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Review

Trade-off Mechanisms Shaping the Diversity of Bacteria

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Strain-to-strain variations in bacterial biofilm formation, metabolism, motility, virulence, evolvability, DNA repair and resistance (to phage, antibiotics, or environmental stresses) each contribute to bacterial diversity. Microbiologists should be aware that all of these traits are subject to constraints imposed by trade-offs, so adaptations improving one trait may be at the cost of another. A deeper appreciation of trade-offs is thus crucial for assessing the mechanistic limits on important bacterial characteristics. Studies of the negative correlations between various traits have revealed three molecular mechanisms, namely, trade-offs involving resource allocation, design constraint, and information processing. This review further discusses why these trade-off mechanisms are important in the establishment of models capable of predicting bacterial competition, coexistence, and sources of diversity.

Trends

Trade-offs have been identified in nearly every important microbial characteristic.

Trade-offs constrain evolutionary adaptations in bacterial properties and prevent ecological fitness in all environments.

The identification and classification of trade-offs has progressed from the ecological and phenomenological to the molecular level.

Artificial control of trade-offs has produced unprecedented understanding of how traits are linked and how intermediate settings of trade-offs behave.

The continuing mutational change of trade-off settings in varying environments is the likely source of a great deal of intra- and interspecies diversity.

The Role of Trade-offs in Microbiology

The observation that biological adaptations have some secondary effects on fitness precedes even the ideas of Darwin. As early as Goethe's Law of Compensation [1], it was recognized that 'in order to spend on one side, nature is forced to economise on the other side'. Interpreted for bacteria, this notion suggests that cellular resources allocated to one characteristic can lead to reduced fitness in another. Such negative correlations between traits are called trade-offs, and their common features and the relationship between two traits are introduced in Box 1.

As more widely recognized with plants and animals, trade-offs constrain the range of phenotypes open to organisms [2,3]. Negative correlations between life-history characteristics, such as longevity, growth rate, offspring number, and resistance to stress or predation, have been observed in a wide range of organisms [4]. As proposed by Levins and discussed by Stearns, the partitioning of resources in food to reproduction or to survival processes such as stress resistance (i.e., resource allocation) may be a cause of trade-offs [2,5]. Although initially proposed for plants, insects, and animals, there is no reason why these notions do not apply to microbes as well.

Trade-offs are recognized to be central to issues ranging from speciation and adaptive radiation to coexistence in communities [6]. As Tilman noted [7], the answer to the great diversity of species on Earth 'may lie in quantifying the trade-offs that organisms face in dealing with the constraints of their environment'. What is utterly amazing is that the natural diversity of bacteria revealed by genome sequences is rarely discussed in terms of trade-offs. Microbiology textbooks, even microbial ecology texts, rarely discuss how trade-offs shape organisms. This review will discuss why microbiologists, especially molecular biologists and biochemists, should put a greater emphasis on understanding how trade-offs underpin both intra- and interspecies diversity in bacteria.

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Box 1. The Essentials of a Trade-off between Two Traits

When two negatively correlated traits (such as the pairs in Figure 1) are measured in a range of natural bacterial isolates (e.g., organisms x_1 to x_5), the magnitude of Trait 1 and Trait 2 can be plotted along the axes as in Figure I. The x_1 and x_5 organisms represent the most extreme settings of the trade-off, having specialized on one or other trait. The black boxes describe the organisms at the two extremes if a growth-resistance trade-off is used as the example. Organisms (x_2 to x_4) can be found at intermediate settings of a trade-off that fall on the curve in Figure I. The curve (light blue) is the cleanest example of a survival-multiplication trade-off shape of *Escherichia coli*, determined using synthetic strains with fixed trade-off settings [14]. This particular curve shape (plotting growth on lactate versus acid resistance [14]) allows organism x_2 to x_4 to have both appreciable resistance and growth in an intermediate setting of the trade-off. In principle, trade-off curves can be of any shape, being linear, sigmoidal, or with convex or concave curvatures [2]. Accurate trade-off shapes are unknown for most pairs of traits however.

Trade-offs allow diversity to develop for two reasons. First, organisms can adapt along trade-off shapes, depending on the environment. For example, organism x_2 could gain fitness in a more stressed environment through the selection of mutations in x_2 that change its trade-off settings to position x_3 (or x_4 or other points to the right along the curve). The consequence of living in a nonconstant environment is that free-living bacteria will develop a variety of trade-off settings. The species-wide diversity of trade-off settings is a consequence of this and is discussed in the text.

