Microbial community structure predicted by the stable marriage problem

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Experimental studies of microbial communities routinely reveal several stable states. While each of these states is generally resilient, exposure to antibiotics, probiotics, or different diets often trigger transitions to other states. Can we predict which specific perturbations will cause such transitions? Here we present a new conceptual model — inspired by the stable marriage problem — which both exhibits these emergent phenomena and makes such predictions. Our model's core ingredient is that microbes utilize nutrients one at a time, while competing with each other. Using only two ranked tables with microbes' nutrient preferences and competitive abilities, we can determine all the stable states as well as the specific perturbations driving a community from one state to another. Using an example of 7 *Bacteroides* species utilizing 9 polysaccharides common to the human gut, we predict that mutual complementarity in nutrient preferences enables these species to coexist at high abundances.

Introduction

One of the major goals of microbiome research is to achieve a mechanistic understanding of the structure, function, and dynamics of microbial communities [1, 2]. The recent rapid proliferation of metagenomics and other -omics data has promoted correlation-based, large-scale statistical analyses of these ecosystems [3]. One common property revealed by these studies is that communities can often exist in multiple or alternative stable states, distinguished from each other by differences in the abundance profiles of surviving species. Examples of this include the human gut microbiome [4, 5], bioreactors [6], and soil communities [7]. Moreover, external perturbations — such as the temporary introduction (or removal) of nutrients (or microbes) — often trigger transitions between these stable states. This is often the basis for the effect of prebiotics and probiotics on the gut microbiome [8, 9] and disturbances in bioreactors or other engineered environments [10]. Our ability to predict and manipulate both these stable states as well as the aforementioned transitions however, remains limited. Developing a deeper conceptual understanding of community structure, we believe, is an important step towards such an endeavor.

Ever since pioneering theoretical work by MacArthur and Tilman [11, 12], resource competition has been a promising approach to modeling stable states in microbial communities. Following Ref. [11], contemporary models of microbial communities typically assume that microbes simultaneously co-utilize several substitutable nutrients as sources of carbon and energy [13, 14, 15, 16, 17, 18]. However, as first described by Monod [19], many microbes tend to utilize these nutrients in a specific sequential order. When exposed to a mixed medium containing

multiple nutrients, microbes begin to grow by first utilizing their most preferred one. Upon the exhaustion of this nutrient, and after a period of stasis known as the lag phase, they undergo a diauxic shift and resume growth using the next available nutrient down in their hierarchy [19]. This continues until all consumable nutrients in the medium that the microbe could grow on are exhausted.

Recent work by Martens and collaborators [20, 21, 22] has established that many species in *Bacteroides* (the most prevalent genus in the human gut microbiome [23, 24]) exhibit this kind of preferential nutrient utilization — with respect to polysaccharides present in a typical diet [25]. Interestingly, even species such as *B. ovatus* and *B. thetaiotaomicron* — which are closely-related evolutionarily — display rather dissimilar polysaccharide preference hierarchies [20]. In addition, many of these *Bacteroides* species are simultaneously present in the gut at high abundances. This is in spite of their similar nutrient utilization capabilities [21, 26] that should have promoted competition and mutual exclusion [27]. This apparent 'habitat filtering' — where potential metabolic competitors are frequently detected together — remains a puzzling observation.

Describing community dynamics where microbes utilize nutrients one at a time can be approached either via mechanistic or conceptual models. To develop mechanistic models however, the main obstacle is that they rely on the knowledge of a large number of quantitative parameters, e.g. growth curves of individual microbes, kinetic rates of adsorption and release of small molecules, etc. The vast majority of these parameters are hard to measure and are currently unknown. Instead, here we propose and study a conceptual model that depends on a much more coarse-grained description of interactions between microbes and nutrients. This approach can help to bridge the gap between statistical analyses based on metagenomic data and a detailed predictive description of community dynamics.

Model

Our model is inspired by a decades-old economics work: the stable marriage or stable allocation problem, developed by Gale and Shapley in the 1960s [28] and awarded the Nobel prize in economics in 2012 (see Box 1). In our application of this problem to microbial communities, a set of 'marriages' constitutes a one-to-one pairing between microbial species and substitutable nutrients. Consider a set of microbes capable of utilizing the same set of fully substitutable nutrients (e.g. carbon/energy sources). A more general case when each microbe could utilize only a subset of all available nutrients (incomplete ranked lists in Box 1) is introduced later on in our study. The central assumption in our model is that every microbe consumes these nutrients one-by-one in a diauxic (or more generally polyauxic) fashion. The order in which nutrients are utilized is encoded in microbe's transcriptional regulatory network combined with diverse post-transcriptional mechanisms of catabolite repression [29, 30]. Detailed kinetic modeling of catabolite repression in even one organism (*E. coli*) is rather complicated and involves up to 63 state variables connected up to 473 kinetic parameters, *most* of which are not known experimentally [31]. The advantage of the SMP-based approach is that it depends only on the ranked microbial preferences towards nutrients, thus bypassing precise measurements of such kinetic parameters. These ranked preferences ranging from 1 (the most preferred nutrient, such as glucose for *E. coli*) to N (the least preferred one) are illustrated in figure 1(A) and may be different even between closely related microbial species [20].

If two or more microbes attempt to simultaneously consume the same nutrient, we refer to this event as competition, whose outcome is determined by the relative competitive abilities of the respective microbes. In our model, the competitive ability of a microbe on a given nutrient

is in direct proportion to the rate at which it uptakes this nutrient from the medium. Thus the microbe with the largest uptake rate would drive that nutrient to the lowest extracellular concentration, thereby preventing other microbes from growing on it [12]. The SMP approach requires only the knowledge of a ranked table of microbial competitive abilities ranging from 1 (the most competitive microbe for a particular nutrient) to M (the least competitive out of M microbes) (see figure 1(B) for an illustration). Competitive abilities of microbes may in general be different for different nutrients.

The final outcome of a competition of microbes for nutrients e.g. in a constantly diluted chemostat is a stable state in which no microbe can switch to a more preferred nutrient *and simultaneously* win the competition with another microbe that is currently utilizing it. The microbial ecosystem will persist in this stable state until it is externally perturbed (e.g. by removal or addition of either microbes or nutrients). Note that our definition of a stable state corresponds exactly to that in the original formulation of the stable marriage problem (see Box 1).

Inspired by the classical diauxic (or polyauxic) growth experiments [19] we assume that microbes are constantly scouting the environment for more preferred nutrients. However, the diauxic shift down to the next nutrient requires the currently consumed (more preferred) nutrient to either be completely exhausted or at least to fall below a certain concentration threshold. In what follows, we ignore the kinetics of this switching behavior including the lag phase. The natural microbial ecosystems relevant to our model may have rather complex dynamical behaviors including long transients, oscillations, and even chaos [32, 33, 34, 35]. However, these lie beyond the scope of the SMP-based approach.

Microbial preferences towards nutrients typically follow the order of maximal growth rates reached when they are present in a high concentration [36]. Using this as a general rule of thumb, we assume that a microbial species' stable-state abundance systematically decreases as it shifts down its nutrient preference list. The exact procedure by which we assign abundances to species in a stable state is described in Materials and methods: Studying complementarity through different ranked interaction tables.

