nature microbiology

Perspective

https://doi.org/10.1038/s41564-023-01511-x

Metabolic exchanges are ubiquitous in natural microbial communities

Received: 25 October 2022

Accepted: 11 September 2023

Published online: 23 November 2023

Check for updates

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Microbial communities drive global biogeochemical cycles and shape the health of plants and animals—including humans. Their structure and function are determined by ecological and environmental interactions that govern the assembly, stability and evolution of microbial communities. A widely held view is that antagonistic interactions such as competition predominate in microbial communities and are ecologically more important than synergistic interactions—for example, mutualism or commensalism. Over the past decade, however, a more nuanced picture has emerged, wherein bacteria, archaea and fungi exist within interactive networks in which they exchange essential and non-essential metabolites. These metabolic interactions profoundly impact not only the physiology, ecology and evolution of the strains involved, but are also central to the functioning of many, if not all, microbiomes. Therefore, we advocate for a balanced view of microbiome ecology that encompasses both synergistic and antagonistic interactions as key forces driving the structure and dynamics within microbial communities.

Microorganisms drive the biogeochemical cycling of elements on a global scale[1] and contribute substantially to determining the health of animals and plants[2]. These vital processes result from the activities of microbial communities that are taxonomically and metabolically highly diverse—sometimes consisting of thousands of different bacterial, archaeal and fungal species[3,4]. Within these communities, complex ecological interactions between community members and their abiotic environment give rise to properties that emerge on a community level and that frequently enhance the performance of a community in terms of growth and persistence well beyond the mere sum of individual contributions[5]. Thus, understanding microbial communities to a point at which the eco-evolutionary dynamics of microbial consortia can be predicted and rationally manipulated in desired ways—for example, in medical or biotechnological contexts—requires knowledge of how ecological interactions among community members determine the function and stability of a given microbial community.

Ecological interactions between two community members are generally classified based on the fitness consequences the interaction has on the interacting partners. Accordingly, any given interaction can either positively (+) or negatively (−) affect each of the two individuals or have no effect (0; that is, neutral interactions). This classification scheme results in several distinct types of ecological interaction (Fig. 1a) that, in the following, will be broadly divided into antagonistic and synergistic interactions.

Antagonistic interactions are those in which one or both interaction partners bear negative fitness consequences from the interaction. This can be due to competition (−/−) for resources or amensalism (0/−), where, for example, one cell releases a substance (for example, a metabolic waste product) that inhibits the growth of the other species.

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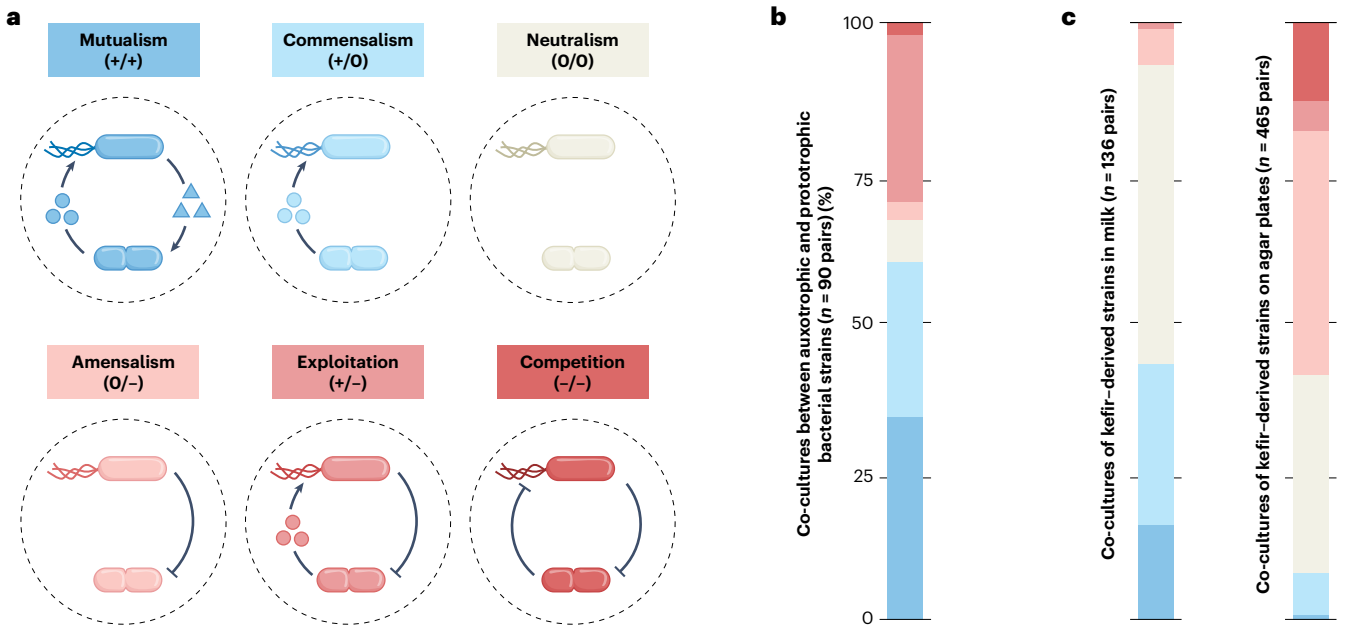

