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Towards a General Understanding of Bacterial Interactions

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Understanding the general rules of microbial interactions is central for advancing microbial ecology. Recent studies show that interaction range, interaction strength, and community context determine bacterial interactions and the coexistence and evolution of bacteria. We highlight how these factors could contribute to a general understanding of bacterial interactions.

Microbial Community Ecology

A central tenet of community ecology is to understand the rules of species interactions and their consequences for community structure, such as species diversity. Historically, microbial interactions and their outcomes were studied to test theories of community ecology (e.g., [1,2]) which were developed for plants and animals [3,4]. This trend has changed remarkably in the last few years with rapid progress in microbial community ecology due mainly to the continued growth of molecular technologies [4,5]. Today, microbial community ecology has become an integral branch of ecology and microbiology and it continues to advance our understanding of the implications of microbial interactions for disease control, food production, climate change mitigation, and biodiversity conservation.

Bacteria are among the most studied microorganisms in microbial community ecology, particularly when it comes to experimental assessments of microbial interactions [4]. Yet, we still lack a consensus for how bacterial species interact, and how those interactions may regulate the diversity of bacteria [6]. This is due to several key challenges in studying bacterial interactions, such as delineating the spatial and temporal scale at which bacteria interact, quantifying the strength of their interactions, dependence of their interactions on abiotic conditions, and constantly varying interactions owing to rapid evolution and changes in bacterial abundance. Three recent studies provide insight into overcoming these challenges [7–9]. These studies independently show interaction range [7], interaction strength [8], and community context [9] as three factors determining bacterial species interaction and the coexistence and evolution of bacteria. We highlight how simultaneous consideration of these three factors can help to achieve a more general understanding of bacterial interactions (Figure 1) and their relevance for building predictive models for microbial community ecology.

Interaction Range, Interaction Strength, and Community Context

Interaction range is the spatial domain in which an individual can interact with other individuals of either the same species or a different species. Usually, the interaction ranges of several bacterial cells are limited to their close surroundings, such as biofilms [10]. However, even within biofilms, some cells are close neighbors while others are distant. Whether bacterial cells in spatially structured biofilms interact with close and distant neighbors is not well understood given the complexity in empirically quantifying the distances between bacteria during their interactions. Dal Co *et al*. [7] used an elegant approach of measuring the interaction range of bacterial cells as the size of the neighborhood from which one bacterial cell can retrieve the amino acids produced by neighboring cells. They highlight that the interaction range of bacteria is short, that is, individuals interact only with their immediate neighbors. More specifically, they used two genotypes of *Escherichia coli* that exchange essential amino acids for their growth. They showed that the growth of one genotype was promoted when most of its neighbors in its interaction range were of the other genotype [7]. This study contributes to a general understanding of how the range of interaction matters for facilitation and coexistence at the cellular level.

While the size of the interaction range of a bacterial cell indicates the distance over which it can affect another cell (Figure 1), the direction (mutualistic or antagonistic) of these bacterial interactions is likely to depend on how bacterial cells modify their immediate environment [11]. Towards this end, Ratzke *et al*. [8] showed that increased nutrient availability promoted the ability of soil bacterial species to modify their environment (e.g., pH values), which subsequently magnified the negative interactions between soil bacterial species. Interestingly, this study highlighted that the strength of negative interactions between bacterial species was mediated mainly by the production of toxic metabolites and could not be attenuated by refreshing nutrients. These strong competitive interactions between bacterial species impeded species coexistence and decreased the stability of the bacterial communities.

There is a growing interest in understanding the roles of evolutionary processes in driving species coexistence [12]. An experimental study by Scheuerl *et al*. [9] demonstrated that bacterial species (obtained from the rainwater in tree holes) had greater evolutionary responses to environmental changes (low pH) when the bacterial communities had a low diversity, presumably owing to weaker competitive interactions. These authors show that strong competitive interactions, as found in the diverse bacterial communities, limit

