

Editorial: Signals to sociality: how microbial communication fashions communities

The unicellular and liquid-dwelling lifestyles of bacteria have historically dominated microbiological studies, yet most bacteria exist in nature in multifaceted communities that are often associated with living and non-living surfaces. Within these communities, bacteria are exchanging information with other bacteria and other organisms, including eukaryotes, to generate coordinated behaviors. Central to this microbial information exchange is communication between cells. The act of communication exists in many forms and is often considered essential for organized group behaviors between individuals and for the development of multicellular organisms. The collection of reviews presented in the thematic issue ‘Signals to sociality: how microbial communication fashions communities’ (bit.ly/MicrobialCom) addresses several outstanding questions in microbial cell–cell communication. These reviews highlight aspects of cell–cell communication through the lens of microbial linguistics (which signals are communicated and how), microbial ecology and evolution (how communication impacts individuals within communities over time), microbial sociology (‘sociomicrobiology’ (Parsek and Greenberg 2005), how communication impacts group behaviors), and microbial chemistry (what the intrinsic nature of these signaling molecules is).

Our knowledge of microbial cell–cell communication is vast and rapidly expanding. Traditional quorum sensing was the first mode of cell–cell communication to be described (Nealson, Platt and Hastings 1970; Engbrecht, Nealson and Silverman 1983; Kaplan and Greenberg 1987; Bassler et al. 1993) and is generally considered to be the control of gene expression in response to cell-population density through the production of and response to freely diffusible small molecules. A large number of organisms produce and respond to more than one quorum-sensing molecule, enabling many ‘conversations’ to be conducted simultaneously. In this issue, Hawver et al. consider the fascinating question of how *Vibrio cholerae*, and other bacteria, distinguish between the quorum-sensing molecule(s) they produce and those to which they respond and adjust their behavior accordingly, a behavior that is metaphorically analogous to leaning in to hear a conversation amidst the din of a cocktail party. The authors discuss how this listening specificity is rooted in the evolution of quorum-sensing receptors with exquisite specificity for their ligand and broaden this discussion to examine why some microbes have evolved greater complexity in their quorum-sensing pathways.

Evolutionary questions about the establishment and maintenance of group behaviors can also be queried with respect to quorum sensing. In this issue, Asfahl and Schuster address

the utility of quorum sensing for testing evolutionary models about cooperation by reviewing broader questions about microbial social behaviors. The authors consider how a community promotes cooperation amongst its constituents and prevents the emergence and proliferation of cheaters that could disrupt the social order. Asfahl and Schuster dissect the current models for cooperation and persuasively argue for the continued use of bacteria and quorum sensing as a tractable model for examining the evolution of social behaviors.

The observation that quorum sensing can control bacterial virulence (Williams et al. 2000) supported investigations into whether disrupting quorum-sensing conversations that lead to sociality could have therapeutic benefits. For example, a quorum-sensing antagonist has been shown to reduce virulence in mice and may prove to be clinically relevant (Starkey et al. 2014). Welsh and Blackwell discuss how such synthetic quorum-sensing molecules could also be used to probe for new biological insights into microbial physiology and community structures. Starting from an inclusive view of quorum sensing from a chemical perspective, the authors provide a refreshing evaluation of what other aspects of the biology and physiology of bacteria could be understood through synthetically altering quorum-sensing pathways, or in other words, how changing to a new ‘microbial dialect’ could reveal unknown behaviors. Significantly, the authors also posit that increasing knowledge about metabolic pathways impacted by quorum sensing has the potential to identify new pathways that could be directly targeted in future drug development.

In a similar vein, Okada and Seyedsayamodst describe how secondary metabolites produced by one organism can be used to probe secondary metabolism in other organisms and even lead to the discovery of novel antibiotics. In reviewing how antibiotics themselves can be potent inducers of biosynthetic pathways when used at subinhibitory concentrations, the authors posit that these small molecules comprise a previously unappreciated ‘microbial vocabulary’ for mediating intra- and interspecies and interkingdom conversations. They further submit the intriguing hypothesis that if antibiotics are a bonafide form of cell–cell communication, antibiotic resistance ‘may be akin to putting headphones on’ and unplugging from the conversation.

The diversity of small molecules produced by bacteria implies that equally diverse processes mediate communication between microbes. These dialogues could be for coordinating populations, as suggested by traditional quorum sensing, managing survival in mixed populations, or navigating changing environmental conditions. Indeed, the majority of bacterial life

exists within communities of organisms that are connected in ways that we largely do not understand. While DNA-sequencing technologies have allowed us to catalog the diversity in these communities, a major challenge is to determine how these communities are organized. Abreu and Taga advocate for an integrated, multilayered approach for 'Google-translating' the chemical and metabolic dialogues that underlie the organization of these communities. Beginning with an overview of the current 'microbiome tool kit' techniques that have been used to document relationships between species in diverse communities ranging from marine ecosystems to our gut microbiota, the authors then describe the challenge of decoding the intricate interactions that structure a given community. These challenges include developing methods for culturing microbes in complex communities in order to interrogate their roles within the community, identifying metabolic connections between organisms, and determining the functions of unknown genes.