Note that in addition to pairwise interactions (relative competitive abilities of any two species on each of the nutrients), our model captures higher-order interactions as well. These interactions are implicitly encoded in the two ranked interaction tables. As we show later, the outcome of the competition between any two species may be rather different depending on the presence or absence of other species. Thus higher-order interactions between species is the emergent property of the SMP model that does not require additional parameters or kinetic coefficients.
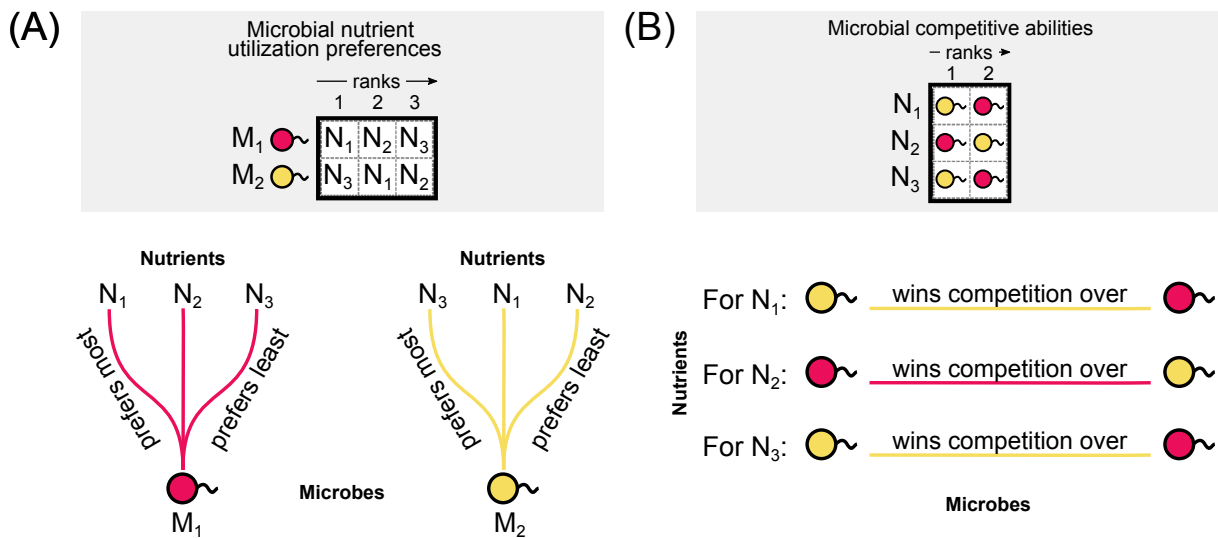
Figure 1: Ranked interaction tables encode microbes' nutrient preferences and competitive abilities.

Two ranked tables with each microbe's preferences towards nutrients (panel A) and their competitive abilities with respect to each particular nutrient (panel B) fully define our model. We illustrate them using 2 microbial species, M_1 and M_2, represented correspondingly by red and yellow circles, and 3 nutrients, N_1, N_2 and N_3. Both species can use all three nutrients. **(A)** Microbial nutrient preferences: the red species prefers nutrient N_1 the most (rank 1 in the table above), N_2 next (rank 2), and N_3 the least (rank 3), while the yellow species prefers nutrients in the order: $N_3 > N_1 > N_2$. **(B)** Microbial competitive abilities: the red species (rank 1) can displace the yellow species (rank 2) in a competition for utilizing the nutrient N_2, but will be displaced by the yellow species when competing for nutrients N_1 and N_3.

Box 1: The Stable Marriage Problem and Gale-Shapley Algorithm

The traditional formulation of the Stable Marriage Problem (SMP) is the following: N men and N women have to be matched pairwise in N 'marriages'. Every person has associated with them a preference list of all members of the opposite sex, ranked from their most preferred marriage partner (rank 1) to their least preferred one (rank N). A matching is 'stable' if it has no 'blocking pairs', i.e. it has no man-woman pair (who are not currently married to each other) who would both prefer each other to their current marriage partners. One can show that stability with respect to blocking pairs is sufficient to ensure stability with respect to a coalition of any size.
Gale and Shapley proved [28] that there is always at least one such stable matching a constructive 'men-proposing' algorithm to find it. According to this algorithm every men first proposes to his top choice partner. If a woman receives more than one proposal, she temporarily accepts the most suited partner according to her preference list and rejects the others. Men rejected during the first round propose to their second choice and so on. If a woman later on receives a proposal that is better than her current partner, she accepts it and releases her previous choice. One can prove that the state achieved at the end of this men-proposing procedure is stable [37]. In general there are many different stable states for a given set of preference lists (around $N\log N$ for random lists but occasionally exponentially many more). One can prove that in the stable state obtained by the Gale-Shapley men-proposing algorithm, every man gets the best partner he can hope to have in a stable state, while every woman gets the worst partner among all stable states. A symmetric women-proposing algorithm results in a (generally different) stable state in which gender satisfaction patterns are reversed. Later work [37] provided a simple algorithm allowing one to find all stable states of a given set of marriage partners. Here one starts with a stable matching (e.g. a men-optimal one) and breaks up one married pair. A man in a broken married pair continues to go down his preference list of women potentially breaking other marriages. If at some point a women from the initially broken pair receives a proposal from a man she prefers to her 'estranged' husband, she accepts it. One can prove that the resulting matching is stable. Furthermore, it is obvious that every man in it is worse-off (or the same), while every woman is better-off (or the same) as in the original matching. This sets a partial hierarchy among all stable states in the problem. Furthermore, this procedure can be used to find which married pair can be broken in order to induce a transition to another specific stable state.
When the set of men and women have unequal sizes, the number of pairs in any matching is given by the size of the smaller set. Furthermore, in all stable states, the partners left without spouses are always the same [37]. Another version of the problem is one with unacceptable partners (partial lists). In this case, one can show that the number of pairs in a stable matching is generally smaller than the number of men and women. As in the previous case, the same set of partners are left without spouses in every stable state [37].
The stable marriage problem still remains a field of active mathematical research. In particular, some of the recent work addresses various aspects and extensions of the original problem, such as the notion of 'universal beauty' [38], truncations and correlations in preference lists [39], scaling behaviors [40], three-dimensional preferences and agents [41] and versions with ties and incomplete lists [42].

Results

Community restructuring following external perturbations

We first consider a simple case in which two microbial species (M_1: red and M_2: yellow in figure 2) utilize two nutrients (N_1 and N_2). The preferences of microbes for these nutrients are complementary to each other: M_1 prefers N_1 to N_2, while M_2 prefers N_2 to N_1. The competitive abilities of microbes are opposite to their preferences. As shown in figure 2 M_2 wins over M_1 in a competition for N_1, while M_1 wins over M_2 in a competition for N_2. There are two possible states of this ecosystem characterized by nutrients: the state A (see figure 2), where M_1 is consuming N_1 while M_2 is consuming N_2, and the state B, where M_1 is consuming N_2, while M_2 is consuming N_1. One can easily check that both states are stable in the SMP sense. That is to say, no microbe could switch to a nutrient it prefers more than the one it currently utilizes and simultaneously win the battle with another microbe which is its current consumer. The state A is the one obtained by the "microbe-proposing" algorithm. It naturally emerges whenever the current set of microbes is introduced to the system when all nutrients are supplied at a high influx. In this case, microbes following the sequence of diauxic shifts end up in this state and remain there until perturbed by addition of other microbes or nutrients, or (possibly transient) removal of the existing ones. Thus stable states in our model satisfy the criteria for alternative states of an ecosystem proposed in Ref. [43].

In what follows we investigate the stability of stable states in our model with respect to two types of perturbation: the introduction of a probiotic (another microbe M_3 shown in purple in figure 2(A)) and a prebiotic (a transient nutrient N_3 in figure 2(B)).

In the case of the probiotic, the community starts at the state A - a natural endpoint of diauxic shifts. A new microbe M_3 (probiotic) is introduced to the community and initially displaces M_2 in the competition for its preferred nutrient, N_2. As a result, M_2 switches over to its next preferred nutrient (N_1) and outcompetes M_1, which was consuming it. M_1 now also switches to its second preferred nutrient N_2 and competitively displaces the 'invader' M_3. M_3 switches to its second nutrient N_1 but loses the competition with M_2 and ultimately disappears from the system. Thus, in spite of its temporary success, the microbe M_3 fails to establish itself in the community. Note, however, that the result of its transient residence was a restructuring of the community from one stable state (A) to another (B). While the initial state A was 'microbe-optimal' (i.e. both microbes consumed their most preferred nutrients in any of the stable states), the transient competitive interactions due to a new microbe pushed the community to a less microbe-optimal stable state, B.

