MICROBIOME

The ecology of the microbiome: Networks, competition, and stability

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The human gut harbors a large and complex community of beneficial microbes that remain stable over long periods. This stability is considered critical for good health but is poorly understood. Here we develop a body of ecological theory to help us understand microbiome stability. Although cooperating networks of microbes can be efficient, we find that they are often unstable. Counterintuitively, this finding indicates that hosts can benefit from microbial competition when this competition dampens cooperative networks and increases stability. More generally, stability is promoted by limiting positive feedbacks and weakening ecological interactions. We have analyzed host mechanisms for maintaining stability—including immune suppression, spatial structuring, and feeding of community members—and support our key predictions with recent data.

The human microbiome contains hundreds of species and trillions of cells that reside predominantly in the gastrointestinal tract (1, 2). These microbes provide many health benefits, including the breakdown of complex molecules in food, protection from pathogens, and healthy immune development (3–6). The gut microbiome is often noted for its ecological stability. Different people may carry different microbial species, but any one individual tends to carry the same key set of species for long periods (6–8). This stability is considered critical for host health and well-being, because it ensures that beneficial symbionts and their associated functions are maintained over time (9–12). Correspondingly, major shifts in microbial community composition are often associated with ill health (4, 13).

Research into gut communities has been characterized by a large volume of empirical work. Nevertheless, we are far from a clear understanding of microbiome communities and, in particular, what promotes or disrupts their stability. There is a pressing need for complementary theory to identify overarching principles and patterns for the microbiome. Some progress has been made through the use of individual-based models (14) and other analyses of two-species communities (15). However, the microbiome contains many diverse species interacting with one another (16), which makes the full system complex and challenging to understand. The field of theoretical ecology has a long history of using network models that are specifically intended to deal with large and complex communities (17, 18). Here we develop ecological network theory to identify the general principles underlying microbiome stability. We then use these principles to identify and analyze candidate mechanisms that a host can use to promote stability in its microbiome. Finally, we show that our key predictions are supported by recent data from the mammalian microbiome.

Seminal work by May suggests that species diversity can be problematic for community stability (17, 19). However, May's work focused on networks where the types of interactions between species are randomly distributed, meaning that +/+ (cooperation) and –/– (competition) interactions occur with half the probability of +/– (exploitation) interactions. Also, whereas ecological competition is thought to be prevalent in natural microbial communities (20), it is commonly assumed that the functioning of microbiome communities rests upon species that engage in cooperative metabolism (+/+)

and provide health benefits for the host (3, 21–24). There is a clear rationale for this assumption. Competition between microbes—captured by the number and magnitude of mutually negative interactions in our models—is associated with both antibiotic warfare (25, 26) and a reduction in the cooperative secretions that promote community productivity (27). Both have the potential to severely reduce the efficiency of any cooperative metabolism that benefits the host (3, 21–24, 28). However, although intuitive, this argument neglects the potential effects of cooperation or competition on the ecological stability of microbiome communities.

To understand ecological stability in the microbiome, therefore, we must consider the specific effects of cooperation and how cooperation interacts with other community characteristics, such as microbiome diversity, to influence community dynamics. To do this, we have developed a dedicated body of theory based on Wigner's semicircle law and subsequent analyses (18, 29, 30). First, we derive a general analytic stability criterion that captures all potential community types, covering the full range of possible interactions and species diversities [Fig. 1 and supplementary method 1 (31)]. We develop our theory for unstructured ecological networks because, unlike in plant-pollinator communities or food webs (32, 33), there is no evidence of strong structuring within microbial communities (16). However, although no single structure type dominates in these communities, our mathematics
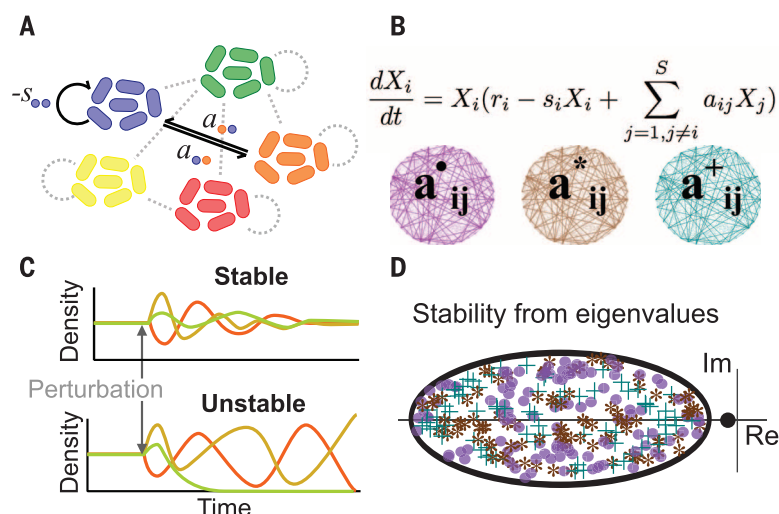

