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MICROBIOLOGY

Taking the bad with the good

Modelling of the interactions between antibiotic production and antibiotic degradation reveals that these opposing activities are key to maintaining diversity in microbial communities.

CARL T. BERGSTROM & BENJAMIN KERR

We commonly expect competitive ecological interactions to be transitive: if ravens displace crows and crows displace jays, then ravens should displace jays as well. But the world does not always work this way. Increasingly, researchers are finding intransitive relationships, in which ravens displace crows, which displace jays, which in turn displace ravens. Intransitive relationships occur in animals[1,2], plants[3,4] and microbes[5,6]. Theoretical models show that species abundances can cycle in intransitive communities, in principle preserving species diversity[7,8]. However, in finite populations, extinction can readily occur when one type cycles to low abundance. In a paper published on *Nature*'s website today, Kelsic *et al.*[9] model an intransitive system in which microbial species produce antimicrobial compounds and exhibit differing sensitivities to the products of their competitors. By demonstrating that antimicrobial degradation can stabilize a multi-species community, the authors suggest a new solution to the puzzle of how bacterial diversity is maintained[10].

To illustrate Kelsic and colleagues' model, consider the rock–paper–scissors (RPS) scenario familiar to many as a game. Imagine three microbial species called Rock, Paper and Scissors, each of which produces a unique antimicrobial compound and is immune to its own toxin. If Rock kills Scissors, Scissors kills Paper and Paper kills Rock, we have the standard situation (Fig. 1a). Each bacterial species must protect itself from the toxin of its victim; for example, Scissors protects itself from Paper's toxin. Kelsic *et al.* focused on a neglected aspect of this protection: it may be non-excludable, meaning that protection may spill over to other species.

Such 'leakiness' may occur if a cell degrades the antimicrobials of a competing species by secreting enzymes that do the job externally, or by deactivating the competitor's antimicrobials once they have entered the cell[11]. Either way, the concentration of the antimicrobial in the environment is reduced. The RPS scenario can be adapted to account for this leakiness. For instance, when Scissors protects itself from Paper's toxin, partial protection would extend to Rock as well — here, Scissors inadvertently helps its own enemy (Fig. 1b, orange line). Kelsic and colleagues develop a mathematical model showing that the 'public good' of leaky protection and the 'public bad' of toxin production can interact to permit stable coexistence between multiple species.

Models with diffusible public goods and public bads are complicated. To improve our intuition about Kelsic and colleagues' model, let us reframe this population-level interaction as a two-player game. Instead of having many toxic microbes interacting with one another simultaneously, we consider pairwise interactions between individuals, each of whom play one of the RPS strategies. Players meet at random and receive a pay-off of 1 for winning or drawing and 0 for losing. They then replicate according to their pay-offs, and faithfully pass on their strategies to their offspring. A population of individuals playing this game undergoes unstable cycles; this scenario corresponds to the mathematical model developed by Kelsic *et al.* when there is no leaky protection. If instead the pay-off for winning is 2, drawing is 1 and losing is 0, we have the RPS game more commonly studied in the literature; this version has neutrally stable cycles[8]. Whether the cycles are neutrally stable or unstable, two of the three strategies will eventually be lost in a finite population (Fig. 1a).

Now suppose that we add one or more 'bystanders' to the game. Within the pair, a would-be winner is ineffectual if its enemy is standing by, and the game ends in a draw. With one or two bystanders, randomly chosen from the population, the chances of having a bystander that can interfere are too low to alter the dynamics qualitatively. But with more bystanders, the dynamics change completely: the community can approach a stable balance of the three strategies, in which all three types can coexist indefinitely (Fig. 1b). The more bystanders that are present, the easier it is for coexistence to be maintained.