In the other illustrative case the community starts in the stable state B, driven there e.g. by consumption of a probiotic microbe (figure 2(A)). A new nutrient N_3 (prebiotic) is transiently added to the diet. The microbe M_2 prefers N_3 to its currently consumed nutrient (N_1) and switches to consume it. The N_1 is now available without competition, so microbe M_1 switches to use it as it stands higher than its currently consumed nutrient (N_2) in M_1's preference hierarchy. After some time the prebiotic N_3 is removed from the diet. The microbe M_1 now switches to N_2 (its second preferred choice after N_3). Thus the community undergoes a restructuring again, this time from microbe-pessimal state B to microbe-optimal A.

These examples illustrate the following general rule: the introduction of microbes and nutrients pushes the community structure in two opposite directions. Specifically, invading microbes increase competition for nutrients and generally result in a community restructuring towards a stable state that is less growth-optimal for microbes. Even short-lived introduction of extra nutrients, on the other hand, relieves this competition and restores the community towards
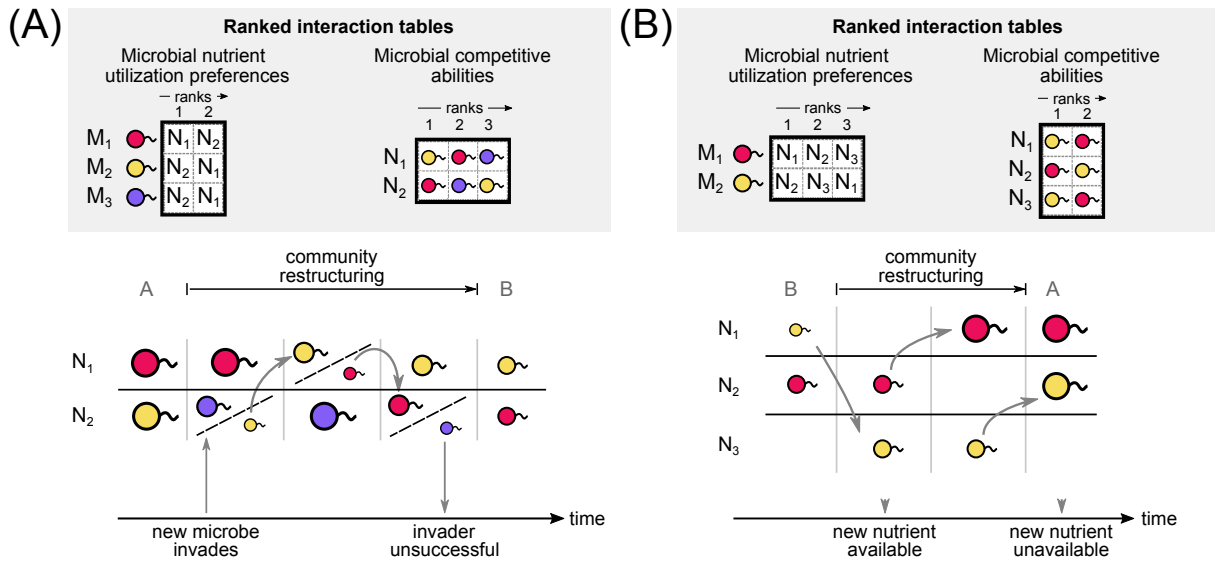
Figure 2: Community restructuring following external perturbations.
Two ranked tables of microbes' nutrient utilization preferences and competitive abilities are shown on top of each panel. Colored circles represent different microbial species M_1, M_2, M_3. The size of each circle corresponds to the rank of a nutrients microbe currently utilizes - bigger sizes correspond to better ranks and thus larger populations. Different nutrients are labeled N_1, N_2, N_3. Oblique dashed lines indicate transient states for microbial competition. **(A)** The introduction of a new probiotic microbe, purple species (M_3), causes red (M_1) and yellow (M_2) species to enter into a competition with the invader. The dynamics of the stable marriage model results in a community restructuring to the state B, such that the red (M_1) and yellow (M_2) species shift their currently utilized nutrients to their second choices. The invading purple species (M_3) fails to establish itself and disappears form the system **(B)** A transient addition of a prebiotic nutrient, N_3, restructures the community from state B back to state A, in which each microbe once again uses its most preferred nutrient.

stable states in which microbes use more preferred nutrients.

Higher-order interactions between microbes enable multiple stable states

In general, the number of stable states increases with the number of microbes and nutrients in the community. In figure 3 we show an example of a community where 7 microbial species compete for 7 distinct nutrients, all of which they can utilize. For a particular set of microbial nutrient preferences and competitive abilities shown as ranked tables in figure 3(A), there are a total of 5 stable states labeled S_1 through S_5.

As understood in the context of the original stable marriage problem [37], the stable states can be arranged hierarchically in the order of decreasing microbe-optimality quantified by the average rank of nutrients consumed by microbes in a particular state. Since rank 1 corresponds to the most preferred nutrient, while rank N corresponds to the least preferred one, lower values for this optimality measure correspond to more microbe-preferred states. The labels of the states $S_1 - S_5$ were arranged in the order of decreasing microbe-optimality , i.e. increasing the average rank of consumed nutrients (see figure 3(B)). Thus the state S_1 is the most optimal for microbes (corresponding to the stable state generated by the 'microbe-proposing' Gale-Shapley algorithm in the SMP (see Box. 1)), while the state S_5 is the least optimal one. The average rank of consumed nutrients in S_1 is equal to 1.7 which means that even in this state, not every microbe gets its most preferred nutrient. This should be compared to its value ~ 2.9 in the state S_5,
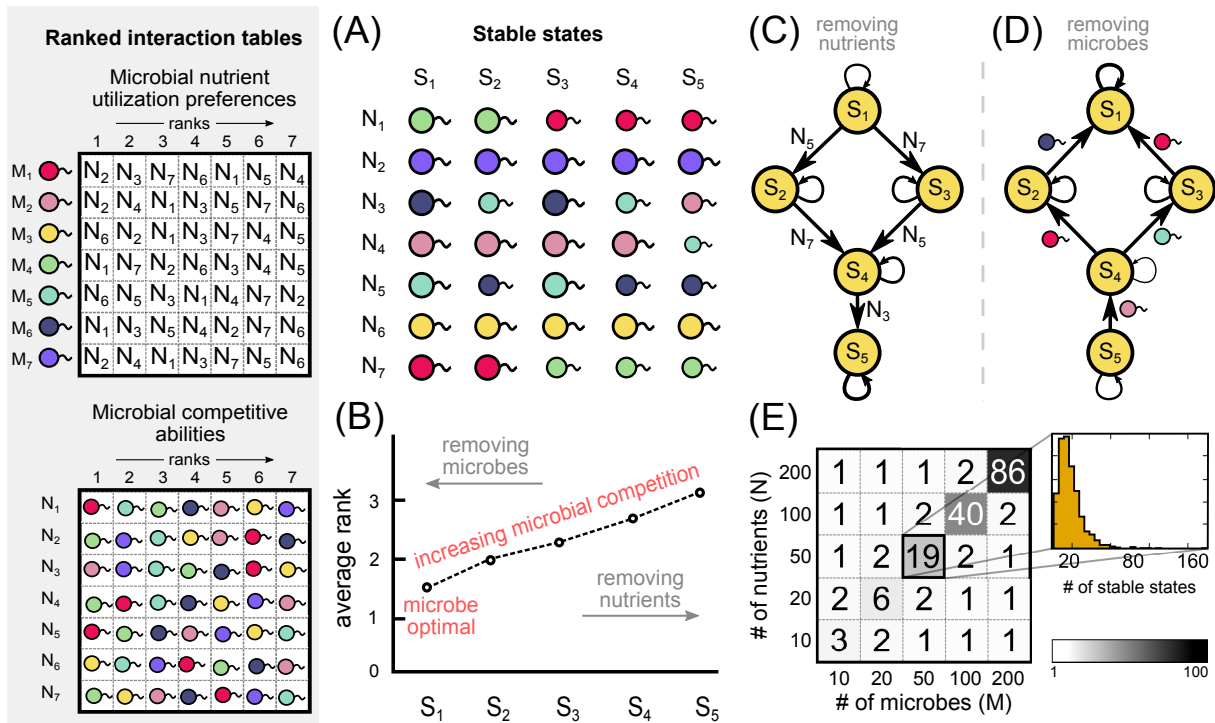
Figure 3: Higher-order interactions between microbes enable multiple steady states. Two ranked tables of microbes' nutrient utilization preferences and competitive abilities are shown on the left. **(A)** The list of all stable states (labeled S_1 through S_5) in the model. In each stable state, every microbe (colored circles with tails; sizes indicative of how preferred the consumed nutrient in a state is) exclusively consumes one nutrient (labeled N_1 through N_7). **(B)** The 'microbe-optimality' of stable states $S_1 - S_5$ (lower is better for microbes) quantified by the rank of the consumed nutrient averaged over all microbes. Microbe-optimality can be improved by transiently removing microbes and deteriorated by transiently removing nutrients. **(C, D)** The stable states are connected via 'restructuring networks'. The community in the model gradually restructures from S_1 towards S_5 by transient nutrient removal (for details, see Results: Higher-order interactions enable multiple stable states) and from S_5 back towards S_1 by transient microbe removal. In this restructuring network, a pair of stable states is connected by a directed link, if the community can transition between these states via transient removal of just one nutrient (removed nutrient and directionality are shown in panel (C)) or of a single microbe (removed microbe and directionality are shown in panel (D)). **(E)** Average number of stable states for communities with different numbers of microbes (M, x-axis) and nutrients (N, y-axis) and randomized interaction tables. (Inset) For $(M, N) = (50, 50)$, we show that the number of steady states (in orange) for 1,000 random interaction tables is Poisson-distributed with mean 19.