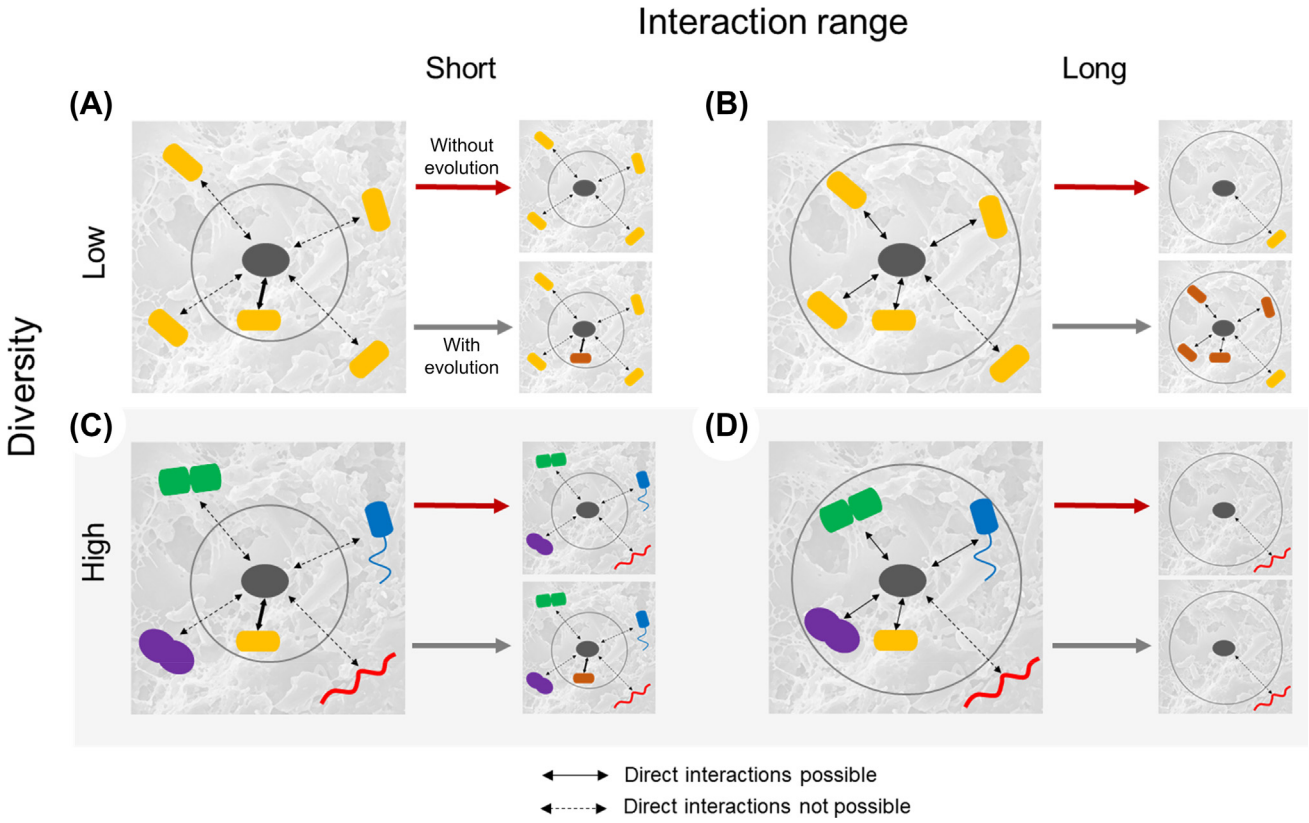

Figure 1. Some General Rules and Outcomes of Bacterial Interactions. Interaction range (short and long), interaction strength (weak and strong), and community context (low and high diversity) affect bacterial coexistence and evolution. We discuss several possibilities for bacterial coexistence using an example of a focal bacterial species (gray filled) and its interaction with neighboring bacterial species. For simplicity, we focus on competitive interactions, but the framework can be adapted to include both competitive and facilitative interactions. (A) Low-diversity, short-interaction range. In a low-diversity scenario, when the gray bacterial species has short interaction range (indicated by the gray circle) and interaction strength (indicated by the thicker double-sided arrows), it excludes its nearest neighbors, like the yellow bacterial species, by its ability to modify the environment (e.g., the pH). However, when considering evolution, such competitive interactions could also lead to diversification (indicated by the emergence of the orange bacteria) when the yellow bacteria can adapt to the new environment modified by the gray bacteria. (B) Low-diversity, long-interaction range. When the same gray bacterial species has a longer interaction range it excludes more yellow bacteria in the absence of evolution, whereas a greater diversification of the yellow bacteria takes place in the presence of evolution. (C) High-diversity, short-interaction range. In this scenario, we illustrate the example of five bacterial species living next to the gray bacteria, but only one of them (the yellow one) falls within the short interaction range. The results are identical to the outcomes shown in scenario (A) despite the difference in species diversity. (D) High-diversity, long-interaction range. When the same gray bacterial species has a longer interaction range it excludes the four neighboring species within its interaction range in the absence of evolution. When considering evolution, Scheuerl *et al*. [9] showed that evolution is constrained when multiple species are interacting (presumably owing to strong interaction strength – not shown in the figure), implying that evolution might not be rapid enough to prevent exclusion of the four neighboring species.

the capacity of bacterial species to evolve, thereby highlighting the importance of 'community context' as a key predictor of bacterial evolutionary dynamics. Taken together, these three recent independent studies [7–9] have provided us with potential general rules on how bacteria interact, and further highlight the often overlooked implications of bacterial interactions for evolutionary dynamics (Figure 1).

