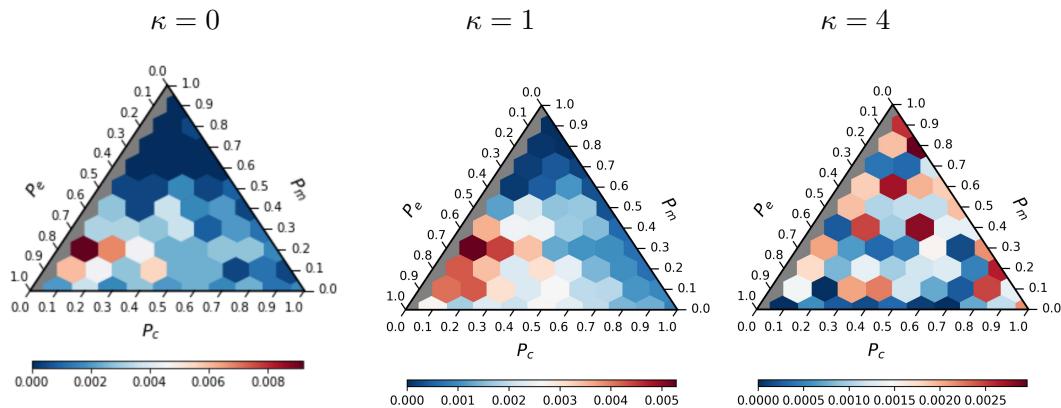


Figure SI.12: UIM framework - Represents ternary plots showing the probability that an equilibrium in the community history shows oscillations in population dynamics for all microbial communities across a range of κ values..

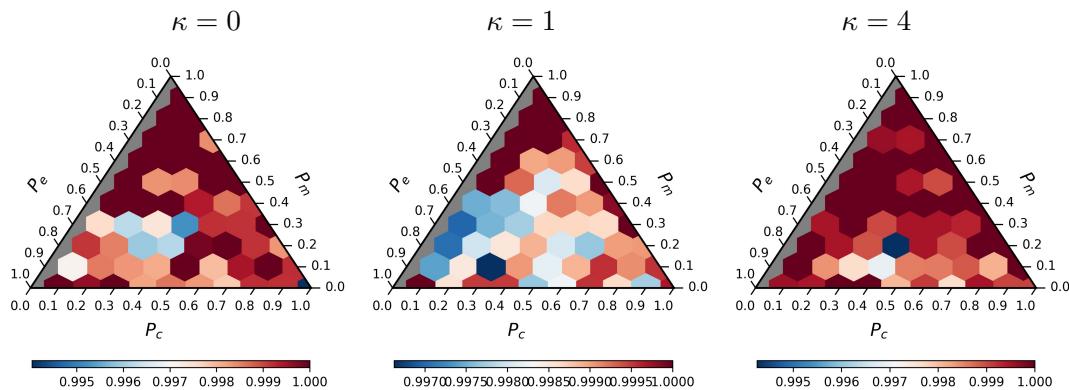


Figure SI.13: UIM framework - Represents ternary plots showing the ratio of stable equilibria observed for microbial communities when assayed with 25 different initial population sizes across a range of κ values.

