Title: Tapping into symbiosis to advance human microbiome research

Authors: Gina R. Lewin[1,2] and Lily Khadempour[3]

Affiliations:
[1]Center for Global Health and Diseases, Department of Pathology, Case Western Reserve University School of Medicine, Cleveland, Ohio
[2]Case Western Reserve University-Cleveland VA Medical Center for Antimicrobial Resistance and Epidemiology, Cleveland, Ohio
[3]Department of Earth and Environmental Sciences, Rutgers University, Newark, Newark, New Jersey

Authors contributed equally
*Correspondence: gina.lewin@case.edu and lily.khadempour@rutgers.edu

Keywords: Commensal, mutualist, parasite, pathogen, microbe-host interactions, symbiont

Tapping into symbiosis to advance human microbiome research

Abstract

In human microbiome research, the term commensal is often used to describe organisms that benefit their hosts. In ecology, where the term originates, a commensal organism has no impact on its host, whereas a mutualist organism benefits its host. While others have recognized this discrepancy in terminology use, old habits are hard to break, and the human microbiome community has continued in this vein. This is our call to action for the human microbiome community to use more precise terminology that appropriately reflects the impact that these microbes have on their hosts. We should use the terms commensal and mutualist when we know the effect on the host, and symbiont when we do not. By using the same terminology as ecologists, we will be able to make use of and contribute to the vast research in the field of symbiosis.

Body

An overarching goal in microbiome research is to understand how the complex communities in our bodies contribute to health and disease, and ultimately, we aim to leverage and control these communities to promote health. To continue advancing this work, we need conceptual frameworks that aid in understanding the relationships between us and our microbiota. Conceptual frameworks can ensure that we avoid doing our science in silos by unifying work across disciplines, and they can help form hypotheses and questions for future research. In human microbiome research, there have been various conceptual frameworks that have advanced our science (1–4). In this perspective, we highlight the symbiosis framework and definitions in connection to microbiome research, with the hope that adoption of this framework will advance our ability to study the human microbiome.

The symbiosis framework helps us to understand and describe the relationship between human hosts and their microbiota. Symbiotic relationships exist on a spectrum between mutualism, where the host benefits, to parasitism (or pathogenesis), where the host is harmed. Between these two extremes is commensalism, where the host experiences no effect. Importantly, these are not discrete categories but exist along a spectrum, and the location along the spectrum can change depending on context (Figure 1). Similarly, the relationship between humans and members of their microbiota can range from beneficial to harmful and the outcomes of the relationship can change depending on context (immune status, other microbes that are present, diet, drugs, etc.) on both ecological and evolutionary scales.

Below we show examples of how both in classic ecological literature and in human microbiomes, we can observe shifts across this axis.

In the ecology and evolution literature, there are countless examples of transitions along the axis of fitness effects (see the excellent review by (5)). Within these examples, there are cases where the shifts can be drastic: Cicadas have repeatedly recruited a fungal mutualist that

provides essential amino acids to its host, but these fungi originate from a parasitic clade, ophiocordyceps, that are typically responsible for insect “zombie” infections (6). Jellyfish and corals (cnidarians) rely on Symbiodiniaceae algae as classic mutualists that provide photosynthates to their hosts, but can become parasitic when the host experiences stress, usually due to extreme temperatures (7, 8). In other cases, the transitions can be more subtle. For example, myxoma viruses were introduced to help control invasive rabbit populations in Australia, but the virus evolved to be less pathogenic and the rabbits evolved increased resistance. Both evolutionary shifts moved the relationship along the spectrum from extremely pathogenic/parasitic to less pathogenic/parasitic (9).