Why do bystanders facilitate coexistence? In the standard RPS game, each type directly hurts its victim and thereby indirectly helps its enemy

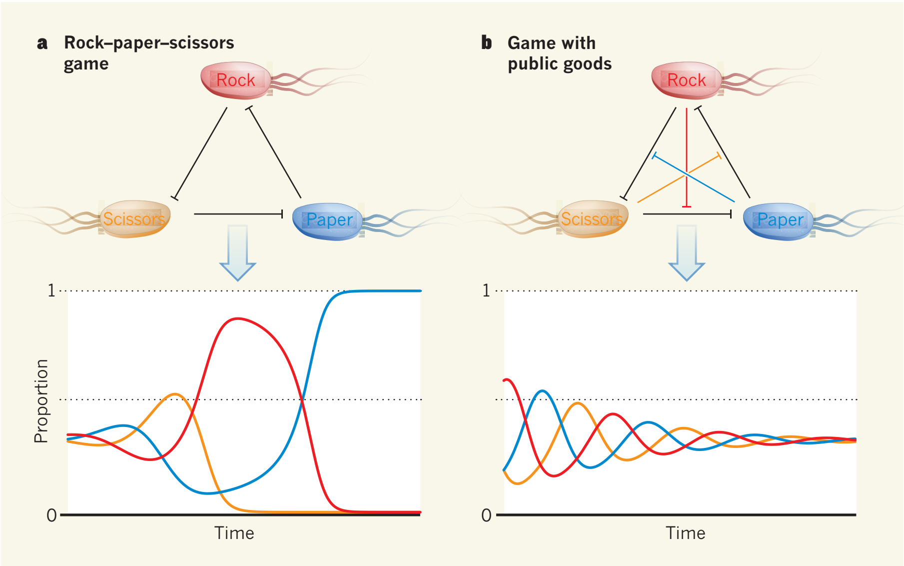

Figure 1 | Cyclical dynamics in a 'rock–paper–scissors' game with public goods. a, In a standard rock–paper–scissors game, rock beats scissors, which beats paper, which beats rock. Here, Rock, Paper and Scissors represent bacterial species, each of which produces an antimicrobial toxin (black lines). Each species is immune to the toxin produced by its victim. Kelsic *et al.*[9] show that, when such immunity is not 'leaky', the proportions of the three species fluctuate in unstable cycles until two of the species are lost. **b**, When immunity is conferred by antibiotic degradation, this protection may spill over to other species (coloured lines). When such 'public goods' are produced in appropriate quantities, the cycles dampen in amplitude and all three types coexist stably.

(its victim's victim). This process occurs in the bystander version of the game as well, but in addition, each type directly helps its enemy. As a player, Paper defeats a Rock partner; and as a bystander, Paper prevents Rock from defeating Scissors. Thus, Paper helps Scissors in two ways: by reducing the proportion of Rock players overall (the indirect route) and by ameliorating the harm that Rock does to Scissors when they meet (the direct route). If one type helps its enemy enough by the direct route, the additional source of feedback halts the proliferation of any type that becomes common, and can stabilize the entire community.

By adding bystanders to the basic RPS game, the model captures the essential biological feature of bacterial interactions that drives Kelsic and colleagues' findings: that bacteria of a first species protect bacteria of a second one when they protect themselves by disabling the antimicrobial compound of a third. Thus, addition of bystanders captures the leakiness of antimicrobial protection. (For a full description of the bystander model and its dynamics, see go.nature.com/yjzkfm.)

Kelsic *et al.* make several important contributions to our understanding of microbial community dynamics. They demonstrate experimentally that one microbe can protect a second from a third. They demonstrate mathematically how bystander protection can stabilize multi-species bacterial communities. They show that their qualitative findings are robust to variation in the form of the model, its parameters, the community structure and the number of species. Finally, they illustrate that the evolution of new strategies need not disrupt stable communities of this sort. In particular, coexistence can be robust against 'cheaters': mutants that obtain a fitness benefit by ceasing to produce public goods or public bads.

The authors also acknowledge several caveats to their work. If bystander protection is excessively weak or excessively strong, species cannot coexist indefinitely. Even if the protection is just right, coexistence will not occur if the starting proportions of each species are too uneven.

Kelsic *et al.* have derived a key theoretical result: that, in principle, multiple microbial species can coexist indefinitely even in a well-mixed environment without spatial refugia. The obvious next step is to return to experimental studies to test whether this mechanism can support bacterial diversity in practice. Is protection strong enough to stabilize coexistence, and can a well-mixed three-species system coexist stably under laboratory conditions? Coexistence can withstand the emergence of cheaters in the model; can it do so in microbial culture as well? We are eager to learn whether, in natural microbial communities with intransitive competition, diversity is promoted when public goods take out public bads. ■

Carl T. Bergstrom *and* **Benjamin Kerr** *are in the Department of Biology, University of Washington, Seattle, Washington 98195-1800, USA.*
e-mails: cbergst@uw.edu; kerrb@uw.edu

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