Outlook

We suggest that interaction range, interaction strength, and community context should be considered simultaneously for a better understanding of bacterial interactions. In particular, considering evolution will enhance our ability to predict variations in a bacterial community in a given environment (some scenarios are shown in Figure 1). Microbial ecologists have consistently emphasized the importance of making microbial ecology a predictive science rather than just a descriptive science as most research in microbial ecology still continues to be on microbial inventories in various environments [3,6]. We believe that, to make microbial ecology more predictive, we need to integrate general rules of microbial interactions to study microbial community diversity, functioning, and

evolution. The rules highlighted by the three studies discussed earlier [7–9] are an important step towards this goal. Future studies can further explore how these rules may affect each other (Figure 1) – for instance, how the interaction range of bacteria and their ability to modify the environment relate to each other. Moreover, it will be important to test the significance of interaction range, interaction strength, and community context for regulating bacterial community structure in the context of bacterial interactions with other microorganisms (e.g., fungi) and their predators (e.g., protists), and also in the context of different and novel environments, such as those created by climate warming and drought.

Acknowledgments

We thank two anonymous reviewers for helpful comments. Z.Z. acknowledges funding from the China Scholarship Council (201606100049). M.P.T. acknowledges funding from the German Research Foundation (DFG, TH 2307/1-1, 2-1).

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https://doi.org/10.1016/j.tim.2020.05.010

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Forum

Bacterial Flagella Loss under Starvation

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The bacterial flagellum is beneficial in most cases but it can become a burden when the energy source is low because it is very costly to assemble and energize for motility. Recent electron cryo-tomography and real-time fluorescence microscopy studies suggest that bacteria can remove their flagella under starvation in a programmed way.

What can one do when facing a food and energy crisis? Imagine that a bacterium is swimming with its flagella in search of food but, for a while, finds nothing. It would then be advantageous for the bacterium to slow down its propeller in order to conserve energy. This can be achieved by a molecular brake (YcgR) or a clutch (MotI) that acts directly on flagellar motor/stator proteins in a c-di-GMP-dependent manner to impede rotation [1,2]. Meanwhile, do not make new or more flagella! This is easy to control since the expression of flagellar components is precisely and tightly regulated at both the transcriptional and translational levels according to environmental cues; however, several recent studies on bacterial flagella have discovered that these actions are not enough to overcome the crisis.

Bacteria Can Disassemble Flagellar Filaments When Nutrients Are Limited

Using negative-stain electron microscopy (EM) imaging, Ferreira *et al*. observed that the flagellation level of some gammaproteobacteria varies greatly at different growth stages, with high numbers of flagella at low cell density but low numbers, or even none, at a later, stationary phase [3]. Further quantitative analysis of the absolute number of flagella – including those attached to bacterial cells and those free in the growth medium – suggests that bacteria lose flagella faster than they synthesize them in the stationary phase. In addition, free flagella in the supernatant contain both the hook and the filament – similar to flagella ejected by *Caulobacter crescentus* – indicating that the observed gamma-proteobacteria are likely ejecting flagella at the base of the hook.

This phenomenon was recently confirmed by another research group who tracked the flagellar assembly and disassembly

Box 1. Multiple Rings in Flagellar Structures from the inside Out

C-ring: a cytoplasmic ring – composed of proteins FliG, FliM, and FliN, and in some cases also FliY – functioning as a rotor switch to change the rotation between clockwise and counterclockwise.

MS-ring: a membrane/supramembrane ring, made of protein FliF, that is predominantly periplasmic and tethered to the inner membrane, interacting with the C-ring.

P-ring: a ring, made of the protein FlgI, embedded in the peptidoglycan layer.

L-ring: a ring, made of the protein FlgH, embedded in the lipopolysaccharide layer, together with the P-ring, serving as bushing for the flagellar rod to rotate.