Fig. 1. Ecological theory and microbiota stability. (**A**) Ecological network theory captures networks of microbial species that interact with themselves (−s) and other genotypes (a_{ij}). (**B**) Coupled ordinary differential equations capture all possible combinations of connectivity, interaction types (e.g., cooperation, competition, exploitation), and species numbers (S) covering any biologically feasible equilibrium microbiota. X_i, density of species i; r_i, growth rate of species i; t, time. Three sample networks are shown. (**C**) Communities that return to their previous densities after perturbation are classified as stable, those that return to their equilibrium faster are categorized as more stable, and those that continue to diverge from the equilibrium are considered unstable (17, 18). (**D**) Linear stability analysis uses the eigenvalues' real (Re) and imaginary (Im) parts, shown plotted here. The largest real part of the eigenvalues underlying a community determines whether, and how fast, the community will return after perturbation. If this quantity is negative, the community is stable; more negative values indicate that the community returns to stability more quickly. The imaginary parts of the eigenvalues predict the extent of oscillations in species densities during a return to equilibrium: Larger imaginary components predict more frequent oscillations. Eigenvalues are shown for the three sample communities from (B) (purple, brown, green), and our analytic bound for their localization (black ellipse). Our analysis also derives one special eigenvalue location that, for some parameters, will lie outside of the ellipse (black dot).

The equation shown in panel B:

$$\frac{dX_i}{dt} = X_i\left(r_i - s_i X_i + \sum_{j=1, j \neq i}^{S} a_{ij} X_j\right)$$

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concurrently analyzes all network arrangements and therefore naturally capture biologically critical network motifs, including chains of cross-feeding metabolic exchanges between species (34). Furthermore, unstructured networks are amenable to comprehensive mathematical analysis, which means we can simultaneously analyze the ecological stability of all possible network permutations as a function of our focal parameters. Specifically, we can account for any variation in the proportion of cooperation (+/+), competition (−/−), exploitation (+/−), commensalism (+/0), and amensalism (−/0) in networks with any combination of connectivity, C, and species number, S [method 1 (31)]. Stability is assessed from the network's eigenvalues, which give three measures of stability: (i) the probability that the community will return to its previous state after a small perturbation, (ii) the population dynamics during this return, and (iii) how long the return will take, which is a form of resilience (35) (Fig. 1).

We first show that May's (17) destabilizing effect of species diversity still holds in communities with any mixture of interaction types. From purely cooperative networks to mixed-interaction networks to purely competitive networks (fig. S1), our model predicts that high species diversity leads to unstable microbiome communities. How though does altering the level of cooperation between species affect microbiome stability? We find that gradually increasing only the proportion of cooperative interactions within communities nearly always decreases the overall return rate and the likelihood of stability [Fig. 2 and

method 1b (31)]. We confirm our analytic results with numerical analyses [Fig. 2B, figs. S3 to S6, and method 1f (31)]. These results contrast with a recent analysis of macroscopic communities, which predicts that ecological stability can be maximized for an intermediate frequency of cooperative interactions (32). In the supplementary materials, we show that our analytical model recapitulates these numerical simulations and that the predictions rest on assumptions that suit macroscopic communities but not the microbiome [method 1g (31)] and figs. S4 to S9] (32, 36).

