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Janus-headed communication promotes bacterial cooperation and cheating

Is quorum sensing useful against infections?

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Bacteria often start certain cooperative actions—e.g., producing "public goods" such as exoenzymes or virulence factors—only when they have reached a critical density. To "measure" the population density of clone-mates in their close neighborhood many bacteria have evolved a simple chemical communication system called quorum sensing (QS).[1] The QS system comprises a few chromosomal genes, some producing and excreting the signal molecules, others coding for membrane receptors and a signal transduction system which pick up the signal from extracellular space and forward it to the genes responsible for cooperation.[2] Cooperation genes are expressed only above a threshold rate of QS signal molecule re-capture, i.e., above the local quorum of cooperators. Regulation by QS would allow the cells to express appropriate behavior only when it is effective, thus saving resources under low density conditions. Therefore, QS has been interpreted as a bacterial communication system to coordinate behaviors at the population level.[2,3] However, its evolutionary stability is somewhat problematic, since cooperative communication is vulnerable to cheating. For example, a signal-negative (mute) strain does not have to pay the metabolic cost of signal production, and a signal-blind (deaf) strain does not pay the cost of responding. Both type of mutants may still benefit from public goods produced in their neighborhood and have actually been observed among environmental and clinical isolates.[4,5] The question then is, under what conditions cheating strains will increase to such an extent that QS breaks down as a regulatory system of cooperative behavior—perhaps with the consequence that the cooperative behavior itself cannot be maintained.

In our paper[6] we analyzed a model of the evolution of QS-regulated cooperation. In fact, QS-regulated cooperation can be viewed as a superposition and interaction between two cooperative behaviors: the cooperative QS communication system, which coordinates another cooperative behavior (e.g., production of a public good). Both forms of cooperation are potentially vulnerable to being parasitized by cheating strains. We allow the reward and the cost of cooperation, the level of dispersal and the sensitivity of the QS system (the signal strength required to induce production of a public good) to vary, and ask for which parameter combinations cooperation and QS will evolve and be maintained, to what extent the presence of a QS system affects the evolution and maintenance of cooperation, how vulnerable the system is for social cheating and how equilibrium levels of QS and cooperation depend on the parameter values.

Our analysis consisted of computer simulations using a cellular automaton (CA) approach: a modeling framework fit for studying the collective behavior of any kind of locally interacting objects—in our case, bacterial cells. The basic structure of a cellular automaton is a square lattice, where each of the grid-points represent a site for a single bacterium; all the sites are always occupied, i.e., bacteria may replace each other, but may not leave empty sites. The inhabitants of the sites may differ at

three genetic loci: locus C for cooperation (production of a public good), the other two for quorum sensing: locus S for producing the signal molecule and locus R for signal response, which includes the signal receptor and the signal transduction machinery that triggers the cooperative behaviour when the critical signal concentration has been reached. Each of these loci can harbour either a functional allele denoted by a capital letter (C, S and R) or an inactive allele denoted by a small letter (c, s and r). Thus the bacteria can have $2^3 = 8$ different genotypes, each paying its own metabolic cost of allele expression at the 3 loci. The expression of the cooperating allele C is conditional on the presence of the signal receptor allele R and a sufficient local concentration of signal molecules in the signal-responsive C.R genotypes, whereas in non-responsive C.r cooperators the allele of cooperation is always expressed. The state of each cell may change in every time unit, according to its own state and that of its immediate neighbors in the lattice. The instructions determining the next state of a cell are the "transition rules" of the cellular automaton. In our model one bacterium may invade a neighbor's node if its metabolic cost of gene expression at the three loci is smaller. The power of the cellular automaton approach rests in the emergent collective properties of the whole lattice of cells it produces. Such emergent properties are the numbers of cells of the different genotypes after a certain number of time units elapsed or the spatial distribution (pattern) of the genotypes.

Our results suggest the following conclusions. First, cooperation only evolves under conditions of limited dispersal, i.e., when daughter cells tend to remain fairly closely together (reviewed in ref. 7 and 8). Second, the presence of cooperating strains in a population always selects for QS and cooperation becomes more common as a consequence of QS. Third, the communication—cooperation system as modeled in our study displays a remarkably rich and complex pattern of social interactions in which cheating and exploitation play a significant role. Two types of cheating strains in particular appear to be present under a broad range of conditions: mutants that are deficient in both the cooperative behavior and also lack the QS system, and mutants that do produce the QS signal molecules, but fail to respond to them with the appropriate cooperative behavior. The latter strains may induce cooperation in other cells, and profit from the resulting production of the public good, but do not pay the cost of cooperation themselves.

Here, we wish to point out the potential relevance of our study for the possibility of medical interventions. The production of virulence factors in a bacterial infection is usually regulated by QS[9,10] and therefore our simulations may provide insights into the evolutionary dynamics within a bacterial infection. This in turn may suggest possibilities of introducing strains with specific mutations disrupting the communication and/or cooperative behavior in order to reduce the virulence of the infection. This has be been discussed in a recent paper which analyses the possibility of medical interventions affecting the evolutionary dynamics in a bacterial infection.[11] In particular, two different scenarios were considered. First, the introduction of social cheats such as strains that do not produce exoproducts and therefore reduce the virulence of the infection. A second scenario involves the use of invasive cheating strains as 'Trojan horses', vehicles for the introduction of genetic traits that may help fight the infection, for example antibiotic sensitivity into a population that was antibiotic-resistant. Brown et al.[11] are careful in pointing out, that although these ideas might work in theory, several practical problems might complicate these intervention strategies. One of the potential complications is the emergence of resistance. The results of our study point to another potential problem. The composition of the bacterial populations appears to be highly sensitive to variations in parameters like the sensitivity to the quorum signal, the mobility of cells within the population and the metabolic costs of the production of the quorum signal and the virulence factors. Small changes in these parameters may greatly influence the resulting level of cooperation (i.e., virulence) and quorum sensing.

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