OPINION

Competition sensing: the social side of bacterial stress responses

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Abstract | The field of ecology has long recognized two types of competition: exploitative competition, which occurs indirectly through resource consumption, and interference competition, whereby one individual directly harms another. Here, we argue that these two forms of competition have played a dominant role in the evolution of bacterial regulatory networks. In particular, we argue that several of the major bacterial stress responses detect ecological competition by sensing nutrient limitation (exploitative competition) or direct cell damage (interference competition). We call this competition sensing: a physiological response that detects harm caused by other cells and that evolved, at least in part, for that purpose. A key prediction of our hypothesis is that bacteria will counter-attack when they sense ecological competition but not when they sense abiotic stress. In support of this hypothesis, we show that bacteriocins and antibiotics are frequently upregulated by stress responses to nutrient limitation and cell damage but very rarely upregulated by stress responses to heat or osmotic stress, which typically are not competition related. We argue that stress responses, in combination with the various mechanisms that sense secretions, enable bacteria to infer the presence of ecological competition and navigate the 'microbe-kill-microbe' world in which they live.

Ecological competition refers to the process by which one individual decreases the survival or reproduction of others, and ecologists have long recognized that this competition can be divided into two major types: exploitative competition and interference competition[1,2]. Exploitative competition is indirect and occurs when one organism consumes the resources of another, such as a polar bear eating a seal and thus depriving another bear of food. Exploitative competition also occurs in microorganisms and is particularly strong when they settle on surfaces and form dense communities, such as biofilms. In these cases, nutrient limitation is common, resulting in strong exploitative competition among both cells of the same genotype and those of different genotypes[3,4].

When exploitative competition occurs purely among cells of one genotype, there is no true competition in an evolutionary sense because all cells have the same evolutionary interests. Under these conditions, evolutionary theory predicts that cells will invest in group-beneficial phenotypes that reduce nutrient competition, such as the production of enzymes that release nutrients from the environment, and these phenotypes do emerge in nature[4]. However, cells also commonly meet and mix with cells of different genotypes, as evidenced by the incredible diversity found in metagenomic analyses of microorganisms in environments as varied as soil, stromatolites and the mammalian gut[5–7]. Although mixed-genotype groups can sometimes engage in mutually beneficial cooperation[8], genotypic mixing is expected to limit the potential for group-beneficial phenotypes because of the potential for 'cheaters', which use the beneficial secretions of other genotypes without themselves investing in the secretion[4].

Further than just limiting cooperation, the strong natural selection that results from exploitative competition among different genotypes is predicted to generate interference competition, the second form of ecological competition. Interference competition is the competition that arises when individuals directly harm each other[2,9–11]. In animals, this form of competition is exemplified by physical fighting. In microorganisms, the emergence of interference competition is well established in the large body of literature about the secretion of products that harm other cells, including antibiotic compounds (reviewed below) and smothering polymers[12,13]. Co-culture experiments show that these secreted factors often determine which genotype prevails in mixed cultures[13,14]. There is also evidence that toxins drive the co-evolution of defensive measures. Antibiotic resistance genes are commonplace in natural isolates and, importantly, evolved many years before the clinical use of antibiotics[15].

There is good evidence, then, that both exploitative and interference competition are prevalent in bacterial communities and strongly influence the outcome of natural selection on bacteria[9–11]. Although it is clear that such natural selection can drive the evolutionary dynamics of social traits such as the secretion of toxins or beneficial molecules, little attention has been paid to the effects of ecological competition on the regulation of these traits. In this Opinion article, we argue that ecological competition has wide-ranging effects on the form and function of bacterial regulatory networks and, in particular, that these effects can be seen in several of the well-studied stress responses.

The competition-sensing hypothesis

Our hypothesis is that bacteria have evolved ways to directly detect and respond to ecological competition, and that these responses are reflected in several of the major bacterial stress responses. We argue that by detecting harmful effects on the cell, stress responses robustly sense ecological competition and allow cells to respond. We call this competition sensing: a physiological response that detects harm caused by other cells and that evolved, at least in part, for that purpose. In this context, the word competition includes all examples of ecological and evolutionary competition. As discussed above, we take ecological competition to be any situation in which one bacterial cell has a negative effect on the survival and reproduction of another bacterial cell. By contrast, evolutionary competition is more restrictive and depends on whether the interacting cells have different evolutionary interests. When exploitative competition occurs among cells of one genotype (hereafter referred to as 'self cells'), evolutionary competition is absent because the cells have the same evolutionary interests. Conversely, when exploitative competition comes from cells of a different strain or species (hereafter referred to as 'other cells'), evolutionary competition also occurs[4].

We do not restrict ourselves to evolutionary competition here because it is important for cells to detect harm irrespective of whether it is caused by self or by other cells. The appropriate response to this competition will depend on the source of the competition. However, the genetic diversity found in many microbial communities might mean that sensing harm will typically indicate both

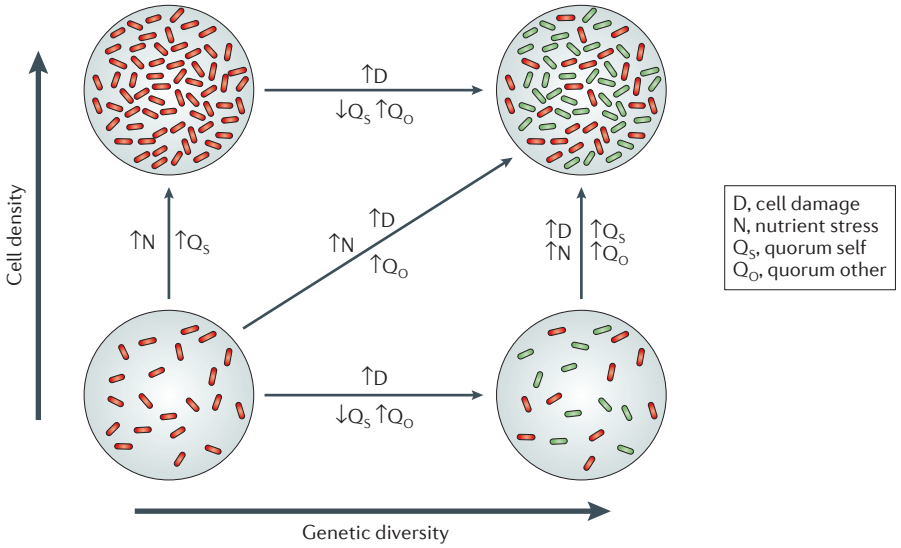


Figure 1 | **The correlated information provided by competition sensing and quorum sensing.** Four scenarios are shown, with the top right representing the most intense ecological competition. There are four potentially correlated cues that can provide information about the degree of ecological competition in a population (see Supplementary information S3 (figure)): nutrient stress (N), cell damage (D) caused by toxins produced by other cells, quorum-related responses to self-compounds (Q_S) and quorum-related responses to compounds produced by other cells (Q_O). Quorum-related responses include recognition of the canonical autoinducers of quorum sensing, but also of any other secretory product that correlates with cell density, such as peptidoglycan fragments[45]. If all genotypes use the same compound (for example, autoinducer 2), Q_S and Q_O collapse into one information source. This simplistic figure already reveals the potential complexities in the use of stress responses and quorum responses to infer ecological competition. To some degree, the two major types of stress response provide separate information; nutrient stress relates to cell density and exploitative competition (moving from bottom to top between scenarios), whereas cell damage relates to genetic diversity (moving from left to right between scenarios). However, for some transitions, such as the diagonal move, the changes in both forms of stress are correlated. Despite this, the combination of the two sources of stress can effectively distinguish the four scenarios. In principle, the quorum responses can also distinguish the four scenarios if it is possible to differentiate the quorum molecules of self and those of others. Finally, another option to distinguish all four conditions is to use cell damage combined with self quorum responses. These correlations are strong when tested with the model described in BOX 2 (see Supplementary information S3 (figure)).

ecological and evolutionary competition. How, though, can a cell assess the strength of ecological competition (FIG. 1)? One way is to indirectly infer the potential for competition via compounds released by self and other cells (for example, via quorum sensing molecules), and we discuss this further below[16–20]. However, sensing the secretions of others does not directly sense the harm caused by ecological competition. By contrast, the well-known stress responses do directly detect a wide range of harmful effects caused by the environment in which the cell exists. Below, we propose that many of the regulatory effects of stress responses are consistent with the evolution of systems that both detect and respond to competition.

