

Research statement

Evolution of cooperation and conflict in microbial systems

Cooperation is a fundamental process in evolution, spanning domains of life and scales of biological organization. From social insect colonies to multicellularity to mutualistic symbioses, throughout the history of life formerly independent biological units have evolved into new integrated wholes. This poses a puzzle, though: how does natural selection favor cooperation over conflict?

The goal of my research program is to understand the evolutionary processes governing (1) cooperation among microbes and (2) the symbiosis between bacteria and their mobile genetic elements. Using a combination of laboratory experiments and mathematical theory, I seek to test and improve social evolution theory by applying it to taxa biologically remote from the animal behavior context in which it was originally developed. Microbes are also fascinating organisms in their own right, and understanding their evolution has important implications for human health.

Cooperation among microbes

An explosion of research over the last ten years has shown that many important microbial phenotypes—including traits involved in pathogenicity, metabolism, and development—are cooperative. But what limits the spread of “cheater” genotypes that benefit from a cooperative trait without paying the fitness cost of producing it? Among animals, most cooperation evolves via kin selection, in which the fitness benefits of cooperation preferentially go to other individuals who also share alleles for cooperation, above chance alone. To determine whether kin selection is also responsible for cooperation in microbes, I derived a novel mathematical formulation of kin selection theory that can be quantitatively applied to microbial systems because it speaks in same terms as the data from laboratory experiments (smith et al. 2010). Applying this new theory to cooperative sporulation in *Myxococcus* bacteria, one of the key model systems in this field, I showed that nonlinear interactions among genotypes play a crucial role in preventing the spread of cheater mutants.

In animals, the genetic structure of social interaction necessary for kin selection is created by genealogical relatedness, but for asexual microbes the causes of social structure are less clear. My current research on cooperative sporulation in *Dictyostelium* amoeba seeks to understand how spatial ecology and microbial behavior interact to create genetic correlations among interacting cells. I’ve found that there is variation among naturally occurring strains for traits that affect social structure, indicating that social structure can itself evolve.

One of the most interesting ways in which social evolution may shape microbial biology is by creating adaptations for social competition. To test this possibility, I formulated an important null hypothesis identifying how nonadaptive processes would affect social microbes (smith et al., submitted). I showed that interactions between some *Myxococcus* variants were consistent with these nonadaptive effects, but those between environmental isolates were promising candidates for adaptive social competition (smith & Velicer, in prep.).

Molecular endosymbionts of bacteria

Bacteria often harbor mobile genetic elements like plasmids and phage that live inside cells but can also transmit themselves infectiously among cells. I use the relationship between these elements and their bacterial hosts to study the processes that cause symbioses to evolve towards mutualism or towards parasitism. In laboratory evolution experiments with plasmids, I tested a prominent hypothesis that parasite virulence evolves according to a trade-off between infectiousness and damage to hosts. I instead found that plasmids evolved to severely reduce bacterial fitness because of competition within hosts (smith 2011). This eventually led to overexploitation and created a tragedy of the commons among plasmids (smith, submitted). These results highlight how social competition among symbionts can strongly affect host-symbiont relationships.

Mobile elements often carry genes for pathogen virulence and resistance to antibiotics. This means that their evolution holds special relevance for human health, but it also creates an evolutionary puzzle: why aren't these genes a normal, stable part of bacterial chromosomes? An underlying issue is how evolution creates genetically coherent individuals out of independent replicators. I've shown that bacterial pathogens are predicted to be especially susceptible to cheating when virulence factors are secreted (smith 2001). Carrying virulence genes on mobile genetic elements may then be a mechanism to enforce cooperation by infecting cheaters with the genes for cooperation. Other research groups have followed up on this hypothesis and shown that mobile elements disproportionately carry genes whose products that are secreted, supporting a key prediction (Nogueria et al. 2009 *Curr. Biol.* 19:1683).

Future directions

My plasmid work unexpectedly identified an avenue of evolution in which plasmids rapidly evolved to lose antibiotic resistance genes and to suppress proliferation of their bacterial hosts—both of which are highly desirable clinical outcomes. In other situations, coevolution between bacteria and plasmids can lead to long-term persistence of antibiotic resistance even after antibiotic selection is removed. In my laboratory, one of our first research goals will be to identify the plasmid, host, and ecological traits that determine which avenue evolution follows. As part of this, we will investigate the potential for human intervention to promote the evolution of bacteria/plasmid antagonism and antibiotic sensitivity.

I am also excited to expand my research program to include bacterial infections of multicellular hosts. The genus *Vibrio* includes both mutualistic and pathogenic species, many of which are experimentally tractable model systems about which we have extensive genetic and ecological knowledge. Plasmid- and phage-borne secreted factors play a key role in many *Vibrio* infections, so one line of research in my lab will be to experimentally assess how social interactions among bacteria within hosts determine infection success and to test whether mobility of these genes can suppress cheating. In collaboration with Ned Ruby at the University of Wisconsin-Madison we will also study conflict and cooperation in the symbiosis between *Vibrio fischeri* and bobtail squid. Goals of this work include: determining the role of virulence factor homologues in mutualistic symbioses, including their effect on bacteria and host fitness; characterizing the association between *V. fischeri* and a phage closely related to that which carries the genes for cholera toxin in *V. cholerae*; and testing the ecological, demographic, and genetic factors theoretically predicted to select for symbionts that are more harmful or less harmful to their hosts.