In the human microbiome literature, we can see similar context-dependent shifts along the axis of fitness effects. The most common examples are opportunistic pathogens, organisms that are typically commensal or even mutualistic but that become pathogens when the host is immunocompromised or if the microbe ends up in the wrong part of the body. For example, *Candida albicans* is commonly present in the human oral cavity, gut, skin, and vagina, without causing disease. However, under some circumstances, *C. albicans* can become pathogenic within those sites, for instance causing oral or vaginal candidiasis, or even causing systemic infection (10). Similarly, *Staphylococcus aureus* can colonize the nose and other sites within the human body without causing disease, and in this state, it may provide benefits to the host, including protection against other pathogens, through trained immunity (11). Yet, within certain hosts or environments (ex. chronic wounds or joint infections), *S. aureus* is able to upregulate virulence factors and promote disease (12). Many members of the microbiota have been reported to cause disease in rare cases. For instance, *Rothia* species are abundant in the oral cavity and upper respiratory tract, where they are thought to behave as mutualists through respiring nitrate and inhibiting pathogens, but in a small number of cases, *Rothia* has been reported to cause infections such as bacteremia, endocarditis, and pneumonia (13). Finally, over evolutionary time, pathogens can shift in virulence, and it is contested if there are underlying rules or patterns for these changes (14, 15). In many cases, pathogens decrease in virulence over time, as in the case of the *Yersinia pestis*, where a decrease in the genomic copy number of a protease virulence factor may have led to decreased mortality towards the end of the first and second plagues (16). In other cases, pathogens have been thought to evolve from less pathogenic ancestors, such as in the case of *Mycobacterium tuberculosis* (17).

There are many different terms that are used to acknowledge the complexity and fluidity of the relationship between humans and members of the microbiota, such as opportunistic pathogen, pathobiont (18), or commensal. Human microbiome researchers routinely refer to any member of the microbiota that does not cause harm as a commensal microbe, encompassing both mutualists and actual commensal microbes, which is imprecise. In addition, if the researchers do not know what effect the microbe has on the host, commensal is often used as a catch-all. This convention arises largely from historical usage. For over 100 years, scientists have recognized that our bodies are covered with bacteria, including our intestinal flora and other potentially pathogenic microbes that are not actively causing disease (19). While Pasteur postulated that microbes were essential for animal survival in 1885, it was not generally accepted that these microbes were beneficial. Instead, over time they were termed commensal

(20), and that terminology has continued, even as our understanding of the human microbiota has expanded to further understand the role of these microbes. Thus, while many modern researchers recognize that the term commensal does not accurately describe members of the human microbiota, they use it as a convenient term.

We recommend that instead of commensal, the term symbiont be used as a general term to describe a member of the human microbiota until more is known about its relationship with the host. Because symbiont does not imply benefits or harms, it also encompasses the nuances of terms like opportunistic pathogen or pathobiont. This shift in terminology is helpful for advancing the human microbiome field. One simple reason is that it is important to be able to differentiate between mutualists and commensals, since they are not the same thing. We should all aspire to use the most accurate terminology when describing our science. Of course, it is not just about terminology, but about understanding the commonalities and differences between pathogenic, commensal and mutualistic microbes. These host-associated, or symbiotic, microbes all require adaptations that allow them to survive in association with a host. One idea that has been proposed is that in order for any microbe to be a symbiont, it first must be adapted to living with a host, regardless of where the relationship exists on the spectrum of fitness effects from mutualism to parasitism (17, 21). Taking this perspective, that first comes symbiosis then comes the particular fitness effects on the host, emphasizes the importance of understanding the underlying host-microbe interactions, no matter where the interaction falls along the symbiosis spectrum.

Understanding the factors that mediate interactions, and ultimately what causes an organism to move along the spectrum towards mutualism or pathogenicity, is a major focus of the symbiosis field, but is also important for identifying therapeutic approaches for improving human health. For example, in the cnidarian-Symbiodiniaceae symbioses, researchers are working to understand the triggers that cause the symbionts to move from being mutualistic to parasitic. It appears that the Symbiodiniaceae increase their production of reactive oxygen species as they shift from being mutualists to parasites of their host (22). Similarly, in the human microbiome, ornithine has been shown as an important metabolite for shifting organisms towards pathogenesis, including in the gut (23) and urinary tract (24). The switch from mutualist to pathogen is not always symbiont-mediated, however. *Bifidobacterium*, a genus of bacteria that are only typically thought of as beneficial in humans can also cause disease under the right circumstances (25). In this study, Esaiassen et al. found that there were no obvious pathogenicity traits found in the disease-causing *Bifidobacterium* strains, but rather the disease was caused largely due to the susceptibility of the host.