Stress responses for defence and attack

In the effort to understand and control bacteria, the responses of bacterial cells to harmful conditions have been intensively studied. As might be expected, bacterial regulatory networks often show strong, clear shifts when cells face physical or chemical challenges, such as high temperatures, low nutrient levels or the presence of antibiotics. A large number of stress response genes have been identified that typically display differential regulation in the face of a particular stressor and promote resistance to that stressor (that is, inactivation of the gene results in decreased stress tolerance)[21].

The potential for links between ecological competition and stress responses are clearest in the study of nutrient stress, for which the typical experimental model is nutrient competition during batch growth in pure culture. Moreover, we discuss in BOX 1 how the major stress responses map onto the traditional distinctions made by ecologists between exploitative competition, interference competition and the abiotic environment. Although it is clear that many stress responses will respond to ecological competition, it could be argued that this is simply a by-product of adaptation to abiotic stresses. To date, the literature about stress responses has focused on traits that help cells cope with stress, such as protection, repair and dormancy[21]. However, it is typically difficult to know whether such coping traits have evolved to deal with biotic or abiotic threats. One possible exception is the observation that stress responses of all kinds tend to promote antibiotic resistance[22], which would be expected if stress were indicative of the threat of toxin attack by other cells. But even in this case, there is ambiguity because a degree of cross-protection is common to many stress responses. Except for highly specific defences like β-lactamase secretion[23], it is difficult to ascertain how often this cross-protection is the result of natural selection for antibiotic resistance, rather than a by-product of selection for something else.

Linking stress responses and competition

The topic of antibiotic resistance brings us to a somewhat neglected phenotype in the study of bacterial stress responses: antibiotic production. Bacteria commonly release toxins that kill other bacteria, and this release occurs both across the membrane and through lysis of a subset of cells of one genotype. The limited overlap between the literature about stress responses and that about bacterial toxin production is illustrated in the recent edited volume on bacterial stress responses[21], which, although impressive, rarely mentions the regulation of antibiotic production. Toxins are particularly useful in discerning evolutionary function because one can typically be more confident that toxins have evolved to influence a biotic target. There are exceptions to this rule, such as pyocyanin, which has multiple potential roles in addition to antibiosis, including effects on metabolism and nutrient acquisition[24]. Nonetheless, one can be more confident of the role of other toxins. This is particularly true for the bacteriocins, which are narrow-spectrum antibiotics that target other bacteria[25]. One prediction of our hypothesis is that stress responses which detect ecological competition will often be associated with the release of toxins, because in bacterial communities, ecological competition normally implies the presence of foreign genotypes (and of evolutionary competition, as described above). By contrast, it should be rare to find toxins that are regulated by responses to predominantly physical stresses, like heat or osmotic pressure.

We carried out a literature search with the goal of summarizing the key regulators of antibiotic production. Regulators are typically inferred from the effects of gene knockouts or overexpression, and it is worth noting that both types of mutation can have confounding pleiotropic effects. In addition, whereas some studies measure toxin levels directly, others infer these levels indirectly using the amount of mRNA from toxin-encoding loci. Furthermore, as we discuss below, we did not include cases in which a specific nutrient source affected toxin production, or those in which certain non-stressful temperatures triggered greater induction than other non-stressful temperatures, as these responses are often difficult to interpret. Such cases and caveats aside, FIG. 2 and Supplementary information S1 (table) summarize the results of our survey, which are in strong agreement with our hypothesis. We find many links between stress responses and toxin secretion, and we also find that the majority of these links are for responses associated with detecting either nutrient stress or cell damage. Specifically, the survey found 85 different associations between a stress response regulator and a toxin (Supplementary information S1 (table)), 81 of which are associated with nutrient limitation and cell damage (that is, ecological competition), compared with only four associated with heat or osmotic stress (that is, abiotic stress). In eight cases, increased stress leads to decreased toxin production. We discuss these exceptions further below and in Supplementary information S1 (table), but note here that there are only six such exceptions out of 81 cases for biotic stresses, whereas these exceptions constitute two of the four abiotic stressor cases.

These data should be interpreted cautiously, as our survey is not exhaustive and there are strong biases owing to the research focus on a few model species. Moreover, some of the data come from groups of related bacteriocins, such as the S-type pyocins from *Pseudomonas aeruginosa*. This said, in each category of biotic stress included in the survey, there are multiple independently evolved associations between a toxin and a stress regulator, as is made clear by the phylogenetic presentation in FIG. 2. These associations can be in the form of non-homologous toxins associated with one stress regulator (for example, both R-type pyocins and S-type pyocins are associated with the recombinase gene *recA* in *P. aeruginosa*) or in the form of non-homologous toxins associated with non-homologous regulators (such as the use of RNA polymerase σ-factors σ^W and σ^E to regulate diverse toxins in response to cell wall damage in *Bacillus subtilis* and *Streptomyces coelicolor*, respectively, as σ^W and σ^E are not closely related homologues[26]). These examples of cell damage responses are notable because treatment of these bacteria with antibiotics results in the targeted cells releasing toxins[27–30]. This suggests that the secretion of toxins via stress responses can

Box 1 | **Stress responses protect against ecological competition**

It is possible to map the major stress responses onto the traditional distinctions made by ecologists among exploitative competition, interference competition and the abiotic environment. In particular, stress responses can be classified as leading to induction through nutrient limitation, cell damage or abiotic stress. As for any such classification, our analysis is complicated by the fact that responses to distinct stressors are often overlapping. For example, heat, osmotic stress and antibiotics might all induce a particular regulator. Nevertheless, the literature normally points towards a primary inducer for each stress response system, and we use this as the basis for our functional interpretation[21].

Responses associated with low nutrient levels

The stringent response. Nutrient limitation has widespread effects on gene regulation in bacteria through the stringent response, which is controlled by the intracellular alarmones guanosine pentaphosphate and guanosine tetraphosphate (collectively referred to as (p)ppGpp) and the ribosome-associated enzymes RelA and SpoT (which are (p)ppGpp synthases and hydrolases). These factors respond to low levels of specific nutrients — including amino acids, glucose, phosphate, iron and fatty acids — and reduce the biosynthesis of macromolecules while simultaneously attempting to restart metabolism.