This method, known as local stability analysis, has the benefits of being both extremely general and able to analyze communities with large numbers of species. However, this approach is only able to analyze whether viable communities are stable when they are close to their equilibrium (37); it provides no information on how communities behave away from this equilibrium. We therefore also develop a second new analysis, based on a different method known as permanence analysis (38) [method 2 (31)]. Permanence analysis is considered one of the most rigorous methods of community analysis, but the numerical analysis of permanence was, until now, limited solely to purely competitive or exploitative communities. Therefore, we expand traditional permanence methods here to study the effects of cooperation. Although this method is very different from local stability analysis, we find the same prediction that cooperation is destabilizing. However, as discussed in the supplementary materials, positive feedbacks arising

from cooperative interactions can still constrain this analysis such that it may underestimate the number of permanent communities. Consequently, we also develop a third method—an individual-based model—to evaluate the relationship between cooperation and ecological stability in a microbial community [method 3 (31)]. Although it is less general than the other methods, our individual-based model is more explicit. It allows us to follow the dynamics of each species over time and to examine additional factors, including explicit spatial structure that puts an upper limit on the community size. This third method again confirms our finding that cooperation is destabilizing for the community (Fig. 2E).

The reason for the destabilizing effect of cooperation in our models is that cooperation causes coupling between species and positive feedbacks. This means that if, for example, one species decreases in abundance, it will tend to pull others down with it and destabilize the system. It has been hypothesized that cooperative and productive microbial communities are the reason for the marked stability of the microbiome (23). However, even though cooperation means that one species is helping another to survive and replicate, and thus might facilitate colonization, this does not equate to stability, because cooperation can create dependency and the potential for mutual downfall. Under these circumstances, therefore, our analyses suggest that the host faces a trade-off: Though increased cooperation within communities is expected to promote overall metabolic efficiency (3, 24, 25, 27), it comes at the cost of decreasing ecological stability.
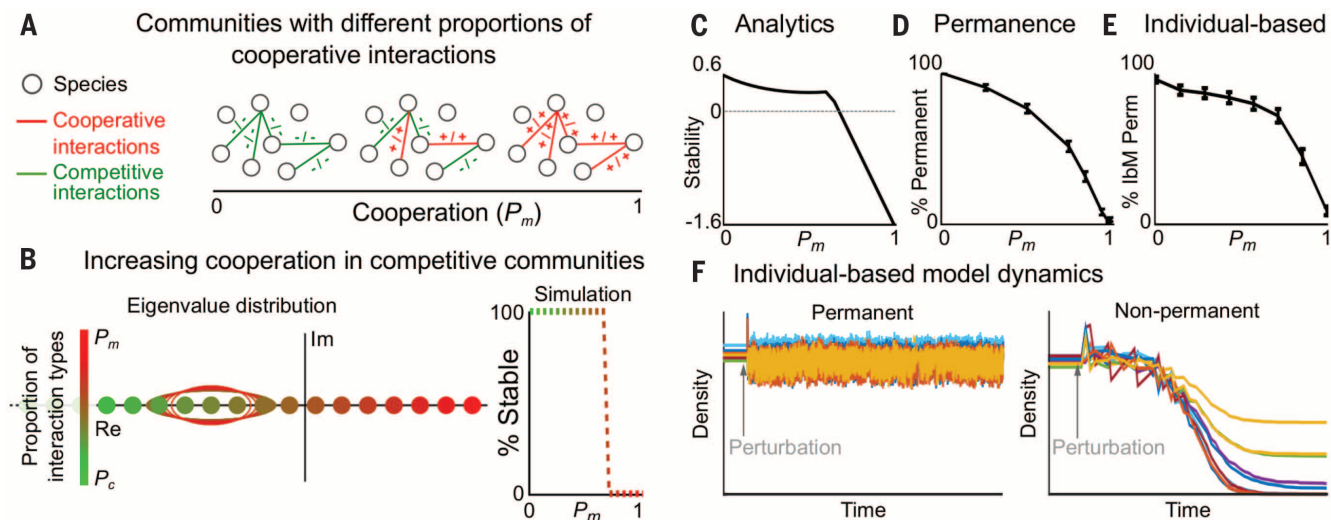