Fig. 1 | Obligate metabolic interactions are frequently synergistic. **a**, Spectrum of ecological interactions that emerge in microbial communities. **b**,**c**, Pairwise co-cultures of prototrophic and auxotrophic bacterial strains[44,45] (**b**) or strains derived from kefir[36] (**c**) reveal that synergistic interactions (commensalism, mutualism) prevail under these conditions (Supplementary Tables 1–4 and Supplementary Information). Colours in **b** and **c** correspond to those in **a**.

Alternatively, interacting cells can also benefit from actively killing or inhibiting other cells in their local environment (that is, exploitation/predation (+/−)), for instance, by releasing toxic substances[6] or through contact-dependent killing mechanisms[7].

In contrast, microorganisms can also profit from the presence of other strains in their local environment. In these synergistic interactions, either one (that is, commensalism (+/0)) or both partners (that is, mutualism (+/+)) can gain fitness advantages from the focal interaction. In many cases, positive interactions result from the exchange of metabolites between different microorganisms. In this way, strains may either expand their biosynthetic capacities or increase their efficiency through the division of metabolic labour. An important yet often difficult-to-answer question in this context is whether the synergistic behaviour giving rise to these benefits has evolved, because it has been favoured by natural selection in the past. If this is the case, the interaction is classified as cooperation, meaning that it incurs a cost to the acting individual and benefits the receiver of the cooperative act[8]. Alternatively, a synergistic benefit can also be a by-product of a behaviour the actor performs to enhance its own fitness. A classic example of this is the release of an overflow metabolite or a metabolic by-product that benefits other cells in the local population[9]. Synergistic benefits can stem, for example, from a transfer of information (for example, quorum sensing) or services (for example, dispersal or protection) between cells[10]. Most widespread, however, is probably a growth facilitation, in which one strain releases a metabolite that is utilized by another. Besides an exchange of compounds that derive from the primary metabolism, such as amino acids, nucleotides or enzymatic cofactors[11,12], this kind of interaction can also rely on the degradation products of complex polymers[13] or the provisioning of extracellular goods such as iron-scavenging siderophores and haem[13,14].

The existence of antagonistic interactions within microbial communities is well in accord with the theory of natural selection. Nutrients are frequently limiting. Thus, competition (−/−) for these nutrients should be widespread. Also, the emergence of exploitative interactions (+/−), in which cells inhibit or kill other strains in their immediate vicinity, can be intuitively understood: cells displaying such harmful behaviours may gain a competitive advantage and thus be able to monopolize locally available resources.

However, the occurrence of synergistic interactions is harder to rationalize. Why do bacteria release metabolites that may provide other cells in their local environment with a competitive advantage? Although some of these compounds are released as overflow metabolites or simply leak through promiscuous transport activities, others incur substantial fitness costs to the producing individuals. Why should microbes invest energy and metabolites to benefit others, rather than using these resources to enhance their own fitness? A major problem that results when cells start to engage in a costly cooperation is that non-cooperating individuals can emerge that reap cooperative benefits without reciprocating. Due to the saving of production costs, these non-cooperators are predicted to increase in frequency within the resident community and, in the long run, even lead to a collapse of the cooperative interaction[8,15]. For these reasons, a prevailing view in the literature is that antagonistic interactions are more common and therefore more important for determining the structure, ecology and evolution of microbial communities than synergistic interactions, which are rare and hence ecologically less relevant[16–20].

However, the picture that emerged over the past decade is more complex. In this Perspective we provide an overview of the main lines of evidence that suggest synergistic metabolic interactions are not only common, but also profoundly impact the physiology, ecology and evolution of microbial communities.