General stress responses. Many bacteria also show a more general response as cell division slows under nutrient limitation. In *Escherichia coli*, this response occurs through the RNA polymerase σ-factor σ^S, which is modulated by (p)ppGpp, and also through cyclic AMP levels and leucine-responsive regulatory protein (Lrp), which respond to glucose and leucine levels, respectively. The level and activity of σ^S can also be induced by other sudden environmental shifts, including DNA damage, an increase in temperature, an increase in osmolarity and a decrease in oxygen availability, which is why σ^S is considered to be a general stress response regulator. The widespread effects of σ^S on bacterial cells include a shift to fermentation, altered morphology, altered membranes and the synthesis of protective and storage carbohydrates. Regulators such as σ^S are often known as stationary phase regulators because of the timing of their activation in batch culture. Importantly, however, they can also activate under continuous growth when there is a continuous but limited nutrient supply (as may commonly occur in biofilms).

Responses to antibiotics and other cellular damage

Envelope stress. Bacteria respond strongly to cellular damage. Envelope stress responses result from perturbations to the membranes or cell wall. In *E. coli*, two of the best characterized envelope stress responses are the σ^E and Cpx responses. The results of induction are diverse but centre on reducing the amount of protein in the periplasm and improving the folding of the protein that is there. Antibiotics induce envelope stress responses in both Gram-negative and Gram-positive bacteria.

DNA damage. A second major class of damage responses occurs owing to DNA damage. The canonical example is the SOS response of *E. coli*, which is commonly induced in the laboratory by ultraviolet light or DNA-damaging antibiotics; these activate the recombinase RecA, which binds to single-stranded DNA. Cell division is inhibited, and DNA repair is initiated by removal of the damaged nucleotides followed by homologous recombination. The SOS response plays a part in DNA repair in many species, including Gram-positive bacteria.

Oxidative stress. Other key inducers of the SOS response are ROS (reactive oxygen species) and RNS (reactive nitrogen species). In addition to the SOS response, several dedicated responses to ROS and RNS have been identified, including those mediated by the SoxR (redox-sensitive transcriptional activator) and OxyR (hydrogen peroxide-inducible genes activator) regulons in *E. coli*. Many antibiotics generate redox-active molecules and cause oxidative stress.

Responses to abiotic environment

Heat stress. The heat shock response is one of the most biologically conserved stress responses. The *E. coli* heat shock response is highly specific and appears to be induced only by a high abundance of misfolded proteins, the levels of which are controlled by the heat shock regulator σ^{32}. The response of the Gram-positive bacterium *Bacillus subtilis* overlaps with that of *E. coli* but is controlled by a more diverse set of regulators.

Osmotic stress. Variability in the total concentration of dissolved solutes in the environment is another form of stress experienced by bacteria. Cells deal with rapid external upshifts in osmotic pressure by pumping in potassium ions or through the use of osmoprotectants like trehalose. External downshifts in osmotic pressure are tolerated owing to mechanosensitive channels that open in response to membrane strain and release solutes from the cell.

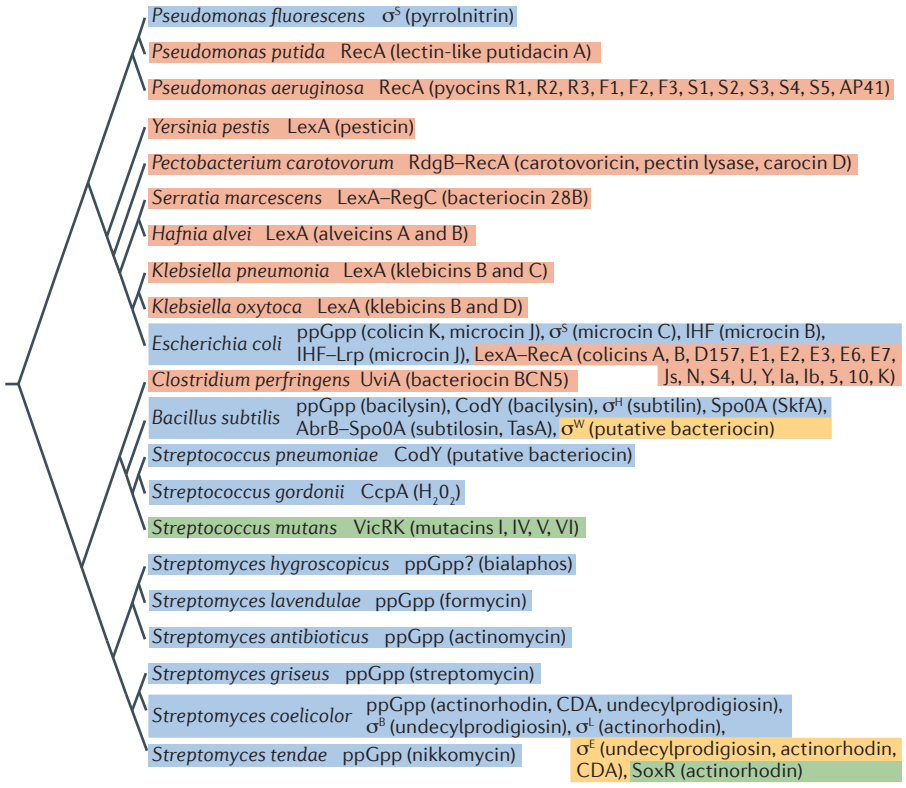


Figure 2 | **Cladogram of bacteria that induce toxin secretion as a result of stress response activation.** Stress response regulators that are known to induce toxin production are shown for each species, with the induced toxin in parentheses. The four types of response shown (BOX 1) are nutrient limitation (light blue), DNA damage (red), oxidative stress (green), and envelope stress (yellow). We include only those cases from Supplementary information S1 (table) for which a regulator is known. Note that oxidative stress induces the production of bacteriocins in Gram-negative species (*Pseudomonas aeruginosa* and *Escherichia coli* in Supplementary information S1 (table)), but these cases are not shown, as they probably occur via DNA damage responses. The phylogenetic analysis was carried out principally with SUPERFAMILY[62], a database of structural and functional annotations of proteins and genomes. *Hafnia alvei*[63] and the majority of *Streptomyces* spp.[64] were placed according to studies using 16S rRNA genes. Details of these associations, as well as associations between quorum sensing and bacteriocin induction, are given in Supplementary information S1 (table). CcpA, catabolite control protein A; CDA, calcium-dependent antibiotic; ppGpp, guanosine tetraphosphate; SkfA, sporulation killing factor.

sometimes be a direct reciprocation to being attacked by toxins, and we return to such toxin kickback below.

Exceptions and future analyses

Although the majority of stress response-regulated toxins fit with our expectations, there are also a few examples that we did not predict (Supplementary information S1 (table)). For example, colicins are released under high temperature and only when the heat shock regulator σ^{32} (also known as RpoH) is present in a cell[31]. However, it is not heat stress that promotes colicin release, but rather a temperature of 37 °C or above. It is possible, then, that cells are responding to being in the mammalian gut, where they must compete for their niche. There is also a link between the production of microcin B and the osmotic stress-induced gene *ompR*, but the function of *ompR* is unclear, as it is not associated with protection against osmotic stress[32,33]. Finally, there are six cases in which toxins are downregulated by nutrient stress. Two of the six exceptions involve pyocyanin, which has diverse functions in addition to antibiosis[24]. However, the other cases more clearly involve antibiotics. For instance, despite conflicting reports, cephamycin C seems to be expressed primarily under exponential growth in batch culture and to be under negative regulation by the stringent response in *Streptomyces clavuligerus*[33]. Such exceptions are important, as they highlight the fact that it is not universally true that antibiotics are positively regulated by stress responses. This is reasonable because some species might reliably meet competitors under high-nutrient conditions. However, such cases of negative regulation of toxins by stress responses seem to represent a minority of the total set of examples.