The second feature needed for diversity to be maintained is the ability of different types to coexist in an environment. Coexistence of organisms is possible with different trade-off settings because the overall fitness of, say x_2 and x_3, may be the same in some environments where both traits contribute to fitness. Equal fitness of x_2 and x_3 could occur in an environment with partial stress and intermediate nutrient availability. This trade-off-dependent coexistence has been experimentally demonstrated [10,14,66].

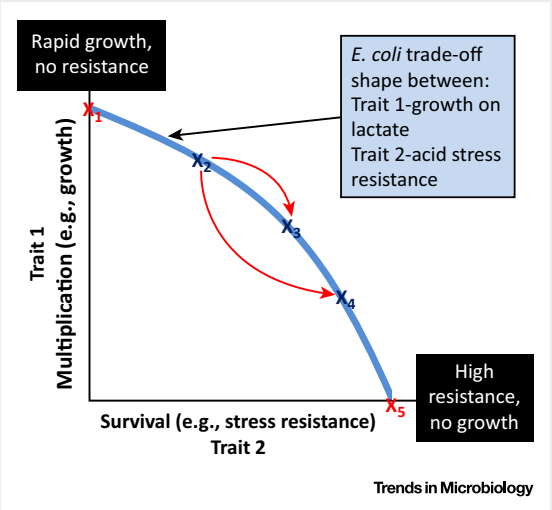


Figure I. A Composite Diagram of the Relationship between Two Traits Exhibiting a Trade-off. The traits in the example involve growth on lactate minimal medium (multiplication) and acid-stress resistance (survival) of *Escherichia coli* strains that have fixed but distinct levels of a global stress regulator. The experimental details for getting the shape plotted in the figure are described in [14]. The symbols x_1 to x_5 represent organisms that have distinct levels of the two traits and which fall on the plotted line.

The precise relationships between traits and the trade-off shapes in Box 1 are difficult to unravel, especially with higher organisms [8]. The partitioning of resources in food to either reproduction or to survival [2,5] is extremely hard to dissect in complex organisms [8], but considerably easier in bacteria [9,10]. The simplicity of bacteria indeed allows trade-offs to be analysed in molecular detail, and bacteria have been particularly useful in demonstrating that alternative molecular mechanisms underpin trade-offs. Progress in this direction is of recognized importance [11,12] because, as stated ever since Stearns [11], 'we have a lot of evidence that trade-offs exist; we have very little understanding of the mechanisms that cause them'. An understanding of trade-offs is important because the mechanisms are crucial in the establishment of credible models capable of predicting the effects of trade-offs on competition and coexistence [13,14].

For microbiologists in general, there needs to be an awareness that a wide range of important bacterial phenotypes are affected by trade-offs. It is not that microbial trade-offs have not been previously reviewed [10], but this topic is often overlooked in the teaching of microbiology. To correct this oversight, the broad impact of trade-off effects on bacteria will be summarized here together with the breadth of functions affected. There has been a steady increase in the number of individual studies in which negative correlations between pairs of bacterial traits have been observed. Just as importantly, it is now being recognized that intermediate trait settings of trade-offs mentioned in Box 1 represent a great deal of the intraspecies diversity in bacteria. I discuss the molecular basis of trade-offs, and their plasticity, and how we can begin to understand the role of trade-offs in maintaining diversity. A novel outcome of these studies, for example, is that the ubiquitous ecological, survival-multiplication trade-offs can be explained by entirely different mechanisms and not just by resource allocation as was historically assumed [2,5,15].

How Trade-offs Determine the Properties of Bacteria

The overview in Figure 1 (Key Figure) shows that many prominent bacterial characteristics display negative correlations to other traits. The pairs of characteristics depicted in Figure 1 were chosen to indicate the breadth of microbial properties affected. Besides the breadth of phenotypes affected, Figure 1 also points to the many cellular processes subject to trade-offs.