698 .1.4 Community characteristics under varying h values

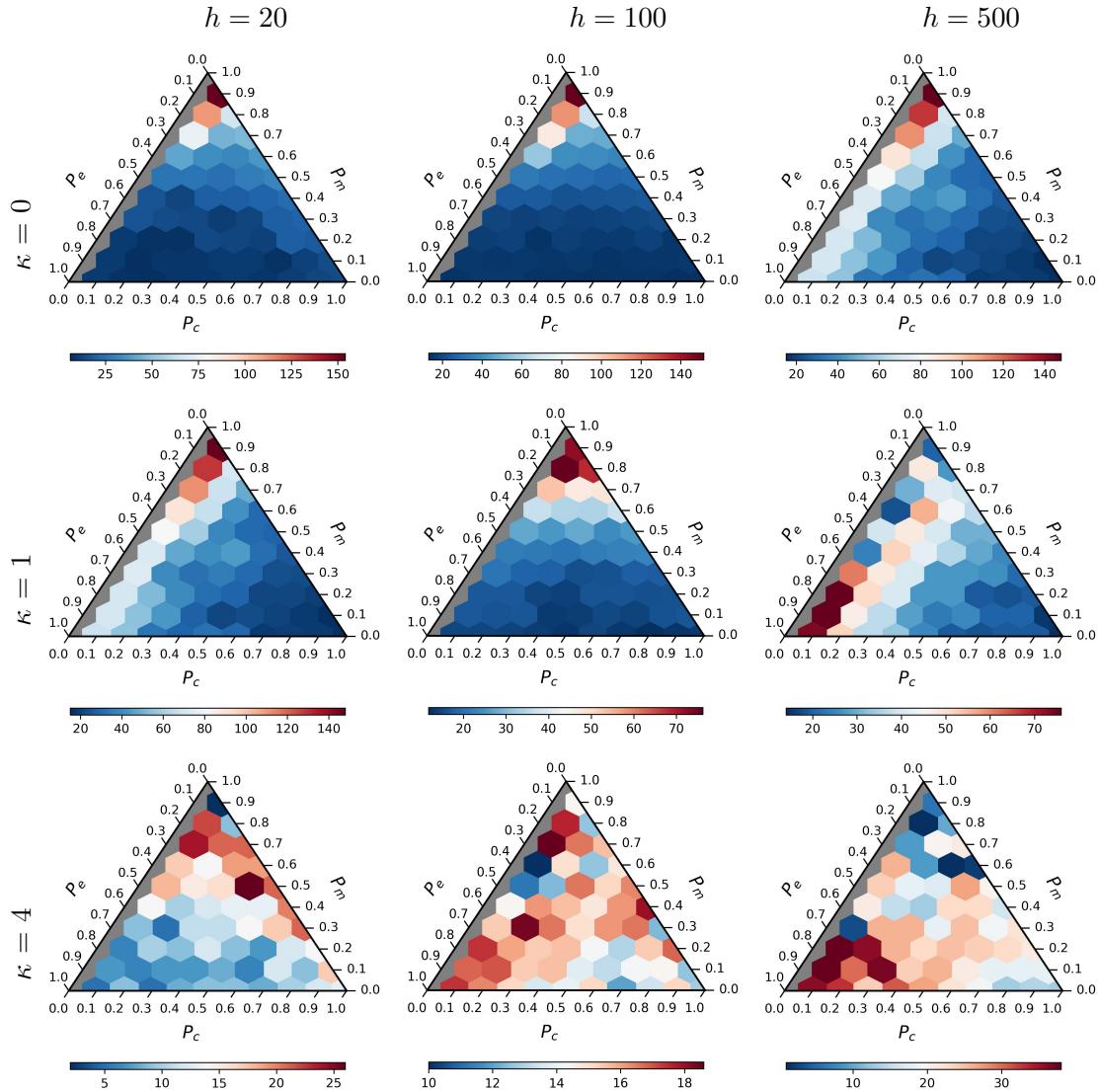


Figure SI.14: UIM framework - Ternary plots representing species richness observed at steady state for microbial communities across different h values. Note that scale of each plot shown above has a different range.