Obligate cross-feeding is common in microbial communities

A transformative insight resulting from studies that analysed the genomes of isolates and high-quality metagenome-assembled genomes (MAGs) of natural microbial communities was that microorganisms are frequently unable to produce all the metabolites they require for growth. These so-called auxotrophic genotypes have been abundantly detected in diverse environments[21–23] (Fig. 2 and Supplementary Table 5). For example, mapping the species identity data of 12,531 microbial communities to reference genomes and using this information to infer

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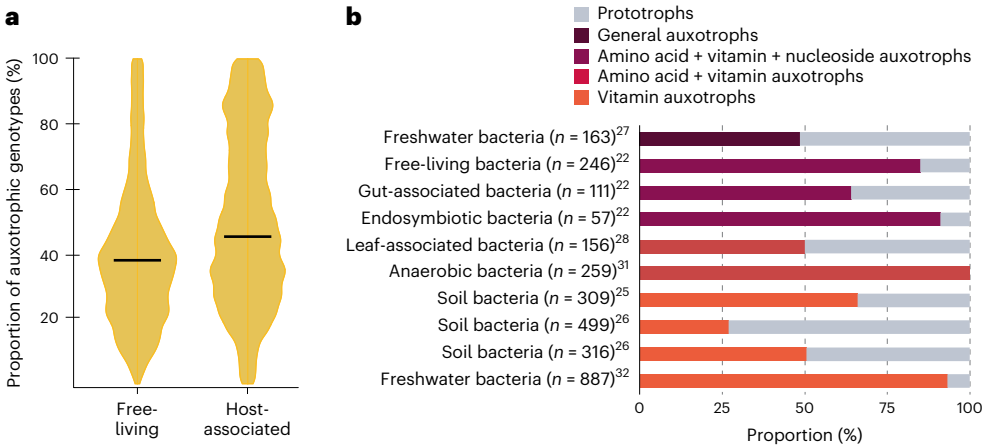

Fig. 2 | Metabolic auxotrophies are common in natural microbial communities. a,**b**, Proportion of auxotrophic genotypes in communities of free-living (n = 7,161) and host-associated (n = 5,370) microbial communities[79] (**a**), as well as in bacteria that occurred in different environments (Supplementary Table 5) (**b**). Black lines in **a** mark the median of distributions. In **b**, general auxotrophs refer to microorganisms that were unable to grow on minimal-medium agar plates. The criteria that different authors have used to define metabolic auxotrophies are summarized in Supplementary Table 5.

metabolic auxotrophies by genome-scale metabolic models revealed that communities of free-living bacteria contained on average 39% (n = 7,161) auxotrophic genotypes, while host-associated communities even comprised 50% auxotrophs[24] (Fig. 2a and Supplementary Table 5). Only one community did not contain any predicted auxotroph[24]. In all other communities, metabolic auxotrophies were common and some communities even seemed to consist exclusively of auxotrophic bacteria[24]. The same pattern was detected in other studies that analysed microorganisms in soil[25,26], freshwater[27] and also in plant-[28] or animal-associated strains[27] (Fig. 2b and Supplementary Table 5). Here, estimated proportions of auxotrophic bacteria or fungi ranged from 41% to 91% of all strains analysed (average = 67%). In many of those cases, abundant and ubiquitous free-living bacteria feature drastically reduced or streamlined genomes[29] and are unable to autonomously produce several essential metabolites, including nucleotides[22,30], vitamins[22,25,26,28,31,32], amino acids[21,22,24,31] or combinations thereof[27] (Fig. 2b and Supplementary Table 5).

What is the source of metabolites that maintains these auxotrophic genotypes in the long run? One possibility is decaying or dissolved organic matter. However, to sustain microbial communities, constant cell growth is required. Without the de novo synthesis of metabolites, a community can at best maintain its current biomass. Thus, if recycling were the sole source of essential metabolites, the community would be likely to shrink due to a conversion of energy into by-products and heat. Indeed, the availability of nutrients in the environments, in which auxotrophic mutants occur, is frequently not sufficient to stabilize their growth over extended periods of time[33,34]. In addition, detritus-derived nutrients should be patchily distributed and be available only temporarily[34]. Thus, although the environmental availability of metabolites may help explain the evolution of metabolic auxotrophies, the generally observed ubiquity of auxotrophic bacteria in structurally very different habitats suggests that metabolites provided by other community members are probably required to maintain auxotrophic bacterial genotypes.

This conclusion is corroborated by studies that analysed microbial ecosystems in fermented food[35]. In milk kefir, for example, obligate metabolic interactions between tens of species have enabled their long-term coexistence[36]. Interestingly, *Lactobacillus kefiranofaciens*, which is the dominant species in kefir, cannot grow in milk. Instead, it relies on other community members to provide it with energy and essential metabolites. In return, it synthesizes a polymeric matrix that ensures the survival and reproduction of other members of the collective (that is, kefir grain).

