ACS SyntheticBiology

Editorial

pubs.acs.org/synthbio

Cell−Cell Communication Special Issue

Microorganisms often use the production and sensing of small molecules as a means of communication. Quorum-sensing (QS) systems allow microbes to sense changes in local population density, coordinate behavior across populations, and often allow single-celled organisms to behave like complex multicellular systems. Synthetic biologists have frequently used QS signal production and sensing components to build cell−cell communication networks and coordinate the behaviors of multiple populations of cells. Such synthetic systems have provided important insights into natural QS systems, ecological interactions, pattern formation, and network behaviors such as oscillations and feedback control. This special issue includes contributions from leading scientists and engineers who have developed new cell−cell communication components, systems, and mathematical models, that can be used to develop the next generation of engineered microbial communities for diverse applications.

Adams *et al.* developed two new sensors that respond to the QS molecule known as autoinducer-2 (AI-2). AI-2 is an interesting target because, unlike many QS systems, it is found in both Gram-negative and Gram-positive organisms. They used directed evolution and identified two variants of LsrR, a transcriptional repressor that blocks transcription in the absence of phosphorylated AI-2. One of the variants, aLsrR, behaves in a manner that is opposite to the wild type, where it blocks transcription in the presence of phosphorylated AI-2 and releases the DNA in the absence of this molecule. They show that aLsrR can be used to lower gene expression levels as a function of cell density. Since most QS systems used by synthetic biologists lead to increases in gene expression as a function of cell density, this represents a valuable new tool for dynamically changing gene expression up or down in response to a cell−cell communication signal.

Silva-Rocha and de Lorenzo demonstrated that new cell−cell communication systems can be built using metabolites as signal molecules. They targeted the toluene degradation pathway from *Pseudomonas putida* because both the enzymes involved in the pathway and key genetic regulators are well characterized. They engineered one strain to recognize toluene and express the catabolic genes that degrade toluene to benzoic acid. A second strain was engineered to sense benzoic acid and turn on the expression of a reporter or a set of genes that lead to the degradation of benzoic acid. Here, the catabolic intermediate, benzoic acid, serves as a synthetic cell−cell communication signal. This work highlights the potential of using metabolic intermediates as new chemical wires between cells.

Hwang *et al.* developed a strain of *Escherichia coli* that migrates toward and kills the opportunistic pathogen *Pseudomonas aeruginosa*. To target *P. aeruginosa*, they engineered *E. coli* to recognize a QS signal naturally produced by *P. aeruginosa*. They first showed that they could use the recognition of this QS signal to restore motility in a strain lacking a key protein involved in the chemotaxis pathway, CheZ. They subsequently engineered the *E. coli* to the express and secrete an antimicrobial peptide and DNAse I in response to the *P. aeruginosa* QS signal and showed that this combination of secreted proteins could both kill the target pathogen and disrupt its biofilms. Finally, they put the motility, antimicrobial, and antibiofilm elements together and assessed whether the *E. coli* would migrate toward the pathogen using a transwell plate system where the strains were initially separated by a membrane. They observed that the "seek and kill" *E. coli* strain both moved toward the *P. aeruginosa* through the membrane and led to both planktonic cell killing and biofilm disruption.

Zomorrodi *et al.* generated a new dynamic metabolic model for analyzing microbial communities. This new model, d-OptCom, builds on previous static models by including substrate update kinetics to enable dynamic metabolic modeling. Synthetic biologists often use microbial auxotrophs, which require an exogenously added compound to grow in minimal media, to make strains to require each other for survival in engineered microbial communities. Here, they showed that the dynamic model, which includes both species and community-level fitness objectives, better predicts the final biomass compositions of pairs of *E. coli* auxotrophs than the static version of their model (OptCom) and alternative models. This model may improve our ability to predict the behavior of such synthetic microbial consortia in the future.

Pai and co-workers showed that a single metric could be used to describe the dominant activation properties of diverse QS systems. They had previously introduced the concept of "sensing potential", which is defined as the cell density at the single point where QS-dependent gene expression reaches a half-maximal level. Here, they explored whether sensing potential could predict temporal dynamics of a QS system. By combining modeling and experiments, they showed that sensing potential could be used to make reasonable predictions of the dynamics of QS activation. This type of approach may improve our understanding of natural QS systems without requiring that all aspects of the networks have been identified and characterized.

My own group reports the design and construction of a genetic AND gate that recognizes a combination of endogenous and exogenous signal molecules. We developed two hybrid promoters that include binding sites for the QS regulator EsaR, which can act as a repressor, and the tetracycline repressor (TetR) or lac repressor (LacI). We first showed that gene expression from the two AND-gate promoters occurs only in the presence of a QS signal and either aTc or IPTG. We also observed AND-gate behavior when the QS signal was sent by a second strain of *E. coli* cells. When we added endogenous QS signal production to our AND-gate promoter containing cells by expressing a signal synthase, we observed that gene expression increased as a function of cell density only in the presence of the appropriate exogenous signal (aTc or IPTG). We believe these systems may

Special Issue: Cell-Cell Communication

Received: April 3, 2014
Published: April 18, 2014

   dx.doi.org/10.1021/sb500231j | *ACS Synth. Biol.* 2014, 3, 197−198

serve as alternatives to other autoinduction strategies, where the exogenous cue adds an extra level of control realtive to a simple QS-based induction system.

Cell−cell communication systems allow synthetic biologists to build networks that go beyond single organisms. A division of labor strategy, where different organisms in a community carry out specialized tasks, can be coordinated using cell−cell communication. We anticipate that such coordination will be essential for broadening the use of microbial communities in real-world applications where a single organism strategy is not possible or inefficient, such as bioprocessing, biosensing, and environmental remediation. We also expect to see synthetic biologists develop new tools that incorporate cell−cell communication relevant to human health increase in the near future, specifically those related to microbe−microbe interactions, novel antimicrobial strategies, and understanding and manipulating the human microbiome.

Cynthia H. Collins

Department of Chemical and Biological Engineering, Center for Biotechnology and Interdisciplinary Studies, Rensselaer Polytechnic Institute, 110 Eighth Street, Troy, New York 12180 United States

AUTHOR INFORMATION

Notes

Views expressed in this Editorial are those of the author and not necessarily the views of the ACS.

dx.doi.org/10.1021/sb500231j | *ACS Synth. Biol.* 2014, 3, 197−198