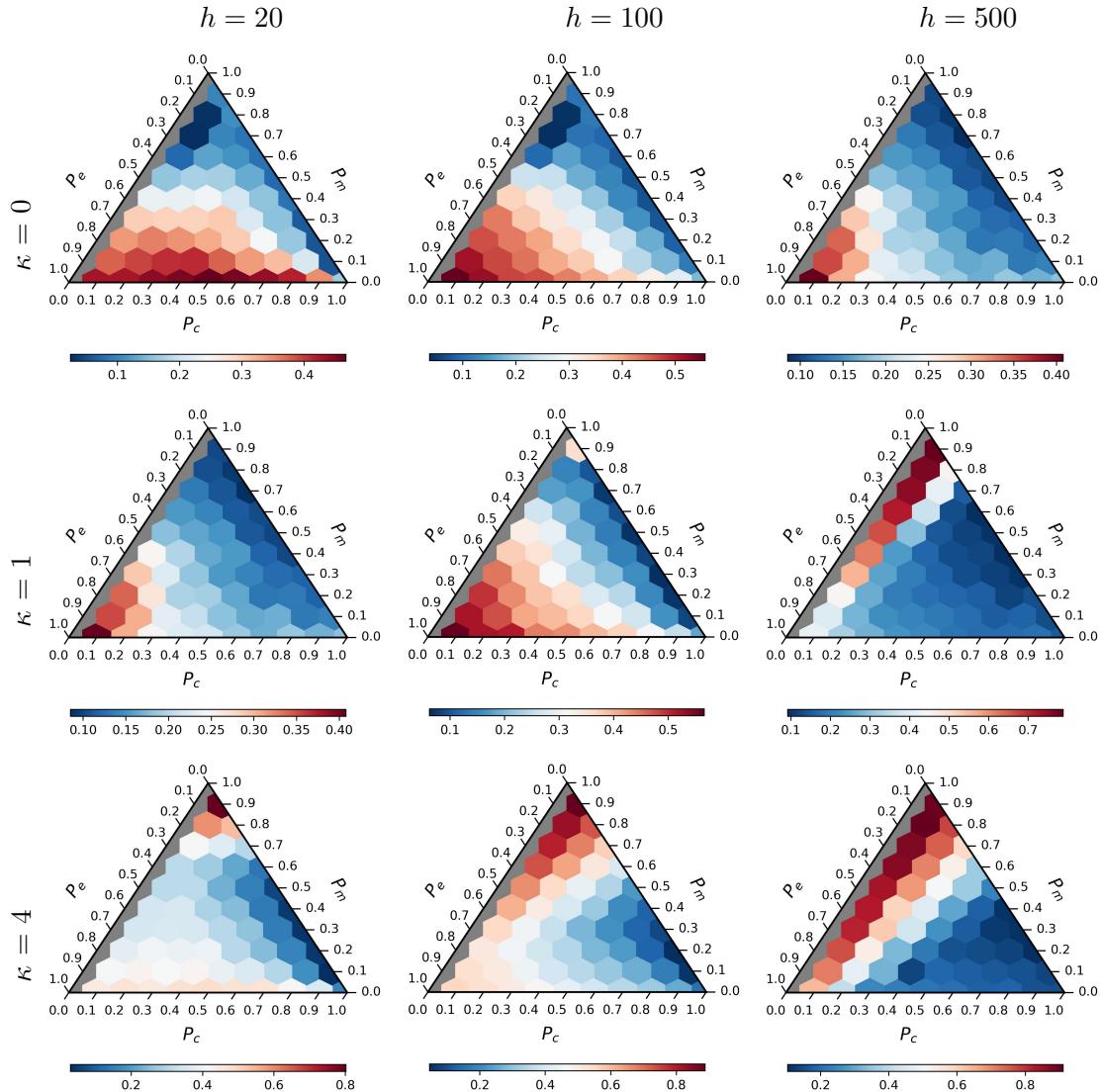


Figure SI.15: UIM framework -Ternary plots representing probability of invasion at steady state observed for microbial communities across different h values. Note that scale of each plot shown above has a different range.