We recognize that the term commensal, as commonly used in the microbiome field, is inaccurate, and limits how we envision the role of the microbiota. By moving to call these microbes symbionts, it emphasizes the complexity of our relationships with these organisms. Many abundant human symbionts are not well studied (26), and there is much to learn about how to promote human health through better understanding their roles. There is rich knowledge in other fields that study host-symbiont interactions, and it is helpful to use the same terminology so we can make use of that knowledge and contribute to it. Our call to action is to ask our

colleagues in the human microbiome research fields to revise their terminology and to adopt the symbiosis framework.

Acknowledgements

This work was supported through NIH grants DP2AI184733 and R03DE035522 to GL and NSF BRC-BIO 2312984 to LK. We thank Apollo Stacy for thoughtful feedback on an earlier version of this manuscript.

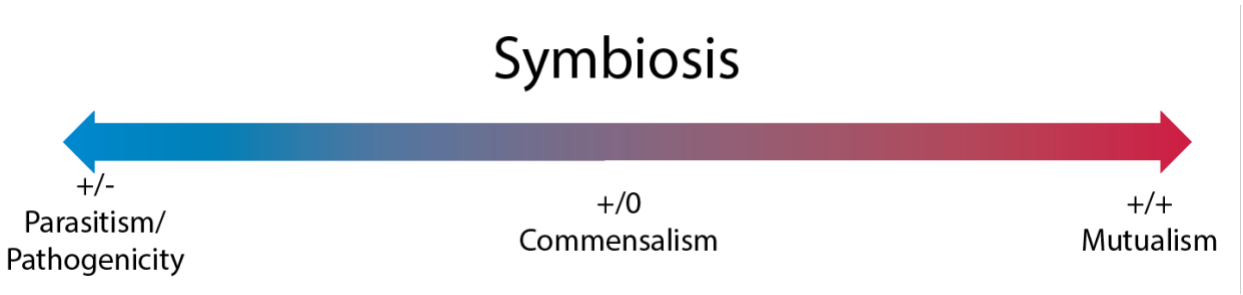

Figure 1. Symbiosis exists on a spectrum where relationships can shift over time and space. For host-microbe interactions, we assume that the microbe benefits across all relationships, but the impact on the host can range from harmful (parasitism) to neutral (commensalism) to beneficial (mutualism).

References

1. Gilbert JA, Lynch SV. 2019. Community ecology as a framework for human microbiome research. Nat Med 25:884–889.

2. Costello EK, Stagaman K, Dethlefsen L, Bohannan BJM, Relman DA. 2012. The Application of Ecological Theory Toward an Understanding of the Human Microbiome. Science 336:1255–1262.

3. Egan S, Fukatsu T, Francino MP. 2020. Opportunities and challenges to microbial symbiosis research in the microbiome era. Front Microbiol 11:1150.

4. Casadevall A, Pirofski L. 2003. The damage-response framework of microbial pathogenesis. Nat Rev Microbiol 1:17–24.

5. Drew GC, Stevens EJ, King KC. 2021. Microbial evolution and transitions along the parasite–mutualist continuum. Nat Rev Microbiol 19:623–638.

6. Matsuura Y, Moriyama M, Łukasik P, Vanderpool D, Tanahashi M, Meng X-Y, McCutcheon JP, Fukatsu T. 2018. Recurrent symbiont recruitment from fungal parasites in cicadas. Proc Natl Acad Sci 115:E5970–E5979.

7. Sachs JL, Wilcox TP. 2006. A shift to parasitism in the jellyfish symbiont *Symbiodinium microadriaticum*. Proc R Soc B: Biol Sci 273:425–429.

8. Allen-Waller L, Barott KL. 2023. Symbiotic dinoflagellates divert energy away from mutualism during coral bleaching recovery. Symbiosis 89:173–186.

9. Kerr PJ. 2012. Myxomatosis in Australia and Europe: A model for emerging infectious diseases. Antivir Res 93:387–415.

10. Schille TB, Sprague JL, Naglik JR, Brunke S, Hube B. 2025. Commensalism and pathogenesis of *Candida albicans* at the mucosal interface. Nat Rev Microbiol 23:525–540.

11. Carlile SR, Cahill SC, O'Brien EC, Neto NGB, Monaghan MG, McLoughlin RM. 2024. Staphylococcus aureus induced trained immunity in macrophages confers heterologous protection against gram-negative bacterial infection. iScience 27:111284.

12. Jenul C, Horswill AR. 2019. Regulation of *Staphylococcus aureus* virulence. Microbiol Spectr 7:10.1128/microbiolspec.gpp3-0031–2018.