Fig. 2. Cooperation reduces community stability. (**A**) Illustration of changing the proportion of cooperative links in networks. P_m, proportion of cooperative interactions. (**B**) Linear stability analysis (also see fig. S2). The plot at left shows solutions for eigenvalue locations as a function of increasing cooperation (shown as increasing redness). The largest value of the real components (x axis) determines whether, and how fast, a return to equilibrium occurs (stability), whereas the imaginary components (y axis) determine the frequency of oscillations in population densities after perturbations (see Fig. 1). The solutions give the position of all eigenvalues in the form of an ellipse, with the exception of a single eigenvalue that corresponds to the average row sum of the interaction matrix (represented by a dot that may lie outside of the ellipse). Increasing cooperation increases the largest eigenvalues; therefore, stability decreases. Solutions hold for any permutation of a community network with a given parameter set [here $S = 100$, $C = 0.7$, $−s = −1$,

standard deviation $\sigma = 0.05$; see method 1b (31) for parameter sweeps showing that cooperation is nearly always destabilizing]. P_c, proportion of competitive interactions. Simulation results are plotted at right. This graph shows the proportion of communities that are stable and confirms our analytic results. (**C** to **E**) The effect of cooperation on community stability, shown with linear stability analysis [(C), also shown in (B)], permanence analysis (D), and individual-based modeling (E). The latter two methods are computationally expensive, which requires us to analyze smaller networks than those studied with linear stability analysis (31). Parameters shown here: $S = 10$, $C = 0.7$, $−s = −0.2$, $\sigma = 0.05$ for 100 samples. Error bars indicate SEM. (**F**) Dynamics of the individual-based model. Permanent communities maintain all of their original species after a perturbation, even if species densities do not return to their initial values. In nonpermanent communities, perturbations to species densities will lead to the extinction of some or all species.

Our model predicts that ecological competition improves microbiome stability. However, a notable feature of the mammalian microbiome is species diversity, and we have seen that high species numbers tend to be destabilizing (fig. S1). Therefore, we investigated how the stabilizing effects of ecological competition interact with the destabilizing effects of increasing diversity. Specifically, we explored whether a diverse and competitive community leads to a stable microbiome. We again turned to local stability analysis, as this method can deal with communities containing many species [Fig. 3A and method 1 (31)]. Although increasing species numbers is a destabilizing process (fig. S1), the concurrent increase in competition introduces negative-feedback loops that have a stabilizing effect. We find a wide range of diversities for which this stabilizing effect dominates the destabilizing effect of increased species numbers (Fig. 3, B and C, and fig. S10). Even though competition may drive inefficiencies, it dampens the destabilizing effects of cooperation that can lead to the loss of community members (Fig. 2F). The key is that the new interactions from the introduction of additional species are competitive (or exploitative) (fig. S11). The additional species need not be other bacteria; phages in microbial communities (39) have the potential for effects comparable to those of the exploitative species in our model (fig. S11) (40).

Our analyses allow us to identify key principles (41) that are important for a stable microbiome

community. In particular, the stabilizing effect of competition reflects the more general principle that dampening of positive-feedback loops promotes stability. Can we use such principles to better understand host biology and, more specifically, how a host should interact with its symbionts? To answer this, we develop a further set of analyses dedicated to clarifying how key features of host biology influence ecological stability. A clear candidate for promoting stability in the gut is the immune system. During dysbiosis and infection, adaptive immunity is thought to help reestablish a healthy microbiome by suppressing species whose abundance is causing harm (3–5, 23). We can add such density-dependent regulation to our model and find that it is indeed stabilizing. Moreover, the reason this occurs is because immune regulation, like competition, will prevent run-away positive-feedback loops [method 1d (31)].