Finally, all major biogeochemical cycles that drive the turnover of organic matter on a global scale essentially rely on the cross-feeding of metabolites among bacteria[37,38]. For example, cells degrading complex molecules such as polysaccharides[13] or toxic pollutants[39] frequently self-organize into networks of cross-feeding bacteria. The biochemical capacities to degrade these compounds are usually distributed among multiple strains, rather than being concentrated in one bacterial genome[40]. This arrangement leads to the emergence of interaction chains, in which microorganisms successively degrade more complex molecules[37,41]. Given that the participating strains depend on the actions of others, the whole consortium benefits from the exchange of metabolites.

In summary, several studies have revealed that metabolic auxotrophies are common in natural microbial communities. However, the need for cell growth effectively rules out metabolite recycling as the sole source of essential metabolites to explain the widespread occurrence of these loss-of-function mutants. Instead, the evolution of metabolic auxotrophies probably leads to the emergence of obligate metabolic interactions among community members, which in turn stabilize auxotrophic mutants in the long run.

Obligate metabolic interactions are frequently synergistic

The approach that is generally used to determine the relative abundance of antagonistic versus synergistic interactions is to perform systematic co-culture experiments with microorganisms that have been either isolated from natural sources or derived from strain collections. In this way, it can be tested whether strains benefit from the presence of other genotypes or grow less as compared to monoculture controls. With this experimental design, the abundance of different interaction types can be quantitatively determined. Several studies applying this approach to culturable bacteria consistently found antagonistic interactions to be abundant, while the proportion of mutualistic or commensalistic interactions only ranged between 2% and 19%[17]. However, some of these studies employed exclusively prototrophic bacteria that can produce all metabolites they require for growth by themselves[42], whereas others[43] used a rich cultivation medium that probably affected the spectrum and amount of metabolites released (for example, by feedback inhibition), thus abolishing all obligate metabolic interactions among strains. A probable consequence of both experimental designs is that metabolically autonomous bacteria competed for the available resources, thus skewing the relative abundance of synergistic versus

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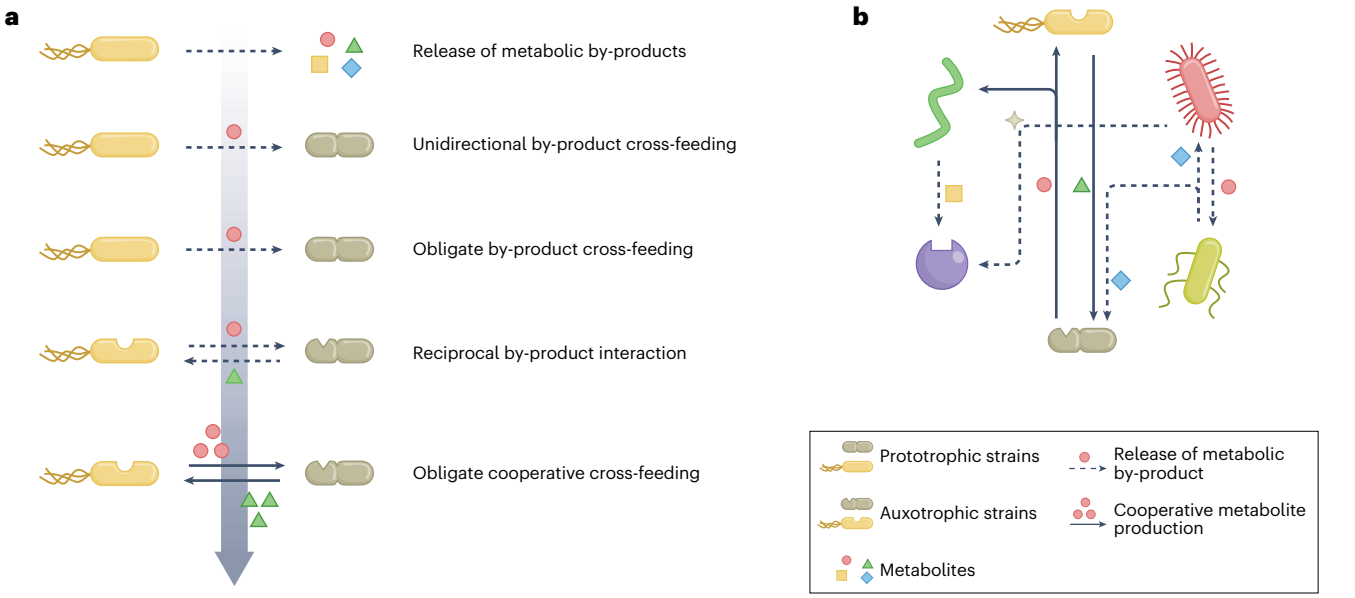

Fig. 3 | Evolution of obligate metabolic interactions within microbial communities. a, The evolutionary transition from metabolic independence to an obligate cooperative cross-feeding interaction is well supported by experimental evidence. This process proceeds in at least four steps, during which both interaction partners develop a metabolic interdependence and start to produce increased amounts of the traded goods. **b**, Bacteria probably exist within a network, within which they exchange metabolites with other members of their local community. The establishment of these networks is driven by the loss of biosynthetic genes as well as benefits that arise when consuming metabolites that have been produced by other strains.

antagonistic interactions. However, how does the pattern change when obligate metabolic interactions are explicitly considered?