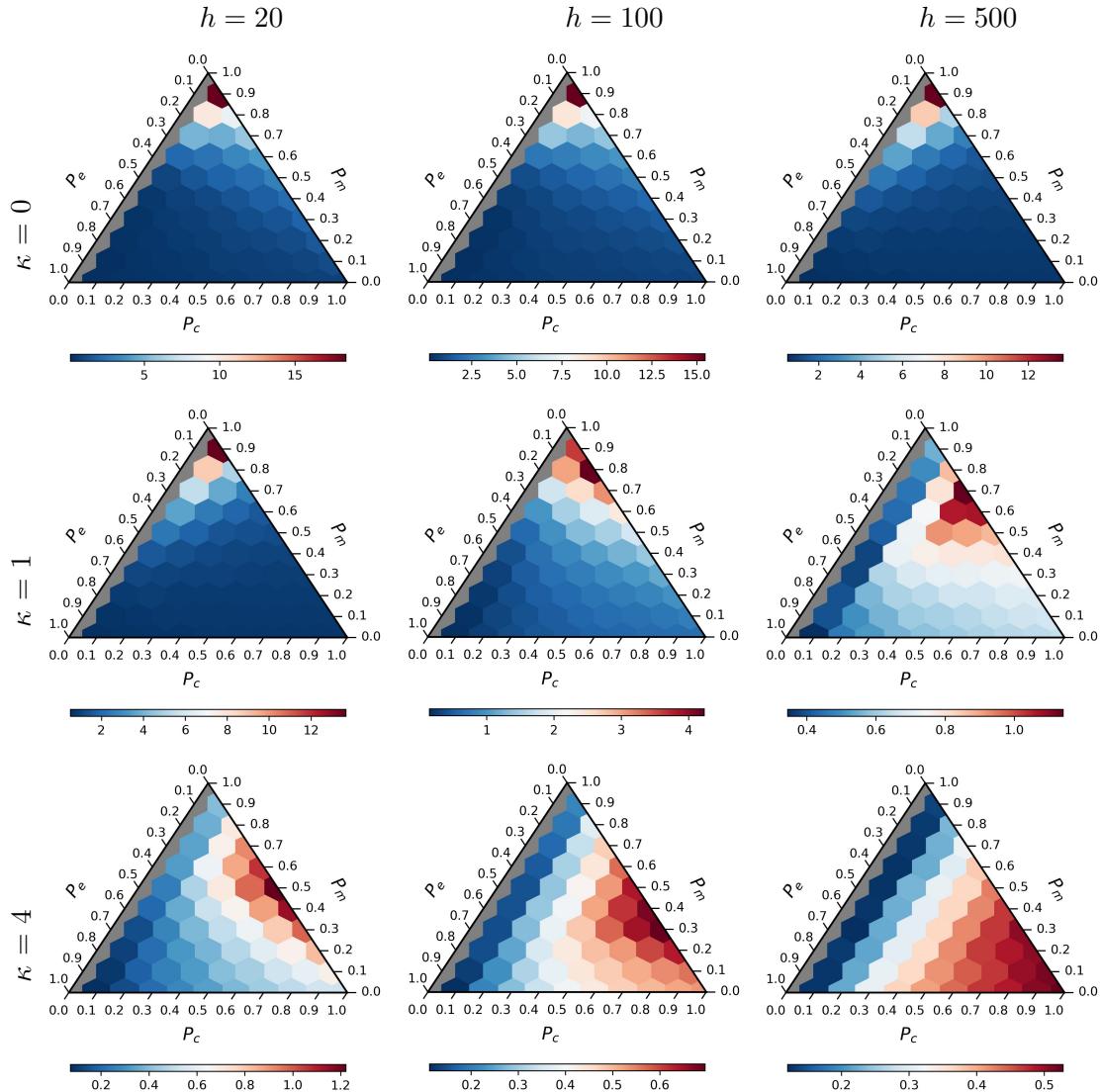


Figure SI.16: UIM framework - Ternary plots representing competitive barrier observed for microbial communities across different h values. Note that scale of each plot shown above has a different range.