The data for the genus *Streptomyces* also illustrate the potential for complexity in the metabolic regulation of toxins. This complexity is also seen in cases in which limitation of a specific nutrient promotes toxin production (cases that we did not consider in our survey). One major class of such examples consists of cases for which the production of antibiotics is increased more by limitation of a preferred carbon source of a species than by depletion of non-preferred carbon sources[34]. These examples fit our basic hypothesis that cells will produce toxins when ecological competition is having the most harmful effects. But there are other examples, such as iron and phosphate depletion promoting pyocyanin production[35], for which it is less clear why the limitation of one nutrient but not another should promote toxin production. One explanation put forward recently is that cells use 'prudent regulation', whereby they make products for secretion only when they have an excess of the nutrients needed to make the product (for example, because a limitation in another nutrient inhibits growth)[36], but a full discussion of these interesting issues is outside the scope of this article.

Diverse regulation of defence and attack

Our general hypothesis that many stress responses function as a way to sense ecological competition is supported by the many links between toxin secretion and nutrient- or antibiotic-induced stress. However, it is also clear that not all biotic stress responses in all species are associated with toxin secretion and, moreover, there is diversity in the regulation of toxins. This includes an important role for quorum sensing and other mechanisms that sense secretions from other cells (Supplementary information S1 (table)). If stress responses simply detect the strength of ecological competition, why is toxin regulation so rich and varied?

Evolution is more likely to co-opt an existing regulator to control a new toxin than to generate an entirely new regulatory pathway. Some of the diversity of regulation in Supplementary information S1 (table), therefore, will be due to historical constraints on molecular architecture. Nevertheless, every species has multiple regulators that can be used, and one can ask why one type of regulation is used over another. To begin to answer this question, one must consider that bacteria live in unpredictable environments and there is

Table 1 | **Examples of toxin regulation based on quorum-related sensing and competition sensing***

Example	Classification	Rationale for classification
Quorum sensing of BlpC induces Blp bacteriocins in *Streptococcus thermophilus*[65]	QR sensing of self (and QR sensing of others)	• Cells release and detect the autoinducer BlpC, which qualifies the process as QR sensing rather than CS • Other strains of the same species might make BlpC and cause bacteriocin induction in a focal strain, hence the process might be QR sensing both of others and of self • The benefit of this regulation might be due to the strong correlation between a high density of the self genotype and the presence of competitors (FIG. 1; BOX 2; Supplementary information S3 (figure))
Peptidoglycan induces pyocyanin production in *Pseudomonas aeruginosa*[45]	QR sensing of others	• Peptidoglycan is shed from cell walls of Gram-positive bacteria and might be a cue that indicates their presence to another bacterium • It is because of examples like this that we use the term quorum-related sensing rather than simply quorum sensing
Starvation induces bacilysin in *Bacillus subtilis* via both (p)ppGpp and GTP[66]	CS of nutrients	• General nutrient limitation is sensed by the lack of a range of metabolites, rather than the presence of a particular secreted molecule • Depending on the ecology, this resource limitation can be caused by other lineages (FIG. 1) • Note that even when a cell always faces the same competitors (so that the mechanism does not detect genetic diversity in a community), nutrient-based induction allows cells to infer the strength of interaction with other genotypes and other useful information (BOX 2)
DNA damage induces colicins in *Escherichia coli*[25,28,30,67]	CS of damage	• DNA damage can be caused by other cells, and the SOS response that is triggered can thus be used as an indication that other cells are present, rather than the organism sensing a specific molecule that other cells produce

CS, competition sensing; (p)ppGpp, guanosine pentaphosphate and guanosine tetraphosphate; QR, quorum-related. *Note that QR sensing encompasses both standard autoinducer-based quorum sensing and more general sensing of molecules produced by other organisms (such as in the pyocyanin example).

therefore a large degree of uncertainty as to their physical and social surroundings. Bacteria can be thought of as decision-making machines: given a set of environmental cues, their genetic network can assess the likely environmental conditions and respond appropriately (a process known as Bayesian inference)[37]. These cues are subject to noise and, sometimes, manipulation by competing genotypes[19], and cells must therefore integrate information from various sources to minimize the influence of unreliable inputs while making use of the available information. Clearly, this decision-making process is not a conscious one. Cells with certain genetic networks outcompete others over evolutionary time. As these networks shape the strategy used by the cell, natural selection pushes genomes toward increasingly advantageous strategies, as though the cells themselves were intentional agents[38].

But in this noisy world, what is the best regulatory mechanism for inferring ecological and evolutionary competition? There are three broad classes of social information that are available to cells and are known to affect cell physiology. The first two we consider to be true competition-sensing systems: the direct effects of nutrient limitation and damage to the cell. The third is the sensing of molecules released by other cells, which does not directly detect ecological competition but can indirectly provide information about the potential for harm caused by other cells (FIG. 1; TABLE 1). This sensing includes the use of autoinducer signal molecules, but also any indicator of density, such as acidity, which correlates with density in lactic acid bacteria[39] (Supplementary information S1 (table)).

To understand the value of the different sources of information, it is first useful to consider more specifically how these information sources can help a cell. As a case study, in BOX 2 (see also Supplementary information S2 (box)) we work through a simple model of nutrient stress-dependent toxin regulation in which a fixed amount of nutrients is used up (akin to a simple batch culture experiment). This model suggests that three key factors favour toxin production: a high density of self cells, a high density of other cells and a late growth stage. These factors are all linked, but each is useful for its own reason. A high density of self cells means that toxin release will be effective, because a high concentration of toxins can be rapidly generated. A high density of other cells means that there are many target bacteria present that might otherwise poison and steal. A late growth stage is most relevant to environments in which a fixed amount of nutrients is available for consumption; at a late growth stage, the most essential early growth phase is over and the costs of investing in toxin secretion are relatively low (BOX 2). For our fixed-nutrient example, it is also the case that if cells leave it too late there will not be enough energy left for substantial toxin secretion. Together, these predictions lead to the hypothesis that secreting toxins at some intermediate level of nutrient stress is an effective strategy.

Our model in BOX 2 considers species that colonize and grow in a particular type of environment, time and time again. Such cells will experience a predictable reduction in nutrients, increase in toxin levels and increase in quorum sensing molecules such that any one of these information sources could be used to coordinate strategies of defence and attack. However, under less regimented conditions, these correlations will weaken (FIG. 1 and Supplementary information S3 (figure)), and one source of information might become a more useful predictor than another when it comes to predicting the density of self and other cells and the growth stage.