To address this issue, we analysed previously published work. First, we determined the kinds of ecological interaction that emerge when prototrophic strains belonging to one of 25 different bacterial species were individually co-cultivated with two auxotrophic mutants of two bacterial species each and their growth was compared to that of monoculture controls[44,45]. Under these conditions, 60% of all interactions had a positive effect on one (26%) or both (34%) interacting partners (Fig. 1b and Supplementary Tables 1 and 2). In this experiment, 31% of interactions affected the fitness of one partner negatively and only 2% of all interactions were competitive (−/−). In a second study, microbial strains derived from kefir were subjected to a similar analysis. In detail, strains were either co-cultivated in milk or on agar plates to determine the spectrum of emergent ecological interactions as before. When the kefir consortium was analysed in its native environment (that is, milk), synergistic interactions prevailed (43%), while exploitative and amensalistic interactions only accounted for 7% of cases (Fig. 1c and Supplementary Tables 1 and 3). When the same experiment was repeated on agar plates, only 7% of pairs formed synergistic associations, and in 59% of cases the interaction had a negative effect on one (46%) or both (13%) interaction partners (Fig. 1c and Supplementary Tables 1 and 4). Together, these two studies highlight how co-culture studies that aim at better representing the diversity of metabolic phenotypes that can be observed in natural microbial communities can shed a completely new light on the interaction landscape of microbial communities.

Obligate metabolic interactions evolve readily

The prevalence of obligate metabolic cross-feeding interactions in nature can be mechanistically explained in a series of laboratory experiments that analyse different steps of the process leading to their emergence (Fig. 3a).

First, different bacterial species commonly release a rich blend of compounds into the extracellular environment, which includes primary compounds such as amino acids and vitamins[44,46]. Metabolite pools that accumulate in this way represent a valuable resource for both auxotrophic and prototrophic strains that occur in the same environment and which take advantage of these metabolites once they reach critical concentrations[47,48].

Second, evidence suggests that auxotrophic microorganisms gain fitness advantages when the metabolite they require to grow is sufficiently present in the extracellular growth environment. For example, several studies have been performed in which auxotrophic genotypes that were unable to produce vitamins, amino acids or nucleosides were competed against the corresponding prototrophic strain[22,49,50]. These experiments consistently revealed that if the local concentration of the metabolite the auxotrophic strain requires for growth is sufficiently high, the auxotrophic mutant gains a fitness advantage over its prototrophic competitor (up to 30%)[22,49,50]. The observed benefits auxotrophic mutants gain are probably due to: (1) the saving of costs to produce the required metabolite when it can be acquired from environmental sources, (2) a faster and energetically less expensive replication of the cells' DNA when the size of the genome is reduced, and/or (3) a smaller number of metabolic reactions occurring in parallel, which makes metabolism more efficient[51]. Accordingly, auxotrophic mutants readily arise when bacteria are serially propagated in nutrient-rich environments[52,53]. Here, the emergence of the observed metabolic auxotrophies is also frequently due to the growth advantages auxotrophic loss-of-function mutants gain relative to strains that still produce the respective compound. Interestingly, a recent study in yeast has shown that metabolic interactions among auxotrophic and prototrophic cells result in an increased production of protective metabolites and prolong the lifespan of the communities[54]. Thus, synergistic metabolic interactions can not only enhance cellular growth, but can also benefit the community by increasing its resilience.

Third, metabolic cross-feeding interactions frequently emerge when auxotrophic bacteria are co-cultivated with other auxotrophs[21,47,55] or metabolically independent (that is, prototrophic) genotypes[28,44,47]. Given that, in such experiments, auxotrophic mutants would be unable to grow alone, an exchange of metabolites with other bacteria is beneficial to one[44] or both[45,56] interacting partners (Figs. 1b and 3a). Moreover, co-culturing multiple auxotrophic strains simultaneously results in

the emergence of synergistic interaction networks that persist for extended periods of time[21,47].

Finally, serially propagating genotypes of the same or different species that engage in reciprocal metabolic interactions has repeatedly been shown to strengthen the synergistic relationship[57–59] (Fig. 3a). If interacting partners are forming spatial aggregates with short spatial distances between cells[60], positive fitness feedbacks start to operate on the reciprocally beneficial interactions that favour increased production levels of the exchanged goods. The resulting cooperative interactions are highly beneficial for the interacting individuals and are therefore maintained despite substantial costs incurred by the overproduction of metabolites.