In addition, Abreu and Taga highlight how assessing the spatial interactions between community members, identifying the signaling molecules present, and determining their mechanism of action will be necessary to identify the fundamental principles that underlie community structure. Shank and Stasulli extend this discussion by providing a detailed survey of the cutting-edge techniques that are being used to detect these specialized metabolites directly within communities. Shank and Stasulli describe multiple novel techniques used to uncover the unseen molecules that surround bacterial communities and that influence the behaviors of individuals and groups of cells. The authors discuss the applications and limitations of these techniques and provide a much-needed guide to these emerging technologies, thereby giving the reader a toolbox for finding new 'languages'. The authors also highlight the increasing use of these techniques to probe community structures on living surfaces, for example, the microbes and small molecules present on the skin of a human being, and consider the potential impact that this increased knowledge can have on understanding the dialogue between bacteria and the eukaryotic members of their local communities.

Although cell-cell communication has mainly been framed as the exchange of small molecules, recent advances indicate that communication is not only chemical but also tactile. Okada and Seyedsayamdost describe how cell-cell contact is necessary to stimulate biosynthetic gene clusters in some cases. Similarly, physical touching as a mechanism for cell-cell communication has been described in the interactions of social microbes and a eukaryotic parasite (Nudleman, Wall and Kaiser 2005; Gibbs, Urbanowski and Greenberg 2008; Budding et al. 2009; Pathak et al. 2012; Cardarelli, Saak and Gibbs 2015; Imhof et al. 2016). Purcell and Tamayo argue that this mode of sensing is likely far more ubiquitous than we currently appreciate given that the majority of bacterial life exists in a surface-associated state, suggesting that microbial touching can convey information metaphorically similar to handshakes between individuals. The authors address how tactile sensing by type IV pili and flagella can stimulate the production of the secondary messenger cyclic di-GMP in both Gram-negative and Gram-positive bacteria. Cyclic di-GMP regulates the transition between motility and sessility in Gram-negative bacteria (Romling, Galperin and Gomelsky 2013), but remarkably this signaling molecule was only detected in Gram-positive bacteria 6 years ago. Purcell and Tamayo provide the first overview of the role of this ubiquitous signaling molecule in Gram-positive bacteria and highlight how cyclic di-GMP similarly regulates sessility in this group of bacteria, suggesting

that its meaning is translated similarly across distantly related organisms.

Similarly, cell-cell communication is present in unicellular eukaryotes. Reid and Latty discuss how eukaryotic microbes can serve as models for cell-cell communication and social behaviors. The authors more broadly consider whether the observed group behaviors of two slime molds (*Dictyostelium discoideum* and *Physarum polycephalum*) are examples of 'collective intelligence'. One definition for collective intelligence is the ability for a group of organisms to perform tasks with greater success and/or efficiency than any given individual within the population as observed for ant colonies (Sumpter 2006), calling to mind Aristotle's quote that the complete is more than the sum of its pieces. Reid and Latty put forward the provocation that both *Physarum* and *Dictyostelium* can be considered models of collective intelligence, following the same guiding principles as for more complex organisms. One is then left considering whether guiding principles developed by studying these eukaryotic microbes could be applied to group behaviors observed in archaea or bacteria.

In the collection of reviews presented in this thematic issue (bit.ly/MicrobialCom), we have selected to highlight a few of the cutting-edge areas into which the field of microbial cell-cell communication is expanding. This collection of reviews by no means covers the entire field, and we look to future reviews and papers that will continue to uncover and explain the elegance of communication and interactive behaviors in which microbes are engaged. Together, these articles highlight that many of the challenging questions in cell-cell communication and behaviors within communities lie at the intersection of multiple fields. Clearly, it will take the coordinated efforts of scientists from multiple disciplines learning and researching together to advance this frontier of research.

We are only starting to identify and learn the microbial languages and behaviors that structure communities. Further understanding of the evolution, ecology and zoology (behavior, structure and physiology) of microbes will continue to unveil the complex communities formed and maintained by these unicellular organisms. As research continues to probe fundamental questions about the formation and emergence of multicellularity (Fairclough, Dayel and King 2010; Alegado et al. 2012; Levin et al. 2014; Anderson et al. 2016; Sebe-Pedros et al. 2016), a more fundamental question arises: whether cell-cell communication was a trait central for the formation of a communal life, shared by common ancestors, or whether it has arisen time and time again for the formation of communities, be they comprised of independent cells or multiple interdependent cells within a single organism.

We would like to thank the authors for contributing these high-quality reviews, the reviewers for improving each manuscript, Alain Filloux for his editorial guidance and the journal staff of FEMS Microbiology Reviews, especially Jennifer Norman and Erwin Ripmester, for their support in assembling this thematic issue on microbial cell-cell communication.

Conflict of interest. None declared.

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