The utility of quorum-related information

As we propose above, the diversity in toxin regulation might be explained by one source of information being more useful than another in responding to adversarial phenotypes. But when would quorum-related information be more useful than a stress response that senses ecological competition directly? Most simply, if the density of self cells is the key factor determining the benefits of toxin secretion, then quorum regulation might be the best regulator, as long as the effects of diffusion are not too variable among different environments[20,40]. Indeed, this is the typical explanation of quorum regulation: clone mates are signalling each other to ensure that there is enough of their own genotype in the population for their secretions (be these toxins or growth-promoting products) to be

Box 2 | **A simple model of regulating toxins by nutrient limitation**

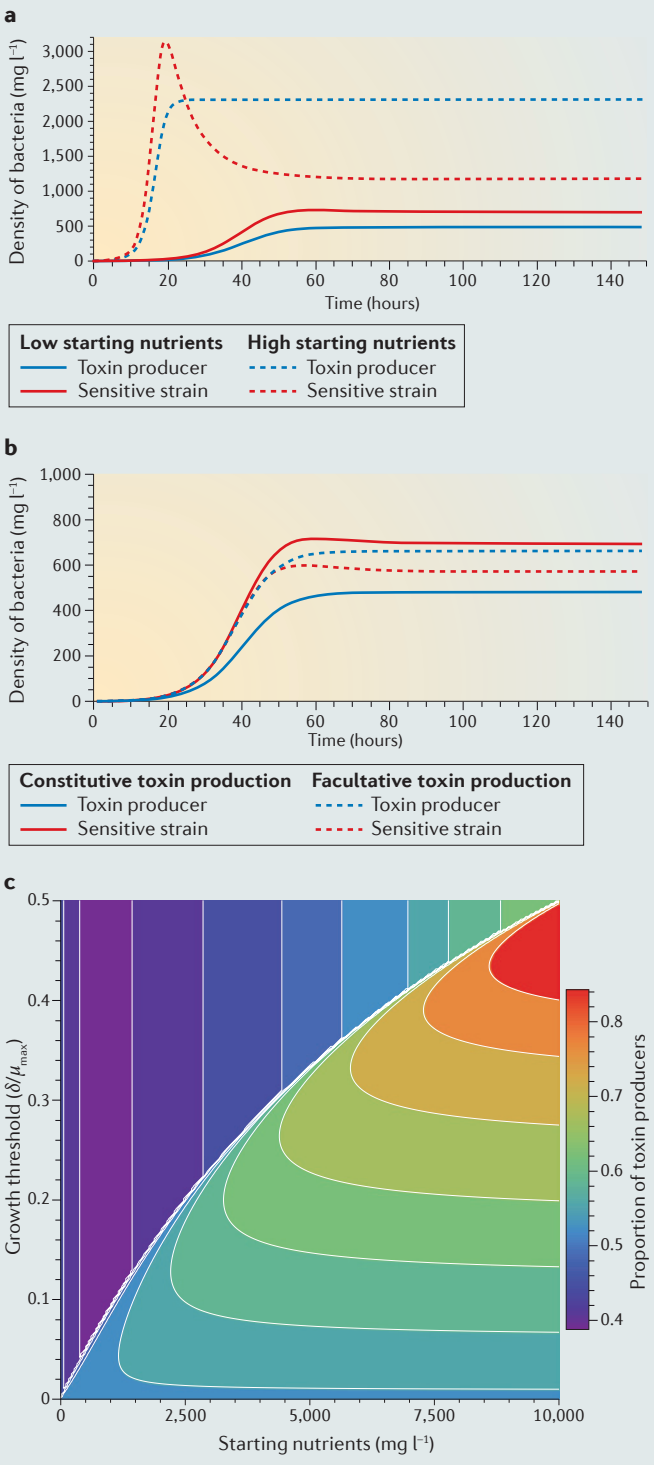
The prevalence of stress-regulated toxins in bacteria (see Supplementary information S1 (table)) can be explained by correlations between stress and competition with another genotype. Non-clonal competition is greatest in high-density, high-diversity environments (top right panel in FIG. 1), and this is where toxins are most effective. Here, we develop this logic with a simple batch culture model of the gradual transition from a high-nutrient, low-competition environment to a low-nutrient, high-competition environment, as caused by cell growth in a fixed amount of nutrients. The evolution of toxin production can be affected by the number of interacting strains[59] and the potential for strains that are immune to toxins but do not produce them[14]. To focus our analysis here, we consider a two-strain scenario in which a toxin-producing strain interacts with a sensitive strain. Readers are referred to Supplementary information S2 (box) for details of the dynamics and parameters used in the model.

Our key question is, how can variation in nutrient levels affect the benefits and costs of toxin use? The variation in nutrient levels can be caused in two ways: first, through variability in the initial conditions, and second, through the progressive depletion of nutrients during growth. We first consider the simple case of competition between a constitutive toxin producer and a sensitive strain[60,61] (see the figure, part **a**). For constitutive toxin producers — that is, cells for which δ (the threshold growth rate below which toxin production is active) is equal to μ_{max} (the maximum specific growth rate) — the key variable is nutrient level at the start of growth, as toxin production in these strains does not respond to changes in nutrient levels as the cells grow. If nutrients are so sparse to begin with (2,000 mg per litre in this model) that cells cannot reach a high density, toxins will never have a strong impact. Consequently, the cost of toxin production is never overcome, and non-producing, toxin-sensitive cells dominate (solid lines). But in high-nutrient environments (here, 10,000 mg per litre), cells can grow to high enough densities for toxins to be decisive and tip the balance in favour of producers[60,61] (dashed lines).

In contrast to the constitutive case, stress-regulated toxin producers (facultative producers) — here, cells for which $\delta = 0.1$ per hour — can defer production until nutrient depletion results in a low growth rate (μ) and thus avoid the high initial costs of production while still enjoying its subsequent benefits when toxins are most effective (see the figure, part **b**). In this scenario, when starting nutrient concentration is low (2,000 mg per litre), a starvation-induced producer turns the tables on a sensitive strain (dashed lines), whereas the sensitive strain would win if toxin production were constitutive in the producing strain (solid lines).

Several model details can affect these results. For instance, if toxin efficacy depends on growth rate, late-term secretion can be less effective. In addition, if the toxin efficacy is sufficiently high, constitutive production could in theory be optimal. Finally, the model assumes that no new nutrients diffuse into the system, as this might also affect conclusions. These and other details deserve more attention in future work, but the adaptiveness of delayed induction seems robust to basic biological assumptions.

We evaluated the model at time 1,000 hours with varying starting nutrient (N_0) levels and δ values, and plotted the results to show the final proportions of producers as a function of N_0 and δ (plotted as a fraction of μ_{max}; see the figure, part **c**). The dividing line is the Monod equation, describing the microbial growth rate in relation to nutrient concentration ($\mu = \mu_{max} N / (K_N + N)$, in which K_N is the nutrient saturation constant, or the value of N when μ is half maximal). The region above the dividing line represents constitutive toxin production because there are not enough nutrients to allow a growth rate above δ, the toxin production threshold. For any starting nutrient concentration in the figure (part **c**), the threshold that maximizes fitness (that is, which results in the highest proportion of toxin producers at 1,000 hours) is below this line, which implies that producing toxin after a delay is typically the best strategy. The figure shows that cells should turn on toxins at some intermediate degree of nutrient stress. Activating at very low nutrient stress (that is, when δ is high) means that production is always on and effectively constitutive. Activating at extremely high stress (that is, when δ is lower than for the facultative producer in part **b**) means that little toxin can be produced because the bacteria are running out of food. In summary, responding to nutrient stress can allow cells to minimize the fitness cost of toxin production relative to its benefits, when these benefits are a function of the strength of interaction with competitors.



effective[16–20]. However, quorum information can also predict the strength of ecological competition and, importantly, might do so earlier than a stress response that detects harm (FIG. 1 and Supplementary information S3 (figure)). Therefore, the prediction of ecological competition might also explain why competition-associated phenotypes like toxin production are under the regulation of the products secreted by self cells. This explanation is particularly relevant for regulated processes that do not need a high density of clone mates to function, such as repair, protection and the production of contact-dependent toxins[41].