Together, the abovementioned studies provide a comprehensive mechanistic basis to account for the evolutionary transition from metabolic autonomy to a state, in which cells engage in an obligate metabolic relationship with one or several other genotypes of the same community (Fig. 3a). Strikingly, all these steps are driven by adaptive advantages. The fact that these results robustly emerge in very different species and under very different experimental conditions suggests that bacteria in natural environments probably face similar selection pressures that favour the emergence of obligate metabolic relationships with other members of their local community (Fig. 3b).

Detecting synergistic metabolic interactions is difficult

Despite the abovementioned findings, studies analysing different ecological systems have repeatedly concluded that synergistic interactions among microorganism are rare[16–20]. Why is this? How can we reconcile the seeming absence of interactions from which one or both partners benefit with the striking role obligate synergistic interactions played in the studies discussed above? One of the main reasons to account for this discrepancy is that commensalistic and mutualistic interactions among bacteria frequently remain undetected. This can be due to several reasons.

First, microbial isolates that are included in laboratory studies are unavoidably a biased subset of the natural microbial diversity[37,61]. Bacteria are frequently isolated from natural communities by plating them on rich nutrient media. However, this procedure favours fast-growing species, thus discriminating against auxotrophic cells and metabolic cross-feeding interactions[62,63]. In fact, the vast majority of free-living bacteria remain uncultivated[64]. Consequently, these strains are not available for co-culture experiments, thus impeding a rigorous experimental assessment of the true distribution of ecological interactions in these communities. In addition, auxotrophic phenotypes may not be caused by genetic mechanisms, but be due to epigenetic change (that is, phenotypic heterogeneity)[65]. Those strategies are exceedingly difficult to identify when only a subset of bacterial strains is isolated.

Second, the way microorganisms are cultivated matters for the likelihood of detecting synergistic interactions. Cross-feeding of metabolites relies on a close physical proximity between partners to prevent loss of the exchanged metabolites by diffusion[57,66]. Microbial cells typically achieve this by cell–cell aggregation in a liquid environment or by growing next to a neighbouring cell on a spatial surface (for example, within a biofilm). For example, in a synthetic yeast community, metabolite producer and consumer cells maintained an average distance of just one to two cell diameters[47]. Thus, experimentally disrupting the conditions under which strains interact under natural conditions is likely to yield an erroneous distribution of ecological interactions. This issue is nicely illustrated in communities of kefir-derived strains, in which the landscape of pairwise interactions switched between largely positive in the native environment (milk) to largely negative on solid medium[36] (Fig. 1c and Supplementary Tables 1, 3 and 4). This means that the experimental approach used to analyse certain interactions needs to be carefully chosen to adequately mimic the natural environment as closely as possible.

Another potential pitfall is that studies analysing more complex interactions frequently mix all interaction partners at once. However, experiments in yeast have shown that combinations of multiple auxotrophs collapsed after mixing, but were able to establish syntrophic growth when the interactions were allowed to form progressively[47]. In the same species, only a small subset of all possible auxotroph–auxotroph combinations (<3%) established syntrophic growth following a simplistic 1:1 co-inoculation[67]. Furthermore, as shown by a recent study on vitamin auxotrophies in leaf microbes[28], careful experimental design is required for detecting auxotrophies, as internal storage can mask these deficiencies by allowing cells to grow for a few generations even in the absence of the required metabolite.

Third, growth-enhancing synergistic interactions (that is, commensalism and mutualism) are, on average, more context-dependent than antagonistic interactions (that is, amensalism, exploitation/predation and competition). This assessment is based on the analysis of the largest experimental dataset that is available at present: 180,408 pairwise interactions among 20 soil bacteria in 40 carbon environments[42] (Fig. 4 and Supplementary Tables 6 and 7). Quantifying the stability of different interaction types across all environments (that is, how frequently does an interaction remain qualitatively unchanged as the environment changes?) (Supplementary Information) revealed that synergistic interactions were significantly more likely to transition to a different interaction type upon changing the environmental conditions (Fig. 4a and Supplementary Table 6), and this shift was generally stronger (Fig. 4b and Supplementary Table 6) than was the case for antagonistic interactions. The same trend emerged when the stability and degree of change were analysed for different species (Supplementary Information). Again, synergistic interactions were, on average, more sensitive to changes of the partner species in pairwise co-culture experiments than was the case for antagonistic interactions (Fig. 4c,d and Supplementary Table 7). These findings demonstrate that, for a given set of conditions (that is, environment and species pair), synergistic interactions are significantly less likely to be detected. This does not mean that synergistic interactions are less common, but rather that their detection hinges on the relevant experimental conditions. In other words, minor differences in the experimental conditions between the laboratory and the natural environment (for example, media composition, oxygen availability and pH) can dramatically affect the result of a co-culture experiment[39,68–70] (Fig. 1c). For example, most experiments in this field have been performed under aerobic conditions. However, the presence of oxygen excludes all strains that prefer to grow in anoxic or hypoxic environments[61]. In this way, the whole plethora of syntrophic intercellular relationships that essentially require anaerobic conditions to establish are systematically excluded[71]. Hence, failing to mimic the conditions strains face in nature is likely curtailing the power to detect synergistic interactions.