where a typical microbe gets its third choice among nutrients.

As discussed in Box 1, the transitions between stable states of the SMP can be realized by transiently breaking a 'marriage', i.e. disrupting a microbe-nutrient pair. As illustrated in figure 3(B), the removal of nutrients from a diet (starvation) generally drives the community further away from the microbe-optimal state (S_1). Indeed, in this case (akin to probiotic case shown in figure 2(A)) microbes need to compete more for the remaining nutrients. Removing a specific subset of microbes (e.g. by antibiotics) has the opposite result: the surviving microbes have fewer competitive interactions for nutrients and hence each one of them would get a better (or same) ranked nutrient according to its preference list. Thus, somewhat counterintuitively, the introduction of antibiotics drives a community towards a microbe-optimal state. As known from the SMP results, the transitions between stable states could be triggered only by the removal of a very specific subset of nutrients or microbes.

These states can thus be arranged in a 'community restructuring network' shown in figure 3(C, D). The transition along a given edge of this network leading further away from the microbe-optimal state could be triggered by a transient removal of a specific single nutrient (figure 3(C)). The transition in the opposite direction (towards a microbe-optimal state) is triggered by the transient removal of a specific single microbial species (see figure 3(D)). Removal of a nutrient leaves the microbe that was utilizing it temporarily without its source of energy. This microbe will then engage in competition with other microbes for the remaining nutrients. This results in a cascade of shifts where microbes begin to utilize less-preferred nutrients, as prescribed by the Gale-Shapley algorithm (see Box 1). If the removed nutrient is reintroduced soon after its removal, the community will return back to its original state, contributing to the community's resilience. In the opposite case, if the nutrient's absence lasts very long, one of the microbial species left without a nutrient will go extinct. However, there is a specific intermediate regime where the nutrient is reintroduced at *just* the right time for its microbial consumer in the new stable state to have recently switched towards it. In this case, such a transient nutrient removal results in a community restructuring from a stable state to another one but less microbe-optimal. A similar restructuring is possible when a microbial species is transiently removed from the community (e.g. by a narrow-spectrum antibiotic) so the nutrient it utilized before the removal is now open for competition from other microbes. If this microbe is reintroduced later at just the right time, the community can restructure towards another stable state which is more microbe-optimal.

These examples (as well as their counterparts in which microbes or nutrients were added to the community as discussed in the previous section and illustrated in figure 2) demonstrate that these stable states are relatively resilient with respect to many transient perturbations. Such resilience is exhibited at two different levels. Firstly, not all perturbations result in community restructuring. Those perturbations that *do* arrange the stable states in a hierarchical 'community restructuring network' shown in figure 3(C). For any two adjacent stable states in this network, there is just one specific nutrient and one specific microbe that can be removed to trigger a transition between them. Transient removal of other nutrients or microbes is shown as self-loops in figure 3(C, D), since these events return the community back to the original stable state. Secondly, even when this carefully selected nutrient or microbe is removed, it must be reintroduced within a specific time interval (not too soon and not too late) to result in a successful restructuring.

The average number of stable states for different combinations of numbers of microbes, M, and nutrients, N, are shown as a grid in figure 3(E). The number of stable states for different (random) realizations of microbe preference lists and competitive abilities for $M = N = 50$ (orange histogram in the inset to figure 3(E)) follows a Poisson distribution (black line in the inset to figure 3(E)).

Complementary prioritization as a mechanism for robust many-species coexistence

The human gut microbiome provides a fertile testing ground for our model. Indeed, as discussed in the introduction, many gut microbes are known to utilize nutrients sequentially. Moreover, recent reports indicate that multiple *Bacteroides* species have been regularly observed at high abundances simultaneously, in spite of a strong overlap in their metabolic capabilities [26]. This overlap is visualized in figure 4(A), where we show a network connecting each of 7 abundant species in the human gut (*Bacteriodes fragilis*, *B. ovatus*, *B.vulgatus*, *B.caccae*, *B.cellulosilyticus*, *B. thetaiotaomicron*, and a recently reclassified member of the *Bacteroidetes* phylum *Parabacteroides distasonis*) with a subset of 9 polysaccharides (starch, mucin, galactan, pectin, arabinogalactan, hemicellulose, cellulose, hyaluronan, chondroitin sulfate) they are capable of utilizing as energy sources (data from [44], see Materials and methods for details). For a sake of brevity in what follows we refer to this set as *Bacteroides* species. What strategies by these microbes would allow their 'robust' co-occurrence in the human gut, i.e. long-term, stable coexistence at high abundances?

The stable marriage problem provides a natural framework in which to look for such strategies. Indeed, by supplementing the utilization network shown in figure 4(A) with a specific set of ranked nutrient preferences and competitive abilities of all participating microbial species, our model can predict which species will survive, how many stable states the corresponding community can be in, and what kind of abundance profiles they will achieve in these states. The latter could be approximated by the inverse of the rank of the consumed nutrient for every surviving microbe in a particular stable state. Indeed, microbes utilizing their preferred (low rank) nutrient are expected to reach high abundances (see Model section for details). It stands to reason that in order to simultaneously achieve high abundances, these species have to successfully partition the set of nutrients among themselves. In the presence of a strong metabolic overlap this requires microbes to have evolved a mutually complementary set of nutrient preferences.