The potential for diversity in quorum-related molecules means that quorum information is useful not only for signalling among self cells, but also potentially for the detection of specific cues produced by other genotypes (that is, for detecting evolutionary competition)[17,19]. A high degree of molecular specificity has the potential to separate quorum information from stress information in that it can identify a particular strain or species that is an evolutionary competitor. For instance, *Proteus mirabilis* strains can detect other strains in the species and isolate themselves from would-be competitors[42], and there is evidence that other micro-organisms might tailor their responses to particular competitors[43]. The existence of strains with receptors for quorum sensing molecules that they do not produce, such as LuxR orphans, is also consistent with one strain monitoring the cues produced by another strain or species[17,19]. Similarly, the abundance of two-component signalling systems in bacteria[44] might be partly explained by natural selection on cells to monitor other strains and species.

The utility of competition sensing

Specificity allows a response to be finely tuned to the threat posed by a particular strain or species, but can require specific detection systems for each cue. Moreover, the producer of the cue has the potential to change it to evade detection. For these reasons, general responses might often be more useful for inferring evolutionary competition. Sometimes, quorum-related molecules can be general. For example, self quorum molecules can predict the presence of other genotypes in so far as density of self and the other cells are correlated (FIG. 1). It is also possible for sensing of quorum molecules from other species to be general for a large class of competitors; for instance, *P. aeruginosa* produces pyocyanin in response to the presence of peptidoglycan, which might indicate the presence of competing Gram-positive bacteria[45]. However, stress responses might often prove to be more useful against competitors than other mechanisms of inferring competition because stress responses more frequently operate independently of competitor identity and provide a direct assessment of ecological competition. In this way, stress responses can be robust, both to variation in community species composition and to evolutionary changes in the chemical signatures of competitors. Furthermore, competition sensing can distinguish between a mixture of harmful and harmless strains on the basis of the key evolutionary currency: their capacity to reduce the fitness of a focal cell.

In summary, we hypothesize that stress responses have two key advantages over other potential mechanisms of inferring competition. First, stress responses detect the property of competitors that will typically be most important for fitness — their harmfulness — and second, these responses provide a general detection system that is not specific to the chemical cues of any one genotype. These factors might often make stress responses a better solution for responding to foreign genotypes than quorum responses. This said, it is also clear that detecting nutrient limitation and detecting toxin-mediated damage are not equivalent. Sensing nutrient limitation is in some ways more similar to the detection of self quorum molecules than to the detection of cell damage (FIG. 1). And in an uncertain world in which other genotypes come and go, cell damage is likely to be the best indicator of evolutionary competition. This is because compared with cell damage, nutrient sensing is less able to distinguish between ecological competition from self versus other genotypes (FIG. 1 and Supplementary information S3 (figure)). Directly sensing damage might have additional benefits. The SOS response reports on DNA damage that can limit the future prospects of individual cells — that is, their reproductive value. Because some SOS-regulated toxins seem to require cell lysis for their activity[46], SOS regulation might allow a strain to select the most damaged cells to respond to an incoming attack[25]. Finally, the fact that the toxin of one strain can make another strain respond in kind — the toxin kickback mechanism mentioned above — has interesting implications. Classic evolutionary models show that such reciprocation can lead to both parties living in peace[47]; however, kickback also raises the possibility of escalating reciprocal rounds of attack and counter-attack[28]. Which scenario is most representative of bacterial systems is an open question.

Clarifications and caveats

We believe that many of the major stress responses are better understood by considering the central role of ecological competition in bacterial evolution. Below, we offer some clarifications of our argument so that it is not misinterpreted.

Not all stress responses involve competition sensing. There are a number of cases in which stress responses are not associated with ecological competition. This includes heat and osmotic stress, as well as pathogens that seem to use their stress responses as an indication of an attack from the host immune system[48]. This use of stress responses is likely to be a recent adaptation, as the major stress responses seem to long predate the evolution of multicellularity[49]. Other potential biotic stressors that are not strictly competition based include the presence of ciliate predators and phages[9]. However, it is not clear that the major stress responses have a central role in these cases[21]. The key known bacterial responses to phages are abortive infection[50] and the CRISPR (clustered regularly interspaced short palindromic repeats) system[51]. These responses appear to function independently of the major stress responses, with the possible exception of some toxin–antitoxin systems that are stress regulated and implicated in phage abortive infection[52].

Competition-sensing systems will not exclusively respond to other genotypes. We predict that harm caused by other cells is often used to detect and infer competition from other genotypes, a hypothesis that is supported by the data in Supplementary information S1 (table). However, we do not predict that competition sensing will respond exclusively to other genotypes. First of all, detection and response to self cells is an important competition-sensing response that probably provides information about competition from both self and other cells (BOX 2). More generally, harmful stimuli in the absence of ecological competition can cause a competition-sensing response to misfire; for example, *P. aeruginosa* produces bacteriocins when challenged by synthetic antibiotics[27]. But a stress response does not have to be a perfect discriminator to be useful for responding to competition, it just has to be positively correlated with competition across different environmental conditions.

Toxin production is not the only response regulated by competition sensing. Some responses to competition involve attack, but others involve defence. We have focused on the attack response, toxin production, in this article because it is difficult to know whether most defensive responses are defences against a competitor or defences against an asocial environment. However, the repair and protective roles of stress responses[22] are just as important as toxin production in ecological competition. For example, in addition to regulating colicin secretion, the SOS response of *E. coli* regulates DNA repair and the use of error-tolerant DNA polymerases that raise the mutation rate[53]. Both these effects on DNA might help in the escape from strong ecological competition. Biofilm formation is another candidate response to competition sensing, as biofilms are both induced by and protective against antibiotics[54]. Conversely, competition sensing can be a response to being in a biofilm in which cells are dense and nutrients are limited[55].

Metabolic shifts might also help cells to compete with other strains and species. Evolutionary theory suggests that cells should use high-rate, low-yield metabolism, such as fermentation in the presence of oxygen, when they face competition from other genotypes[56]. It is interesting, then, that stress responses regulate a range of metabolic changes, including a shift towards fermentation, in response to antibiotics. These changes have been taken as evidence that antibiotics function more as signals than as toxins in nature[57,58]. Our interpretation is that antibiotics from other genotypes function as signals only in the sense that a cell can benefit from detecting ecological competition before it becomes bactericidal. However, in evolutionary terminology, this would make antibiotics cues rather than true signals because true signals require that the sender benefits from signalling[17,19].

Conclusions

Most bacteria face the potential for intense ecological competition from both their own genotype and other genotypes[9–11]. Our hypothesis is that this competition has had a strong effect on the evolution of bacterial regulatory networks. In particular, when ecological competition implies the presence of other genotypes, these networks should drive responses that both defend cells and allow them to counter-attack. Our work makes the distinction between two major classes of mechanism that cells use to detect ecological competition. The first is the detection of specific secreted products of cells, including quorum sensing and related responses. This will often involve a specific receptor to detect other cells via their secreted compounds. The second class of mechanism is the stress responses that directly detect ecological competition in a process we call competition sensing (TABLE 1). By responding to harm itself, competition sensing is not specific to the competitor, which can be a strength in diverse microbial communities, as it will not misidentify a harmless foreign strain as a threat.

