The hidden social networks of microbes

by Gina Lewin

In your mouth there are billions of bacterial cells growing on your teeth and below your gumline. These microbes are not each alone in a little bubble, but instead interact with each other and with your human cells. Undoubtedly, these interactions are important; they determine the behavior of individual microbes, the composition of your oral microbiome, and ultimately, the development of cavities and gum disease. But conceptualizing these interactions and understanding their impact is a huge challenge.

As a microbial ecologist, there is no way I can study the millions of possible pairwise interactions among the hundreds of species in our oral microbiota, not to mention any higher-level interactions. Instead, I must prioritize my efforts. I assume that due to the spatial structure of the oral microbiota, not all of these possible interactions are actually occurring. Further, many of the interactions likely have only a minuscule impact on the overall behavior of the community, the evolution of the microbes involved, or the progression of diseases. Yet, this still leaves an unknown, and possibly vast number of important interactions to try to understand, leading me to ponder basic, unanswered questions. When and how do microbes within a community interact? And potentially even more importantly, when and how do those interactions matter?

These questions are not unique to the oral microbiota. A better understanding of microbial interactions is important across environments, from our microbiome, to soil and plant-associated communities, to the microbes driving carbon cycling in our oceans. There is a basic science value in understanding these important, complex communities. Additionally, scientists hypothesize that altering key interactions can allow us to shift our communities, for example from a diseased state to a healthy state. To determine whether this is actually feasible requires researchers to identify the key interactions and to understand the implications of microbial interactions on both ecological and evolutionary timescales. Thus, while I research the oral microbiota because of its importance to human health, ease of study, and interesting spatial and temporal community dynamics, I hope that my work has broad relevance across systems.

Biomusings

Recently, in collaboration with my co-authors, I studied the interactions formed by the oral pathogen *Aggregatibacter actinomycetemcomitans* (*Aa*) in pairwise coinfection with 25 different microbes in a mouse abscess infection model. Each of these 25 microbes altered the set of essential genes that *Aa* needed to survive in the abscess, implying that each microbe interacted with *Aa* in some manner. Further, we found that each interaction altered *Aa*'s essential genes in a unique way.

Many of the interactions in these experiments with *Aa* were indirect, likely mediated through the mouse and its immune system. This type of interaction, transmitted through a eukaryotic host, the environment, or other members of the microbial community, are undoubtedly pervasive. For example, a number of publications have emphasized the role that pH can play in shaping soil communities. Microbes, including transient community members, can alter the pH, impacting a community's composition and function, and even its antibiotic resistance.
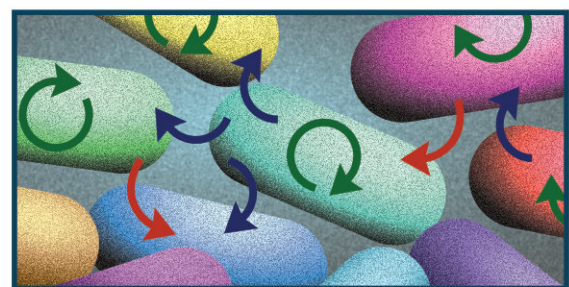
In my coinfection experiments, other interactions may have been directly between *Aa* and the coinfecting microbe, mediated through processes such as cross-feeding, exploitative competition, or chemical warfare. Yet, it is difficult to know when the microbes were directly interacting. Microbes must be near each other, on a micron scale, to be able to interact through many known mechanisms. Microbial communication via diffusible molecules or cell-cell contact usually requires relatively close quarters between the cells, as does cross-feeding or contact-dependent warfare. However, if microbes are not close by, does that mean they simply thrive in different microenvironments and do not interact? Or does that mean they once were in close proximity, but then distanced due to negative interactions?

It suffices to say that interactions within a microbial community are complex, and defining each interaction is not trivial. Thoughtful experimental designs and detailed analyses continue to uncover fascinating interactions within communities that are key to human health or ecosystem functioning. Moreover, we are still discovering new mechanisms that microbes use to compete or cooperate. This work is critical as it informs our understanding of how interactions can alter microbial community ecology, evolutionary trajectories, and even ecosystem-level processes.

Individual-scale interactions

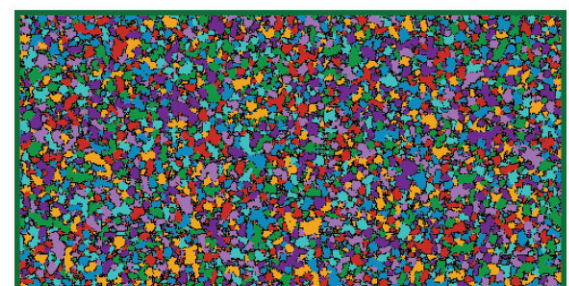complex feedback

Eco-evolutionary scales

Specifically, recent work across environments has illuminated the importance of microbe-microbe interactions in shaping the ecology of communities. By definition, interactions are key to community ecology, influencing aspects ranging from a community's composition and function, to its stability, to the ability of organisms to invade.

Understanding ecological interactions can also help explain how low abundance species have an over-sized impact. Low abundance microbes known as keystone pathogens are thought to be able to shift a community from a healthy to a diseased state. The classic exemplar in the oral microbiome is *Porphyromonas gingivalis*. It is thought that *P. gingivalis* alters the local immune environment, providing opportunities for other pathogenic bacteria to thrive. More broadly, the idea of keystone species is important in microbial communities for conceptualizing how low abundance organisms can shift the ecology of a community through direct or indirect interactions.

On an evolutionary timescale, a lot of exciting work has recently highlighted the importance of polymicrobial interactions. While studies on the long-term evolution of individual species in isolation have been groundbreaking and critically informative, studies have also shown that evolutionary trajectories differ when organisms are within a community. For example, the presence of a community can slow the rate of evolution of antibiotic resistance, a pressing global challenge. Further, in plant biomass degrading communities, the evolutionary and functional outcomes of focal organisms varied depending on the community diversity. These studies remind us that the community is a critical determinant of microbial evolution.

To further complicate matters, interspecies interactions themselves can evolve. This phenomenon has been studied in simple communities where, for instance, obligate mutualists both evolved to have a more stable and productive interaction. Evolution of increased stability has also been observed in simple cross-feeding interactions. However, as mentioned above, the taxonomic and functional diversity of the community itself influences evolutionary trajectories, so it remains unknown how these findings will scale.

These examples demonstrate that interactions are critically important in microbial ecology and evolution. However, in many cases, it is not known which polymicrobial interactions influence the behavior and evolutionary trajectory of microbes. It is an exciting time in microbial ecology as we continue to integrate the chronicling of microbial interactions and the assessment of their impact. Together, this work is promising and important, advancing our understanding of the microbial communities that define our lives.

Gina is postdoctoral fellow in the lab of Marvin Whiteley at Georgia Tech. She is broadly interested in polymicrobial interactions and is currently studying microbe-microbe interactions in the oral cavity. Previously, Gina completed her PhD under the mentorship of Cameron Currie at University of Wisconsin-Madison. For more information, see her publications or find her on Twitter.