We quantify the complementarity of microbes' top preferences by calculating the number of competing pairs of microbes that have the same most-preferred nutrient. This number can vary between 0 (perfect complementarity; figure 4(B) [top case]), about 6 (for random preferences; figure 4(B) [middle case]) and potentially up to $M(M-1)/2$ (for maximal conflict in these lists; figure 4(B) [bottom case]). This latter case of maximal conflict would occur if all microbes would share the same nutrient as their most-preferred [38]. For the network shown in figure 4(A), there is no such nutrient and the number of competing pairs for maximal conflict is 11 (bottom case in Fig 3(B), has five microbes making 10 pairs competing for pectin, while the remaining 1 pair competes for hemicellulose). Our intuition is confirmed by testing many such preference lists of each of these 3 categories (complementary, random and maximal conflict) and calculating the average microbial abundances in each case (see box plots in figure 4(C)). As expected, the average abundance is the highest in the case of complementarity, lower for random preferences, and lower still for maximal conflict.

Perfect complementary between the top preferences of 7 microbes would require careful orchestration over evolutionary times. However, these choices are encoded in regulation of specific Polysaccharides Utilization Loci (PULs) controlled by microbial transcription regulatory networks and have been shown to be quite flexible [26]. Thus the complementarity of top nutrients choices required for robust coexistence of *Bacteroides* species in the human gut is entirely plausible and, indeed, has been in part reported in Ref. [20].
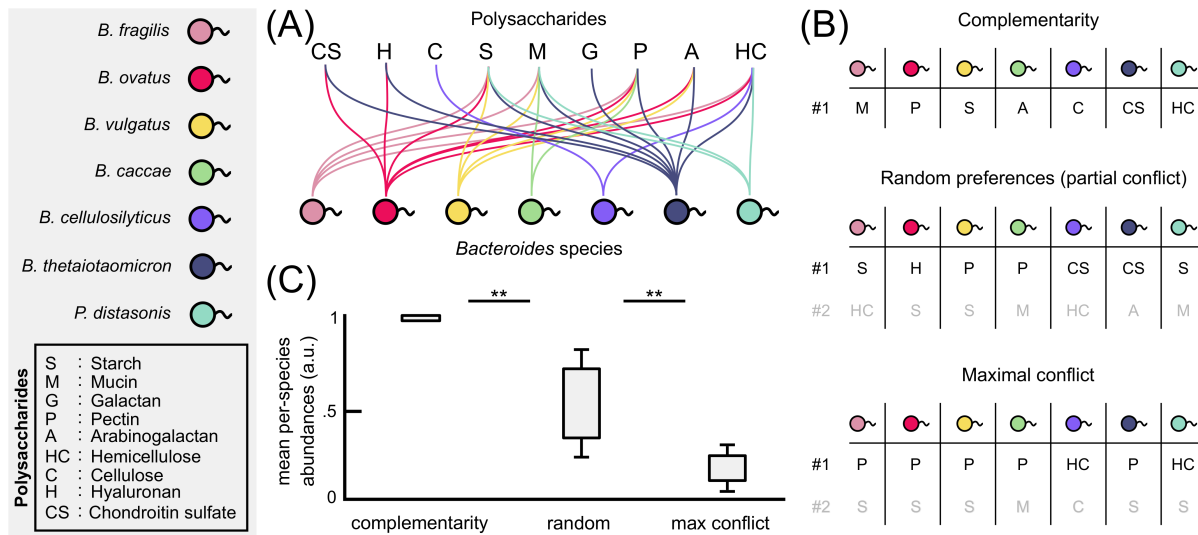
Figure 4: Complementary polysaccharide prioritization allows robust coexistence in gut *Bacteroides* species.
(A) The polysaccharide utilization network of *Bacteroides* species in the human gut (data taken from [44]). The character labels represent 9 different polysaccharides: starch (S), mucin (M), galactan (G), pectin (P), arabinogalactan (A), hemicellulose (HC), cellulose (C), hyaluronan (H), chondroitin sulfate (CS) — known to be frequently present in human diets (legend in the box on the left), whereas the colored circles represent 7 different *Bacteroides* species routinely found in human gut microbiome: *Bacteriodes fragilis*, *B. ovatus*, *B.vulgatus*, *B.caccae*, *B.cellulosilyticus*, *B. thetaiotaomicron*, *Parabacteroides distasonis*. Undirected links between microbes and polysaccharides indicate a species' ability to metabolize that polysaccharide. **(B)** Examples of microbial nutrient preferences (the most preferred nutrient of each of the microbes) are sorted into three categories: complementary (top) where microbes' top preferred nutrients (#1) are all distinct from each other; random (middle) preferences where all ranked lists are randomly generated; and maximal conflict (bottom) which represents the maximum intersection between the sets of top (#1) and second (#2) preferred nutrients of different microbes. **(C)** For 1,000 randomly sampled microbial preferences from each category, we simulated the stable marriage model to compute the expected per species microbial abundances (see Materials and methods: Studying complementarity through different ranked interaction tables) for each case as box plots. The box plots quantify the distribution of average microbial abundance assumed to be inversely proportional to the rank of utilized nutrient. The average abundance is the largest in the case of complementary nutrient choices, All differences between distributions of abundances in each category are highly statistically significant according to the Kolmogorov-Smirnov test with a *P*-value threshold of 0.01.

Discussion

(Co-)evolutionary extensions

In the results presented above, we describe a conceptual model of microbial competition for sequentially utilized nutrients. This model can exhibit rich behaviors such as dynamic restructuring and multiple stable states connected by a hierarchical transition network. All of this complexity is captured in just two ranked tables: one with microbial nutrient preferences and the other with their competitive abilities for different nutrients. The competitive interactions summarized in these tables are just starting to be explored experimentally. In fact, the first experimental results relevant to communities within the human gut have already been reported [20]. Specifically, these results demonstrate the preferences and competitive abilities of 2 *Bacteroides* species for 9 particular polysaccharides.

In the absence of experimentally determined preferences, the naïve expectation would be to use randomized nutrient preferences and competitive abilities. However, as shown in figure 4, the results for random preference tables qualitatively disagree with experimental observations of robust coexistence of multiple species (e.g. *Bacteroides* in human gut) competing for the same set of nutrients. Our model shows that complementarity in nutrient preferences of the most prevalent microbes enables such coexistence. This is consistent with co-evolution of complementary nutrient preferences in the set of microbial species that frequently co-occur [20, 45].

Co-evolved nutrient preferences also help explain the prevalence of habitat filtering in many naturally-occurring microbial communities [15, 46, 47, 48], i.e. the observation that many metabolically overlapping species can stably coexist with each other. This apparently paradoxical observation is unsurprising in the light of our results: given that nutrient preferences in microbial species are controlled by transcriptional regulation, they can be relatively easily modified in the course of co-evolution to ultimately become complementary to each other (at least in part).

Apart from the *Bacteroides* case shown in figure 4(C), we did not explore other possible correlations in the ranked interaction tables which might also result from species co-evolution. For instance, a correlation between how preferred a nutrient is for a given microbial species and how competitive that very species is in at acquiring it. Indeed, one might expect microbes to have higher-than-average competitive abilities for those nutrients that they prefer to consume first. However, these two characteristics are controlled by different parameters. While diauxic shifts typically happen in the order of decreasing maximal growth rates of a microbe on a nutrient at high concentration [36], the competitive abilities are determined by growth rates when the nutrient concentration is very low (i.e. below K_m in the Monod growth law [19]). Based on the known SMP results [37] one expects such correlations to reduce the number of stable states. A perfectly correlated preferences and competitive abilities would result in a unique stable state of a microbial community.