This view of bacterial responses to competition hides many complexities that we have only touched on briefly (BOX 2). For example, it is clear that both quorum-related responses and competition sensing might also provide information about when to secrete products that carry a density-dependent benefit, which can be independent of ecological competition. Furthermore, we do not yet understand why species differ in the mechanisms they use to regulate competition-associated phenotypes like toxin secretion. Finally, we do not know whether the original function of nutrient or damage stress responses was in ecological competition. It is conceivable that stress responses originally arose for abiotic factors and were only subsequently co-opted for competition sensing. As data from more species become available, phylogenetic analyses can look for evidence of ancient links between stress response regulators and toxins or toxin regulators, although the subsequent diversification of toxins might obscure the ancient character states. Another potential approach is experimental evolution following the evolution of stress response regulators under conditions of varying types and degrees of ecological competition. Whatever the precise relationship between the origin and current function of stress responses, it seems inevitable in modern ecosystems that key stimuli for many of the stress responses will be the effects of other cells, and the frequent association of stress responses with toxin production suggests that modern bacteria use these stimuli as information. In this way, stress responses can function as social barometers that enable bacteria to assess and respond to ecological competition.

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1. Birch, L. C. The meanings of competition. *Am. Nat.* **91**, 5–18 (1957).
2. Case, T. J. & Gilpin, M. E. Interference competition and niche theory. *Proc. Natl Acad. Sci. USA* **71**, 3073–3077 (1974).
3. Hansen, S. K., Rainey, P. B., Haagensen, J. A. J. & Molin, S. Evolution of species interactions in a biofilm community. *Nature* **445**, 533–536 (2007).
4. Nadell, C. D., Xavier, J. B. & Foster, K. R. The sociobiology of biofilms. *FEMS Microbiol. Rev.* **33**, 206–224 (2009).
5. Gans, J., Wolinsky, M. & Dunbar, J. Computational improvements reveal great bacterial diversity and high metal toxicity in soil. *Science* **309**, 1387–1390 (2005).
6. Burns, B. P., Goh, F., Allen, M. & Neilan, B. A. Microbial diversity of extant stromatolites in the hypersaline marine environment of Shark Bay, Australia. *Environ. Microbiol.* **6**, 1096–1101 (2004).
7. Dethlefsen, L., Eckburg, P. B., Bik, E. M. & Relman, D. A. Assembly of the human intestinal microbiota. *Trends Ecol. Evol.* **21**, 517–523 (2006).
8. Foster, K. R. & Wenseleers, T. A general model for the evolution of mutualisms. *J. Evol. Biol.* **19**, 1283–1293 (2006).
9. Little, A. E. F., Robinson, C. J., Peterson, S. B., Raffa, K. F. & Handelsman, J. Rules of engagement: interspecies interactions that regulate microbial communities. *Annu. Rev. Microbiol.* **62**, 375–401 (2008).
10. Hibbing, M. E., Fuqua, C., Parsek, M. R. & Peterson, S. B. Bacterial competition: surviving and thriving in the microbial jungle. *Nature Rev. Microbiol.* **8**, 15–25 (2009).
11. Foster, K. R. & Bell, T. Competition, not cooperation, dominates interactions among culturable microbial species. *Curr. Biol.* **22**, 1845–1850 (2012).
12. Xavier, J. B. & Foster, K. R. Cooperation and conflict in microbial biofilms. *Proc. Natl Acad. Sci. USA* **104**, 876–881 (2007).
13. Nadell, C. D. & Bassler, B. L. A fitness trade-off between local competition and dispersal in *Vibrio cholerae* biofilms. *Proc. Natl Acad. Sci. USA* **108**, 14181–14185 (2011).
14. Kerr, B., Riley, M. A., Feldman, M. W. & Bohannan, B. J. Local dispersal promotes biodiversity in a real-life game of rock–paper–scissors. *Nature* **418**, 171–174 (2002).
15. D'Costa, V. M. *et al.* Antibiotic resistance is ancient. *Nature* **477**, 457–461 (2011).
16. Fuqua, W. C., Winans, S. C. & Greenberg, E. P. Quorum sensing in bacteria: the LuxR-LuxI family of cell density-responsive transcriptional regulators. *J. Bacteriol.* **176**, 269–275 (1994).
17. Diggle, S. P., Gardner, A., West, S. A. & Griffin, A. S. Evolutionary theory of bacterial quorum sensing: when is a signal not a signal? *Philos. Trans. R. Soc. B.* **362**, 1241–1249 (2007).
18. Waters, C. M. & Bassler, B. L. Quorum sensing: cell-to-cell communication in bacteria. *Annu. Rev. Cell Dev. Biol.* **21**, 319–346 (2005).
19. Keller, L. & Surette, M. G. Communication in bacteria: an ecological and evolutionary perspective. *Nature Rev. Microbiol.* **4**, 249–258 (2006).
20. Hense, B. A. *et al.* Does efficiency sensing unify diffusion and quorum sensing? *Nature Rev. Microbiol.* **5**, 230–239 (2007).
21. Storz, G. & Hengge, R. (eds) *Bacterial Stress Responses* 2nd edn (American Society for Microbiology Press, 2011).
22. Poole, K. Stress responses as determinants of antimicrobial resistance in Gram-negative bacteria. *Trends Microbiol.* **20**, 227–234 (2012).
23. Bagge, N. *et al. Pseudomonas aeruginosa* biofilms exposed to imipenem exhibit changes in global gene expression and β-lactamase and alginate production. *Antimicrob. Agents Chemother.* **48**, 1175–1187 (2004).
24. Price-Whelan, A., Dietrich, L. E. P. & Newman, D. K. Rethinking 'secondary' metabolism: physiological roles for phenazine antibiotics. *Nature Chem. Biol.* **2**, 71–78 (2006).
25. Chavan, M. & Riley, M. in *Bacteriocins: Ecology and Evolution* (eds Riley, M. A. & Chavan, M. A.) 19–43 (Springer, 2007).
26. Staroń, A. *et al.* The third pillar of bacterial signal transduction: classification of the extracytoplasmic function (ECF) σ factor protein family. *Mol. Microbiol.* **74**, 557–581 (2009).
27. Brazas, M. D. & Hancock, R. E. W. Ciprofloxacin induction of a susceptibility determinant in *Pseudomonas aeruginosa*. *Antimicrob. Agents Chemother.* **49**, 3222–3227 (2005).