Fourth, ecological interactions among microorganisms are frequently highly dynamic. For example, due to shifts in resource use, interactions that are initially competitive can become neutral or even mutualistic at later stages of the co-cultivation period[72]. This variation needs to be considered when ecological interactions between two or more interacting microorganisms are analysed.

Finally, determining the growth rate of a given strain in a single condition is often a poor indicator of its resistance to stress. Frequently, slow-growing cells are much better at tolerating adverse conditions than fast-growing strains. For example, yeast cells that rely on lysine uptake mount a better resilience against oxidative stress[73]. Hence, determining the Darwinian fitness of a strain requires both quantification of its growth rate as well as its ability to persist in challenging environmental conditions.

Although technically more difficult than detecting antagonistic interactions (Fig. 4), it is demonstrably possible to isolate and analyse strains from natural environments and be able to detect the focal metabolic interactions. Here, the procedure that is used for strain

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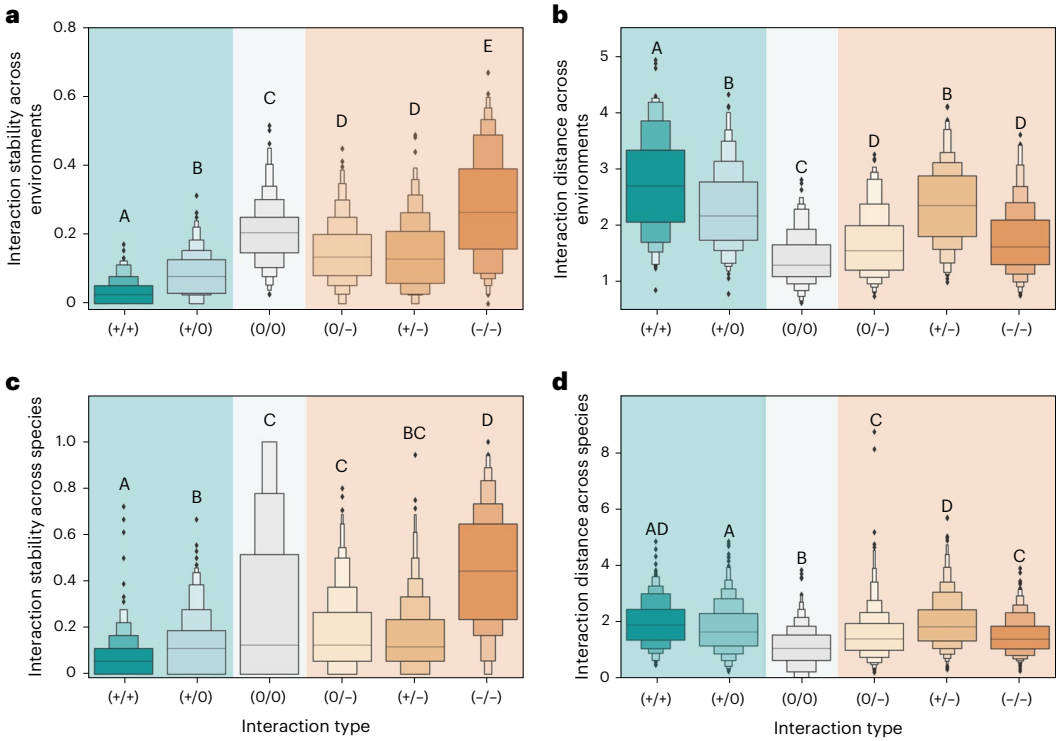

Fig. 4 | Synergistic interactions are more context-dependent than antagonistic interactions. a–**d**, Letter-value plots show the stability (**a**,**c**) of different ecological interactions across environments (**a**) and species (**c**), as well as the interaction distance (**b**,**d**) across environments (**b**) and species (**d**). Interaction stability is defined as the probability that the interaction type remains unchanged when the environment changes (**a**) or when one of the interacting species changes (**c**). Interaction distances is the average Euclidean distance between the interaction in the original and changed environment (**b**) or species (**d**). Data are taken from ref. 42. Different letters indicate significant differences between groups (Bonferroni-corrected Dunn's test: $P < 0.01$) (Supplementary Information and Supplementary Tables 6 and 7). The plots show the median (centre line), and boxes in both directions always indicate half of the remaining data (that is 50%, 25% and so on) until outlier values (black dots) are reached.