The other direction that can be explored by supplementing our stable marriage model with the evolutionary dynamics is that of metabolic specialization: what is the optimal number of nutrients a microbe should use in a given environment? For a stable diet (or, more, generally, a reliable influx of the same set of nutrients in the environment), it makes sense that microbes would ultimately evolve mutually complementary and a highly specialized subset of preferred nutrients. However, this would not fare well for microbes surviving in fluctuating environments. Therefore, another case worth exploring is an evolutionary model where environmental variation affects microbial nutrient preferences and competitive abilities. Microbes may make a choice between being broad generalists and narrow specialists (we see examples of both in *Bacteroides*; see figure 4(A)). An intriguing possibility is that this might be connected with a mathematical

concept known as reduced (or Gale-Shapley, GS) preference lists [37]. For a given microbe, these lists include only a subset of nutrients that it can utilize, either in any of the possible stable states or during a transition from one stable state to another. Given that the probability of being able to grow on nutrients absent from such a list is low, microbes may — over evolutionary times — start to lose the ability to utilize such resources. At the same time, microbes would improve their competitive abilities for the remaining nutrients (those utilizable and present in their GS lists), which in turn could possibly reinforce the initial set of stable states (see chapter 1.2.4. of reference [37]. This evolutionary dynamics may provide a path to partial or complete specialization of microbes.

In principle the decision between co-utilization and sequential consumption of resources is a complex one [49]. Our model can naturally incorporate the trade-offs between the utilization of one versus many catabolic pathways. This can be accomplished by making specialists (microbes capable of utilizing only a few nutrients) to be on average more competitive for these nutrients than generalists (capable of utilizing many or all available nutrients). Co-utilization of nutrients corresponds to ties in ranked lists in the stable marriage problem [42]. The effect of such trade-offs on the number and nature of stable states in our model remains to be explored in a future study.

Adding metabolic byproducts to the model

A key driver of diversity in real-life microbial communities often lies in the metabolic byproducts generated by resident species. Indeed, in the presence of metabolic byproducts the number of microbial species in the steady state is no longer limited from above by the number of externally provided nutrients. Recent models [15, 50] and experiments [15, 51] demonstrate that a diverse microbial ecosystem may be supported even by a single externally provided nutrient. The *Bacteroides* species used in our study are also known to grow on each other's metabolic byproducts [45]. That may be the reason why *B. thetaiotaomicron* survives while losing the competition to *B. ovatus* on all 8 polysaccharides studied in reference [20] (see figure 4 from that reference). The stable marriage model described above allows for a natural multi-layered generalization involving metabolic byproducts generated by microbial species. One starts with a single layer composed of abundant primary nutrients (e.g. polysaccharides in the case of a human gut shown in figure 4(A)). The microbes (such as *Bacteroides* species in figure 4(A)) would compete, or, alternatively, complementarily utilize these nutrients and generate the second layer of nutrients composed of their metabolic byproducts (or products of extracellular metabolic degradation). These byproducts in turn allow for a new set of microbes capable to grow and possibly generate the next layer of byproducts. To simplify the rules of assembly of such communities one would prevent microbes from upper layers to compete for nutrients in layers below them. Indeed, the concentration of nutrients is expected to rapidly decrease with a trophic layer [50]. Hence such 'metabolic downgrading' of microbes would be usually unfavorable and thus selected against.

An extension of our stable marriage model with metabolic byproducts would give rise to a microbial ecosystem with multiple trophic layers similar to the ecosystems studied in [50]. All the results of this earlier study including distributions of species' abundances and prevalences as well as correlations between these two properties are directly transferable to this model. Indeed, similar to [50], in the stable marriage problem with byproducts, every microbial species utilizes exactly one nutrient and generates a certain number of byproducts. Thus, the food web topology in the stable marriage model with byproducts would correspond to multiple trees, each growing from a single primary nutrient. These trees would generally change as the community switches from one stable state to another. A more realistic implementation of the marriage model with

byproducts involving a compendium of gut microbes and nutrients larger than the top layer shown in figure 4(A) would require a more detailed description of byproducts generated by the catabolic breakdown of each of the nutrients. These data are currently incomplete [52], and thus such an extension is beyond the scope of the present study.

Towards dynamical variants of the model

Above, we were focused on investigating the stable states of microbial communities, to predict which our model needs only two ranked tables: namely microbial nutrient preferences and competitive abilities. However, in many cases, the dynamics of transitions between these states and of community's equilibration to each of them is equally important. To model these, one needs to know many detailed and mutually interconnected parameters such as growth rates [53, 54], kinetics of nutrient utilization [55], transcriptional dynamics [20, 26, 36], etc, most of which are hard to determine experimentally and currently unknown.

A dynamics of the human gut microbiome as well as that of many other microbial communities could be approximated by a batch-fed bioreactor: with discrete batches corresponding to influx of nutrients following food intake and dilution corresponding to excretion, both cyclic events. When thinking about the transient phase of such a batch-fed bioreactor, one needs to consider the possibility of a transient co-utilization of the same nutrient by several microbes. How can one adapt our model to this possibility? (a) One of the variants of the stable marriage problem known as the hospitals/residents problem [28, 37] provides one possible starting point for such an adaptation. In this problem a hospital (a nutrient in our case) can accommodate more than one resident (a microbe). A variant of the Gale-Shapley algorithm allows one to easily find stable states in this problem. (b) Many of our current results would still stand in this case. Consider, for example, a positive correlation between microbial abundances and their nutrient choice complementarity shown in figure 4(C). In a batch-fed reactors with frequent transfers, many microbes co-utilizing the same nutrient cannot grow to high abundances since their overall biomass is limited by the amount of the nutrient they consume. However, if each of them would be using a different nutrient (complementary to the other microbes) the total biomass would be maximized.

Another generalization of our model is when the nutrients considered by microbes are not substitutable, but instead are of different kinds, e.g. separate carbon and nitrogen sources both essential for microbial growth. An extension of the model in this case would require a microbe to choose one source of each 'kind'. This would correspond to a marriage problem with more than two sexes. As far as we are aware, these modifications of the SMP have not been developed yet, though this possibility has been explored in works of science fiction [56, 57].

Finally, in our basic model we assume an absolutely strict hierarchy of nutrient preferences with no 'ties', whereas in some cases, microbes may not strictly prefer one nutrient over another and may even simultaneously co-utilize a subset of them. Such a possibility can easily be incorporated into our modeling framework. In fact, model variants with partial lists and ties are a topic of active current mathematical research in the stable marriage problem [42].

Higher-order interactions between microbial species

Higher-order interactions between different community members have recently been brought to light as an important factor contributing to composition, stability, and diversity of microbial communities [58, 59, 60, 61]. A bottom-up method for predicting the set of co-existing microbes was recently proposed [54]: one first determines the outcomes of all competitions between species

pairs, and subsequently extends it to competitions between species triplets, and so on. This "bootstrap" approach to taking higher-order interactions into account needs to be modified for microbial communities described by the Stable Marriage Problem (SMP). Indeed, in SMP, the set of survivors depends on the complete set of species introduced to the ecosystem. Generally speaking, the presence of a given species in a stable state is only weakly correlated with its ability to survive in pairwise competitions. In the SMP if a species is present (or absent) in one stable states it is present (or absent) in all of them. When a competition experiment is carried out on a medium containing many nutrients, the survival of two (or more) generalist species competing against each other is all but guaranteed: they would typically be capable of coexisting on a set of non-overlapping resources. Higher-order interactions between species are also crucial in determining the abundance profile of the stable state in our model. Indeed, as evident from figure 3(D), a temporary removal of just one resident microbe is capable of switching the ecosystem to another stable state, in which all microbes have higher or equal abundances than they had originally.

While pairwise competition experiments on a *complete medium* are not very informative for predicting the set of surviving microbes and their stable states, those carried out on each of the *individual nutrients* sampled one-by-one are the key to determining the rank order table of microbes' competitive abilities — one of the two key ingredients of our model. The other rank tables could be deduced from polyauxic shift experiments in which individual microbes are grown on a complete medium.