28. Majeed, H., Gillor, O., Kerr, B. & Riley, M. A. Competitive interactions in *Escherichia coli* populations: the role of bacteriocins. *ISME J.* **5**, 71–81 (2010).
29. Cao, M. *et al.* Defining the *Bacillus subtilis* σ^{W} regulon: a comparative analysis of promoter consensus search, run-off transcription/macroarray analysis (ROMA), and transcriptional profiling approaches. *J. Mol. Biol.* **316**, 443–457 (2002).
30. Walker, D. *et al.* Transcriptional profiling of colicin-induced cell death of *Escherichia coli* MG1655 identifies potential mechanisms by which bacteriocins promote bacterial diversity. *J. Bacteriol.* **186**, 866–869 (2004).
31. Cavard, D. Effects of temperature and of heat shock on the expression and action of the colicin A lysis protein. *J. Bacteriol.* **177**, 5189–5192 (1995).
32. Wood, J. in *Bacterial Stress Responses* 2nd edn (eds Storz, G. & Hengge, R.) 133–156 (American Society for Microbiology Press, 2011).
33. Liras, P., Gomez-Escribano, J. P. & Santamarta, I. Regulatory mechanisms controlling antibiotic production in *Streptomyces clavuligerus*. *J. Ind. Microbiol. Biotechnol.* **35**, 667–676 (2008).
34. Sanchez, S. *et al.* Carbon source regulation of antibiotic production. *J. Antibiot.* **63**, 442–459 (2010).
35. Jensen, V. *et al.* RhlR expression in *Pseudomonas aeruginosa* is modulated by the *Pseudomonas* quinolone signal via PhoB-dependent and -independent pathways. *J. Bacteriol.* **188**, 8601–8606 (2006).
36. Xavier, J., Kim, W. & Foster, K. A molecular mechanism that stabilizes cooperative secretions in *Pseudomonas aeruginosa*. *Mol. Microbiol.* **79**, 166–179 (2011).
37. Perkins, T. J. & Swain, P. S. Strategies for cellular decision-making. *Mol. Syst. Biol.* **5**, 326 (2009).
38. Gardner, A. Adaptation as organism design. *Biol. Lett.* **5**, 861–864 (2009).
39. Hindré, T., Pennec, J. P., Haras, D. & Dufour, A. Regulation of lantibiotic lacticin 481 production at the transcriptional level by acid pH. *FEMS Microbiol. Lett.* **231**, 291–298 (2004).
40. Darch, S. E., West, S. A., Winzer, K. & Diggle, S. P. Density-dependent fitness benefits in quorum-sensing bacterial populations. *Proc. Natl Acad. Sci. USA* **109**, 8259–8263 (2012).
41. Hayes, C. S., Aoki, S. K. & Low, D. A. Bacterial contact-dependent delivery systems. *Annu. Rev. Genet.* **44**, 71–90 (2010).
42. Gibbs, K. A., Urbanowski, M. L. & Greenberg, E. P. Genetic determinants of self identity and social recognition in bacteria. *Science* **321**, 256–259 (2008).
43. Garbeva, P., Silby, M. W., Raaijmakers, J. M., Levy, S. B. & de Boer, W. Transcriptional and antagonistic responses of *Pseudomonas fluorescens* Pf0-1 to phylogenetically different bacterial competitors. *ISME J.* **5**, 973–985 (2011).
44. Laub, M. T. in *Bacterial Stress Responses* 2nd edn (eds Storz, G. & Hengge, R.) 45–58 (American Society for Microbiology Press, 2011).
45. Korgaonkar, A. K. & Whiteley, M. *Pseudomonas aeruginosa* enhances production of an antimicrobial in response to *N*-acetylglucosamine and peptidoglycan. *J. Bacteriol.* **193**, 909–917 (2011).
46. Braun, V., Patzer, S. I. & Hantke, K. Ton-dependent colicins and microcins: modular design and evolution. *Biochimie* **84**, 365–380 (2002).
47. Maynard Smith, J. & Price, G. R. The logic of animal conflict. *Nature* **246**, 15–18 (1973).
48. McGannon, C. M., Fuller, C. A. & Weiss, A. A. Different classes of antibiotics differentially influence Shiga toxin production. *Antimicrob. Agents Chemother.* **54**, 3790–3798 (2010).
49. Kültz, D. Evolution of the cellular stress proteome: from monophyletic origin to ubiquitous function. *J. Exp. Biol.* **206**, 3119–3124 (2003).
50. Chopin, M.-C., Chopin, A. & Bidnenko, E. Phage abortive infection in lactococci: variations on a theme. *Curr. Opin. Microbiol.* **8**, 473–479 (2005).
51. Marraffini, L. A. & Sontheimer, E. J. CRISPR interference: RNA-directed adaptive immunity in bacteria and archaea. *Nature Rev. Genet.* **11**, 181–190 (2010).
52. Hayes, F. & Van Melderen, L. Toxins-antitoxins: diversity, evolution and function. *Crit. Rev. Biochem. Mol. Biol.* **46**, 386–408 (2011).
53. Roth, J. R., Kugelberg, E., Reams, A. B., Kofoid, E. & Andersson, D. I. Origin of mutations under selection: the adaptive mutation controversy. *Annu. Rev. Microbiol.* **60**, 477–501 (2006).
54. Hoffman, L. R. *et al.* Aminoglycoside antibiotics induce bacterial biofilm formation. *Nature* **436**, 1171–1175 (2005).
55. Collet, A. *et al.* Impact of *rpoS* deletion on the proteome of *Escherichia coli* grown planktonically and as biofilm. *J. Proteome Res.* **7**, 4659–4669 (2008).
56. Pfeiffer, T., Schuster, S. & Bonhoeffer, S. Cooperation and competition in the evolution of ATP-producing pathways. *Science* **292**, 504–507 (2001).
57. Davies, J., Spiegelman, G. B. & Yim, G. The world of subinhibitory antibiotic concentrations. *Curr. Opin. Microbiol.* **9**, 445–453 (2006).
58. Gillor, O. in *Bacteriocins: Ecology and Evolution* (eds Riley, M. A. & Chavan, M. A.) 135–145 (Springer, 2007).
59. Gardner, A., West, S. A. & Buckling, A. Bacteriocins, spite and virulence. *Proc. Biol. Sci.* **271**, 1529–1535 (2004).
60. Frank, S. A. Spatial polymorphism of bacteriocins and other allelopathic traits. *Evol. Ecol.* **8**, 369–386 (1994).
61. Wloch-Salamon, D. M., Gerla, D., Hoekstra, R. F. & de Visser, J. A. G. M. Effect of dispersal and nutrient availability on the competitive ability of toxin-producing yeast. *Proc. Biol. Sci.* **275**, 535–541 (2008).
62. Gough, J., Karplus, K., Hughey, R. & Chothia, C. Assignment of homology to genome sequences using a library of hidden Markov models that represent all proteins of known structure. *J. Mol. Biol.* **313**, 903–919 (2001).
63. Dauga, C. Evolution of the *gyrB* gene and the molecular phylogeny of *Enterobacteriaceae*: a model molecule for molecular systematic studies. *Int. J. Syst. Evol. Microbiol.* **52**, 531–547 (2002).
64. Labeda, D. *et al.* Phylogenetic study of the species within the family *Streptomycetaceae*. *Antonie Van Leeuwenhoek* **101**, 73–104 (2012).
65. Fontaine, L. *et al.* Quorum-sensing regulation of the production of Blp bacteriocins in *Streptococcus* thermophilus. *J. Bacteriol.* **189**, 7195–7205 (2007).
66. Inaoka, T., Takahashi, K., Ohnishi-Kameyama, M., Yoshida, M. & Ochi, K. Guanine nucleotides guanosine 5′-diphosphate 3′-diphosphate and GTP co-operatively regulate the production of an antibiotic bacilysin in *Bacillus subtilis*. *J. Biol. Chem.* **278**, 2169–2176 (2003).
67. Jerman, B., Butala, M. & Žgur-Bertok, D. Sublethal concentrations of ciprofloxacin induce bacteriocin synthesis in *Escherichia coli*. *Antimicrob. Agents Chemother.* **49**, 3087–3090 (2005).

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Competing interests statement

The authors declare no competing financial interests.

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