Dampening positive feedbacks is an important route to stability. A second key principle affecting stability in our models is the strength of interactions between species. Processes that weaken interactions between species will generally promote stability, as these processes reduce the coupling that drives instability. Redundancy can promote stability when a few strong cooperative interactions are replaced by several weaker ones [method 1e (31) and fig. S13]. But a key candidate mechanism by which a host can actively weaken ecological interactions is through the introduction of spatial struc-

ture (27, 42). In particular, introducing spatial structure (e.g., patchy growth with limited mixing) (fig. S14) between species is known to reduce the strength of between-species interactions without reducing interactions within a species (42). Implementing this effect in our models greatly improves the potential for community stability (Fig. 4). We predict, therefore, that a host can benefit from compartmentalizing species within gut communities to control interactions and limit the risk of extinctions.

Another candidate mechanism to influence microbial interactions is host epithelial feeding. Nutrients are provided for symbionts from the epithelial surface, especially during starvation periods, when lumen nutrient concentrations are less abundant (43). Recent work has shown that knockout mice lacking the ability to feed the microbiota with fucose show a significantly decreased community diversity (44). There is also the potential for some specificity in host feeding that occurs through fucose residues whose digestion relies on specific enzymes (43, 45, 46). In the context of our models, feeding is expected to promote the stability of communities, provided that such feeding can preferentially weaken interactions between cooperating species by, for example, providing an alternative carbon source to that involved in microbial cross-feeding (Fig. 4B and fig. S12).

So far we have studied communities that are intrinsically limited by their own interactions. Feeding has the potential to alter this by causing populations to grow until they are extrinsically limited by the capacity of the host. Though high symbiont population sizes might harm a host for reasons unrelated to stability (47), we can nevertheless use our individual-based model to examine the effect of this scenario on ecological stability. Specifically, we ask what happens if feeding, or any process that drives high intrinsic growth rates, causes communities to expand until they become extrinsically limited by the capacity of the host environment. We find that such communities are stable to further perturbations (Fig. 4C), even those that start with many cooperative interactions. Therefore, the possession of strongly growing communities that are extrinsically regulated by the host is another potential route to ecological stability. However, after expansion, these communities are much less cooperative, because the increase in population densities means that species are now competing for the limited capacity of the host (Fig. 4C). Once again, we find that ecological stability is associated with competition.

Although the stability and composition of gut microbial communities are considered central to the benefits they provide to a host (9–12), we lack a clear understanding of what underlies the stability of microbiome communities. Here we have developed a body of theory to identify key principles underlying microbiome stability. We have also shown how these principles allow us to reinterpret and predict key features of host biology, including immune suppression, the potential for spatial structuring, and host feeding of microbes. Can we use existing data to test whether the principles we have identified are indeed at work in real communities? Currently, few data are available on

Fig. 3. Introduction of species can stabilize a network of cooperators.
(**A**) Illustration of increasing species number and competition (green) in a network that originally contained only cooperating species (red). (**B**) Eigenvalue distribution changes after the addition of competitor species to 100 cooperating species ($C = 0.7$, $-s = -1.75$, $\sigma = 0.05$). As in Figs. 1 and 2, the eigenvalues are contained within ellipses, except for one eigenvalue that may lie outside of the ellipse. Crucially, this latter eigenvalue is reduced when we add competitive species (i.e., the dot moves left), which results in a stabilizing effect. However, the ellipse containing all other eigenvalues becomes wider with additional species, leading to a reduction in stability once the ellipse contains the rightmost eigenvalue (i.e., once the dot moves inside the ellipse).