Summary

In this study we present a new conceptual modeling approach that provides mechanistic insights into several phenomena in microbial communities, specifically: the existence of multiple stable states and inter-state transitions, as well as restructuring, and resilience of these states. Our model assumes that several microbes utilize nutrients sequentially (diauxie or polyauxie). The stable states of the model are fully determined by two ranked tables for each microbial species: one summarizing their preferred order of utilization of nutrients, and the other their competitive abilities to acquire this nutrient relative to other microbes. Such multiple stable states have been experimentally observed before [7, 62, 63], and in our model they are both resilient to many perturbations, while being susceptible to restructuring by others. The particular perturbations we consider in this study are the transient removal or addition of nutrients or of microbes.

Further, our model makes specific predictions regarding the metabolic preferences of naturally co-occurring species that have strong metabolic overlap. Specifically, we make the case for complementarity in top nutrient preferences in these species. We take a specific example of *Bacteroides* species in the human gut microbiome and demonstrate that complementarity of their preferred polysaccharides can enable them to stably coexist at high abundances.

Note that while — in this manuscript — we discuss the stable marriage problem in the context of microbes being paired with nutrients, our approach potentially has a broader scope. In particular, instead of matches between microbes and nutrients, one may also consider matches between mutually interdependent microbes (say cross-feeding pairs or cross-protected pairs) or other types of exclusive one-to-one matching between relevant ecosystem entities.

Materials and Methods

Enumerating all stable states

For any general case of preference lists in the stable marriage problem (SMP), there exist multiple 'stable states' (see Box 1 for what we mean by 'stable'). There are several algorithms to enumerate all these states, though we used in our study one that is intuitive and connects well with microbial communities: the so-called 'breakmarriage' algorithm [37,64]. For our problem this algorithm involves starting from one of the stable states (e.g. microbe-optimal one) and then successively *breaking* each of the microbe-nutrient pairs by removing either a microbe or a nutrient. A transient removal of a specific nutrient has the possibility of triggering a transition of the community to another stable state in which all microbes are worse off (or equal) in terms of the preference rank of the nutrient they consume. These transitions are shown as downward pointing arrows in Fig. 3(C). Conversely, a transient removal of a specific microbe could trigger a transition to a stable state in which all microbes are better off (or equal) in terms of the preference rank of the nutrient they consume (upward pointing arrows in Fig. 3(D)). Below, we list the specific details of the 'breakmarriage' algorithm.

One starts with the microbe-optimal stable state obtained through the Gale-Shapley algorithm (see [28]) in which every microbe plays the role of the active party and thus gets the best nutrient in any stable state. In the example illustrated in figure 3(B), this corresponds to the state S_1. One chooses an implicit ordering of microbes (say for convenience, in increasing order from M_1 to M_M for M microbes) in which one attempts to break microbe-nutrient pairs.

Upon breaking a pair (in our example, N_5 and the teal microbe M_5), the microbe in that pair (M_5) is left without a nutrient, and therefore shifts down to (i.e. 'proposes marriage to' in the SMP jargon) the next nutrient in its preference list (N_3). If M_5 is more competitive than the current consumer of this nutrient (the dark blue microbe, M_6) with respect to the nutrient N_3, it competitively displaces this current consumer (M_6). (If not, the microbe (M_5) continues to shift down its preference hierarchy until it finds a nutrient it can utilize.) Every time a microbe is left without a nutrient, it continues to down-shift its nutrient preference list and attempts to competitively displace other microbes using these nutrients (in our example, M_6 now moves to attempt to use N_5). If along this sequence, the original nutrient whose pair was broken (N_5) is 'proposed' to by another microbe (here, by M_6), and if M_6 *can competitively displace its original partner* (M_5 in our case), a 'rotation' is said to have been successfully completed and the new state is guaranteed to be stable (here, that state is S_2 shown in Fig. 3(B)). If any of these steps fails, the attempted rotation is unsuccessful and one reverts back to the previous stable state and then attempts to break the *next* microbe-nutrient pair according to our implicitly chosen order.

For any of the new stable states (say S_2 described above) found through this procedure, one repeats this procedure using this state as the initial stable state to find even more stable states. When all microbe-nutrient pairs in all such obtained stable states have been attempted to be broken, the algorithm is terminated. This procedure is guaranteed to enumerate all possible states for a chosen set of ranked interaction tables.

Studying complementarity through different ranked interaction tables

We sampled a large number of possible interaction tables, i.e. preferences towards nutrients and competitive abilities for subset of core gut microbes adapted from [44] in a following way:

In principle, there are close to 10^{131} such possibilities, and it is thus not possible to sample *all* such tables. Instead, we compartmentalize such interactions in three broad categories: complementary, random and maximal conflict.

In complementary interaction tables (see figure 4(C) [top case]), we construct random interaction tables with the following constraint: microbial preferences for the top (most preferred) nutrient must be made maximally distinct, i.e. with no overlap if possible. To construct interaction tables in this category, we begin by picking a microbe at random and assigning it a nutrient it can utilize at random. We then remove this nutrient as a possible top choice for all other microbes. We then randomly pick another microbe (without replacement) from the full set and assign it another random nutrient. We continue this until all microbes have been assigned a distinct most preferred nutrient. In case a chosen microbe has no choice left, we discard that particular interaction scenario and start a new one.

Random interaction tables provide a null interaction scenario for our model (see figure 4(C) [middle case]) and are thus used to set the naïve expectation for competition and conflict within these gut microbes. In this scenario microbial preferences towards nutrients are selected by a random permutation independently chosen for each of the microbes.

In interaction tables with maximal conflict (see figure 4(C) [bottom case]), we construct random interaction tables with the following constraint: we attempt to maximize the number of conflicting pairs (NCP) for the set of microbes (see Results: Complementary prioritization as a mechanism for robust many-species coexistence). For this, we pick a microbe at random and then randomly pick a nutrient it can utilize as its most preferred (top choice). For all other microbes in our set that can utilize this nutrient, we set it as their most preferred nutrient as well. We continue until all microbes have been assigned a most preferred nutrient and then randomize the rest of the interaction tables.

In all three cases described above the competitive abilities of microbes for each of the nutrients are set by a random permutation.

Each specific pair of interaction rank tables (one for microbial preferences and another, for their competitive abilities) represents a possible competitive scenario in the human gut. We construct 1,000 tables for each case. We then use the Gale-Shapley algorithm [28] to find the microbe-optimal stable state of the possible *Bacteroides* community and the breakmarriage algorithm (see Materials and methods: Enumerating all stable states) to find the overall number of stable states. In the microbe-optimal state, we compute the relative rank of each microbe's utilized nutrient in their preference lists, i.e. the rank of the utilized nutrient relative to how many nutrients that microbial species is known to utilize. The inverse of this relative rank is used (in a.u.: arbitrary units) as a predictive measure of its species abundance in the resultant community. We repeat this procedure for all microbes in the community and then normalize the abundances of all microbes to add up to one so that the relative abundance for each species is between 0 and 1.