isolation can be optimized to adequately represent strains showing certain phenotypic characteristics (for example, metabolic auxotrophies) or that coexist with other partner cells (mixed cultures[74]). The corresponding approaches should in particular aim at mimicking the natural environmental conditions as closely as possible (that is, oxygen and nutrient availability, degree of spatial structuring and so on)[75]. These attempts could be informed by genome sequences or untargeted metabolomics and take advantage of novel procedures that have been developed to identify metabolic relationships in vivo (for example, ichip[76]). Moreover, recent advances in our ability to detect and quantify metabolic interactions between cells, for example, via ^{13}C-based proteomics[48,77], provide a powerful methodological approach to uncover previously hidden interactions. In particular, attempts to isolate and analyse co-cultures of naturally co-occurring strains are promising approaches for gaining a more realistic perspective on the prevalence of synergistic interactions in microbial communities.

Conclusion

The astounding microbial diversity of our planet is testament to the collective metabolic capabilities of microbes. Ample evidence from broad, in situ metagenomic analyses and laboratory-based studies reinforces the interpretation that bacterial fitness is frequently not a property of individual cells, but rather a consequence of metabolic interactions between numerous strains (Figs. 1 and 2). For example, including auxotrophic bacteria in co-culture experiments instantaneously gives rise to beneficial metabolic interactions[44] (Fig. 1b,c). The resulting interdependencies are demonstrably pivotal to both the structure and function of natural microbial communities[5,13,23,24,36,74]. However, this view is at odds with the interpretation that synergistic microbial interactions are rare[17]—a conclusion that is largely due to the inherent difficulty to identify and analyse commensalistic or mutualistic metabolic interactions (Fig. 4). A categorization of ecological interactions that is exclusively based on the growth rates that strains achieve in pairwise co-culture experiments is probably too simple and does not adequately reflect the true complexity of intercellular interactions that emerges when indirect and higher-order effects are taken into account[78].

Answering the question of which kind of ecological interaction prevails in microbial communities is not just of academic interest. Instead, it holds the promise to revolutionize the way we think about microbial life in general. If the recurring pattern that microorganisms mainly exist within interconnected metabolic networks is confirmed, this would have far-reaching consequences for the ecology and evolution of both individual strains and whole collectives. For example, how does natural selection operate on these systems? How can such a decentralized system survive in the face of environmental fluctuations? How can we meaningfully study these complex systems?

Thus, as a first step to address these issues, representative microbial interactions should be analysed under ecologically relevant conditions. In this way, a mechanistic understanding of the dynamic interplay between synergistic and antagonistic interactions can be gained that shapes the structure and functioning of a given microbial community.

Data availability

All data are derived from published sources (see Supplementary Tables 1 and 5 for an overview). The raw data used to generate Figs. 1, 2 and 4 are provided in the Supplementary tables that are mentioned in the figure legends. The raw data that were used to calculate the values shown in Fig. 4 are provided at https://zenodo.org/badge/latestdoi/652204203.

Code availability

The code that was used to calculate the values shown in Fig. 4 is provided at https://zenodo.org/badge/latestdoi/652204203.

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Acknowledgements

We thank the entire Kost laboratory for helpful discussions, as well as F. Zorrilla, S. Giri and L. Oña for sharing data and helping with preparing graphs. C.K. is funded by the German Research Foundation (DFG: SFB 944, P19, KO 3909/2-1, KO 3909/4-1, KO 3909/6-1, KO 3909/9-1) and the Volkswagen Foundation (Az: 9B831). K.R.P. acknowledges support from the UK Medical Research Council (project no. MC_UU_00025/11) and European Research Council (ERC; grant agreement no. 866028). Work on microbial metabolic interactions in the Ralser laboratory is funded by the ERC under grant agreement no. ERC-SyG-2020 951475, the Wellcome Trust (IA 200829/Z/16/Z), as well as the Oxford–Berlin Centre for Advanced studies. S.L.G. is funded by SciLifeLab and the Swedish Research Council VR (grant no. 2022-03077). J.F. acknowledges support from the Israel Science Foundation (grants nos. 883/22 and 3395/20) and the Volkswagen Foundation (Az: 9B831).

Author contributions

C.K. performed the literature search with inputs from all authors. C.K. and J.F. analysed the data. C.K., K.R.P., J.F., S.L.G. and M.R. contributed to the writing of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41564-023-01511-x.

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Peer review information *Nature Microbiology* thanks Thomas Bell, Megan Frederickson and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.