A Adding competitors to a cooperator network

○ Species
— Cooperative interactions
— Competitive interactions

Competing species

B Eigenvalue distributions

Competing species: 0   75   250   1250

C

unstable   stable   unstable

(**C**) Ecological stability as a function of the number of added competing species (solid black line). Competitors are initially stabilizing because they reduce the proportion of cooperative interactions (P_m, blue line). Eventually, however, adding competitors begins to have a destabilizing effect, which corresponds to the widening of the ellipse in (B). This behavior holds for a wide range of self-regulation strengths ($-s$, dotted black lines). Note that we do not apply permanence analysis or the individual-based model here, as these analyses are limited to low species diversities (31).
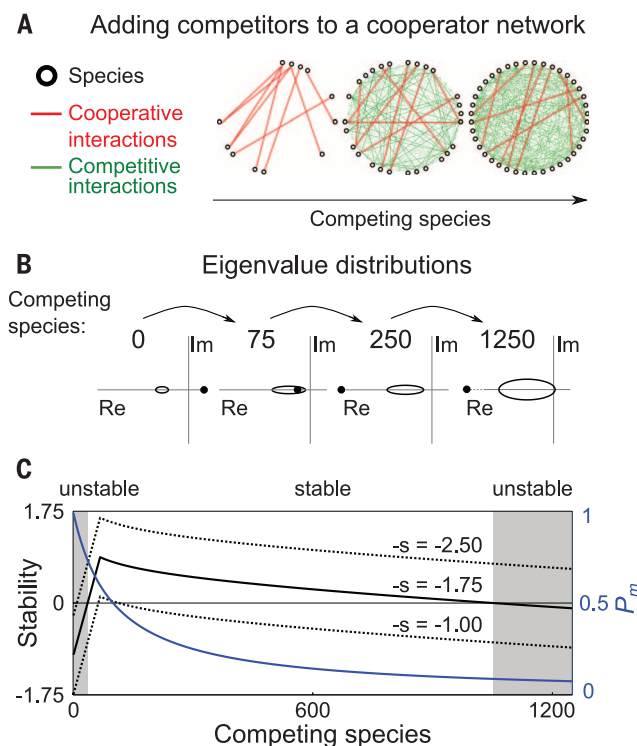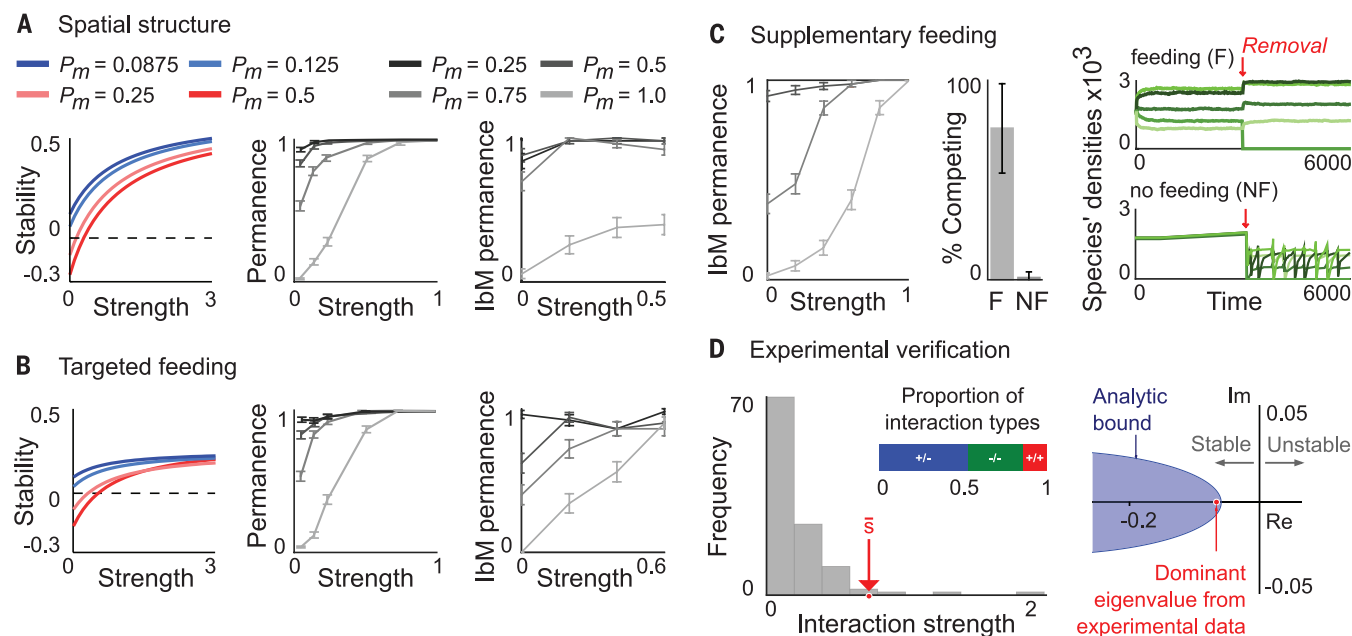
Fig. 4. Host strategies to promote ecological stability. (**A**) Spatial structure promotes ecological stability in linear stability analysis (LAS) (left), permanence analysis (PA) (middle), and an individual-based model (IbM) (right). (**B**) Targeted feeding. Host-supplied nutrients that weaken cooperative interactions promote ecological stability. We observed an exception for which targeted feeding may destabilize more competitive communities in the IbM ($P_m = 0.25$), but the effect is weak. (**C**) Nontargeted feeding may stabilize communities when it increases the growth rates of all species such that they become limited by the host's capacity (left). However, limited space means that most previously cooperative species become competitors. Competition is demonstrated by removing one species from a community and observing increased densities for most remaining species (middle) ($P_m = 0.9$). F, feeding; NF, no feeding. IbM time-series plots show that feeding can stabilize communities upon species removal (right). (**D**) (Left) Empirical interaction parameters (mouse microbiome communities) (16) confirm our predictions: Most interactions are weak (less than self-interaction, s) and predominantly competitive or exploitative, with a small set of cooperative interactions [experimental validation in (31)]. (Right) Our general analytical model predicts stability in a real community, using community parameters from the mouse data set (S, C, P_m, P_c, σ, s). In (A) to (C), LAS: $S = 300$, $C = 0.7$, $-s = -1$, $\sigma = 0.05$; PA and IbM: $S = 10$, $-s = -0.2$; error bars indicate SEM. PA and IbM are computationally expensive and require smaller communities.