Acknowledgments

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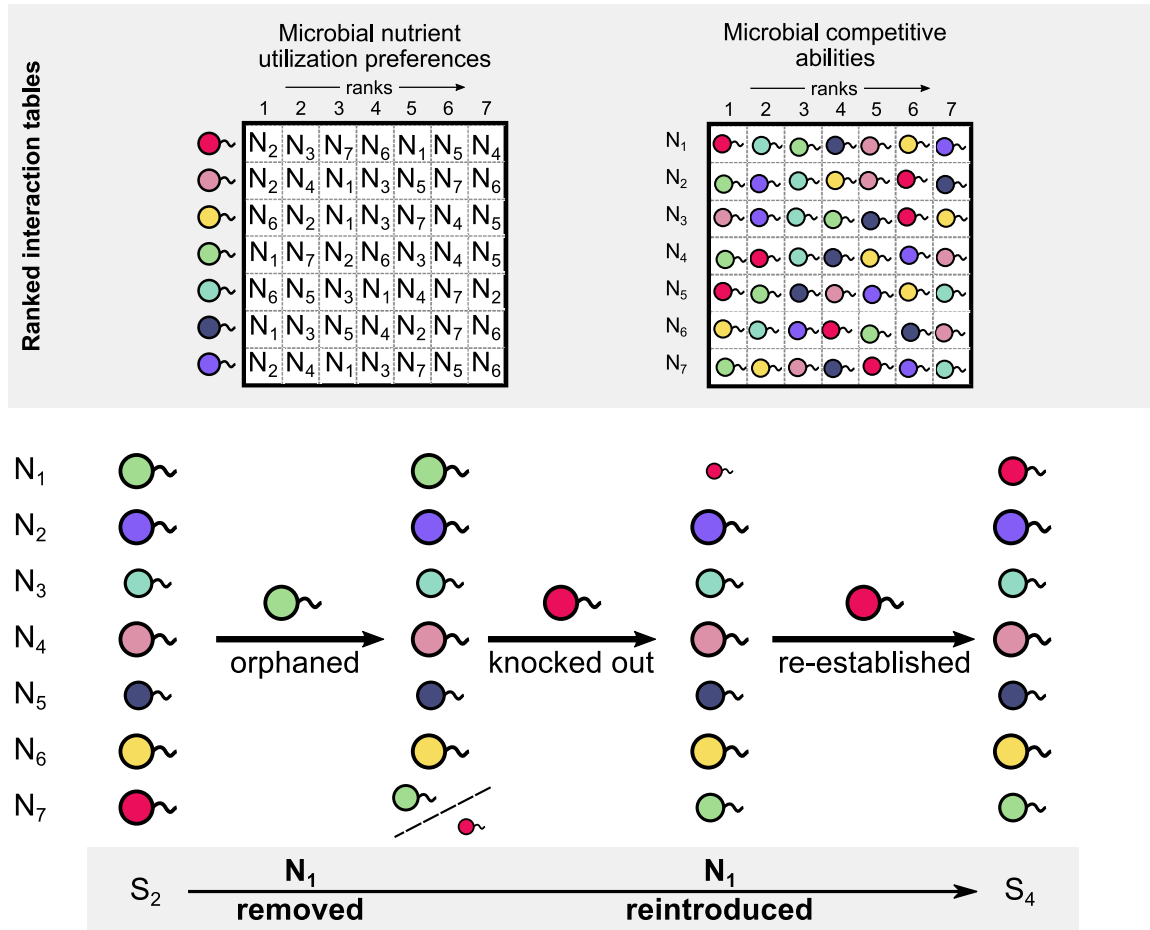
Figure Supplements

Figure S1: Specific steps during community transitions from one stable state to another.
A detailed step-by-step breakdown of how the microbial community in our example in figure 3 of the main text can transition from one stable state (here S_2) to another (here S_4) via a very specific perturbation: the removal of nutrient N_1 and its reintroduction at the specific time-point shown thereafter. First, the green microbe is left without its preferred growth nutrient (N_1). It then attempts to compete for its next preferred nutrient, N_7, competitively displaces the red microbe, which can then re-establish on N_1 reintroduced at that specific time. The resultant community now exhibits the alternate stable state, S_4.
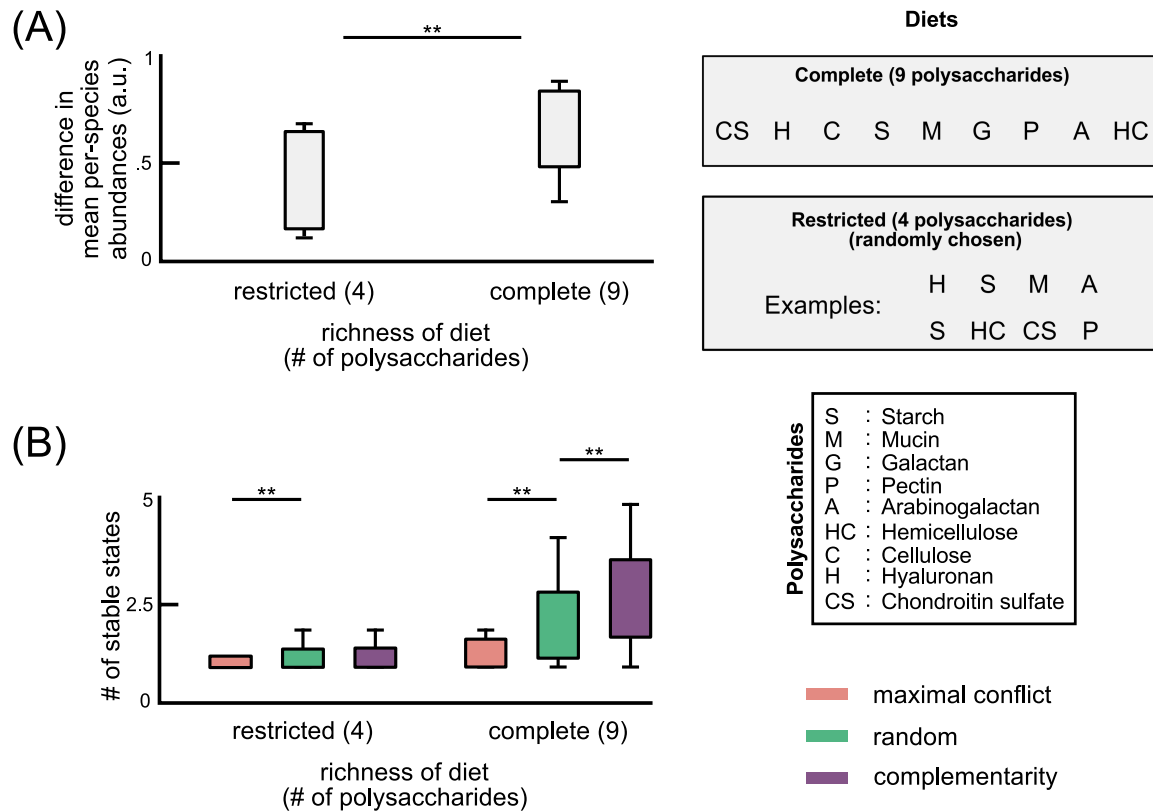
Figure S2: Contrast between restricted and complete diets in *Bacteroides* species.
(A) In figure 4 in the main text, we show that using different nutrient preferences (complementary, random and maximally conflicting) for a realistic community of *Bacteroides* species can result in different species abundance profiles. Specifically, complementary lists lead to higher abundances for all *Bacteroides* species, whereas conflicting lists result in low abundances. However, we showed this assuming a complete 'diet' with all 9 consumable polysaccharides available. Here, we show that the difference between communities with complementary and conflicting preferences (in our model) shrinks when the diet is 'restricted', i.e. when only about half the polysaccharides are available, and randomly selected. This is consistent with an increased expectation for complementary nutrient preferences between co-occurring microbes in environments with richer diets. **(B)** The number of stable states, as described in the main text (see Materials and methods: Enumerating all stable states) for all three cases of microbial nutrient preferences for restricted and complete diets. Complete diets typically have a higher number of stable states (typically ~ 2) for complementary preferences than either random or conflicting preferences. In some cases, the number of stable states is higher (i.e. $4 - 5$), and these cases are more likely if the preferences are complementary. (In all cases, we use the Kolmogorov-Smirnov test to compare distributions, with a P-value threshold of 0.01.)