13. West SR, Suddaby AB, Lewin GR, Ibberson CB. 2024. *Rothia*. Trends Microbiol 32:720–721.

14. Diard M, Hardt W-D. 2017. Evolution of bacterial virulence. FEMS Microbiol Rev 41:679–697.

15. Kun Á, Hubai AG, Král A, Mokos J, Mikulecz BÁ, Radványi Á. 2023. Do pathogens always evolve to be less virulent? The virulence–transmission trade-off in light of the COVID-19 pandemic. Biol Futur 74:69–80.

16. Sidhu RK, Fiol GM, Lê-Bury P, Demeure CE, Bougit E, Beau R, Balière C, Kwasiborski A, Caro V, Klunk J, Salkeld DJ, Carmichael A, Varlık N, Poinar D, Earn DJD, Bolker BM, Dushoff J, Golding GB, Rascovan N, Dussurget O, Holmes EC, Pizarro-Cerdá J, Poinar HN. 2025. Attenuation of virulence in *Yersinia pestis* across three plague pandemics. Science 388:eadt3880.

17. Supply P, Marceau M, Mangenot S, Roche D, Rouanet C, Khanna V, Majlessi L, Criscuolo A, Tap J, Pawlik A, Fiette L, Orgeur M, Fabre M, Parmentier C, Frigui W, Simeone R, Boritsch EC, Debrie A-S, Willery E, Walker D, Quail MA, Ma L, Bouchier C, Salvignol G, Sayes F, Cascioferro A, Seemann T, Barbe V, Locht C, Gutierrez M-C, Leclerc C, Bentley SD, Stinear TP, Brisse S, Médigue C, Parkhill J, Cruveiller S, Brosch R. 2013. Genomic analysis of smooth tubercle bacilli provides insights into ancestry and pathoadaptation of *Mycobacterium tuberculosis*. Nat Genet 45:172–179.

18. Jochum L, Stecher B. 2020. Label or concept – what is a pathobiont? Trends Microbiol 28:789–792.

19. Connell WT. 1911. Human carriers of disease. Canadian Medical Association Journal 1:325–334.

20. Mackie TJ, McCartney JE. 1928. An Introduction to Practical Bacteriology. William Wood & Company, New York.

21. Wiesmann CL, Wang NR, Zhang Y, Liu Z, Haney CH. 2022. Origins of symbiosis: shared mechanisms underlying microbial pathogenesis, commensalism and mutualism of plants and animals. FEMS Microbiol Rev 47:fuac048.

22. Amario M, Villela LB, Jardim-Messeder D, Silva-Lima AW, Rosado PM, Moura RL de, Sachetto-Martins G, Chaloub RM, Salomon PS. 2023. Physiological response of Symbiodiniaceae to thermal stress: Reactive oxygen species, photosynthesis, and relative cell size. PLOS ONE 18:e0284717.

23. Smith AB, Jenior ML, Keenan O, Hart JL, Specker J, Abbas A, Rangel PC, Di C, Green J, Bustin KA, Gaddy JA, Nicholson MR, Laut C, Kelly BJ, Matthews ML, Evans DR, Tyne DV, Furth EE, Papin JA, Bushman FD, Erlichman J, Baldassano RN, Silverman MA, Dunny GM, Prentice BM, Skaar EP, Zackular JP. 2022. Enterococci enhance *Clostridioides difficile* pathogenesis. Nature 611:780–786.

24. Hunt BC, Brix V, Vath J, Guterman LB, Taddei SM, Deka N, Learman BS, Brauer AL, Shen S, Qu J, Armbruster CE. 2024. Metabolic interplay between *Proteus mirabilis* and *Enterococcus faecalis* facilitates polymicrobial biofilm formation and invasive disease. mBio 15:e02164-24.

25. Esaiassen E, Hjerde E, Cavanagh JP, Simonsen GS, Klingenberg C, Infections NSG on IB. 2017. Bifidobacterium bacteremia: clinical characteristics and a genomic approach to assess pathogenicity. J Clin Microbiol 55:2234–2248.

26. Jensen PA. 2025. Ten species comprise half of the bacteriology literature, leaving most species unstudied. bioRxiv 2025.01.04.631297.