ecological interactions within the microbiome. Nevertheless, we can validate our approach and test our key predictions with recently published data on interactions in the mouse gut microbiome (16). Stein et al. used time-resolved metagenomics and machine learning to infer the interactions within communities. In Fig. 4D, we use these data to parameterize our general model and show that it correctly predicts stability within a real community. In addition, we plot the distribution of ecological interactions within the mouse microbiome. As we predicted, ecological interactions tend to be both noncooperative and weak [Fig. 4D and method 4 (31)].

In conclusion, microbiome communities consist of many interacting species, making it difficult for a host to exercise control over each species individually. However, our work emphasizes that hosts can act as ecosystem engineers that manipulate general, system-wide properties of their microbial communities to their benefit. Identifying when and how hosts alter their symbionts' ecology will be important if we are to comprehend the dynamics of microbiome communities. More generally, although there is a vast and rapidly growing body of data on the mammalian microbiome, little attention has been paid to the strength or sign of ecological interactions. To understand and manipulate the microbiome, we will need to dissect and engineer the interactions within these critical communities.

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Science

The ecology of the microbiome: Networks, competition, and stability

Katharine Z. Coyte, Jonas Schluter and Kevin R. Foster

What makes the gut microbiome stable?

Classically, we think of our microbiome as stable, benign, and cooperative. Recent experimental work is beginning to unpick essential functions that can be attributed to the stable microbiota of humans. To be able to manipulate the microbiome to improve health, we need to understand community structure and composition and we need models to quantify and predict stability. Coyte *et al.* applied concepts and tools from community ecology to gut microbiome assembly. Independently developed models converged on a surprising answer: A high diversity of species is likely to coexist stably when the system is dominated by competitive, rather than cooperative, interactions.
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