In Table 1, these and > 30 other examples of negative correlations are brought together for the first time, revealing the remarkably broad importance of trade-offs in shaping microbial

Key Figure

The Breadth of Bacterial Characteristics Affected by Trade-offs

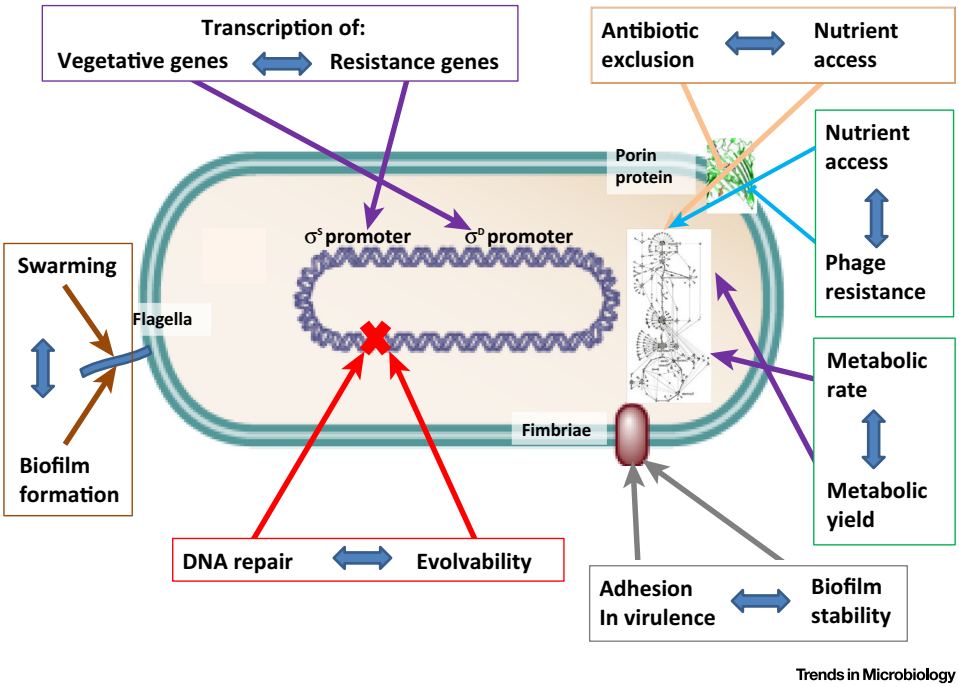


Figure 1. The diagram shows pairs of characteristics linked by double-headed arrows in which an increase in one trait is accompanied by reduction in another. The references describing these pairwise costs and benefits in different environments are in Table 1 and the text, together with further related examples.

Table 1. Examples of Trade-offs Affecting Important Characteristics of Microbes

Trade-offs Affecting:	Benefit in One Environment	Resulting Cost in Another Capability	Organisms and Properties Affected	Refs
Nutrient Utilization and Metabolism	Increased metabolic flux, faster growth rate	Reduced growth yield	Yeast trade-offs between the rate and efficiency of conversion of sugars into offspring. The *Escherichia coli* yield-flux trade-off is also affected by growth rate, being more efficient with slow growth.	[25,26,29–31]
	Increased affinity and higher fitness for low levels of nutrient	Reduced maximal uptake rate	In *E. coli* adapted to micromolar sugar levels, glucose transport involves a high-affinity, high-energetic-cost transporter. At high glucose levels a lower-affinity, high-flux transporter is used.	[33,34]
	Phosphate source assimilation	Reduced carbon-source incorporation	Optimisation of phosphate incorporation in *E. coli* by reduced incorporation of carbon by shifting metabolic pathways	[32]
	Lactose uptake	Reduced growth fitness	High *lac* permease expression in *E. coli* helps lactose uptake but is a major physiological burden to the cell.	[35]
	O_2 access at an air–water interface	Reduced Fe acquisition	In *Pseudomonas aeruginosa*, pellicle formation confers a growth advantage under static conditions, but pellicle cells show a nutritional trade-off between oxygen and iron acquisition.	[68]
Antibiotic Susceptibility	Fosfomycin resistance	Impaired growth when cultured with glycerol-3-phosphate or glucose-6-phosphate as substrate	An *E. coli cpxA* mutant lacking phosphatase activity results in constitutive activation of its cognate response regulator, CpxR, and reduced transport of fosfomycin but also reduced sugar phosphate transport.	[46]
	High nutrient permeability through large-channel porins	Antibiotic access elevated leading to growth inhibition	Gram-negative bacteria with no porins or porins with lower channel permeability are more resistant to polar antibiotics but are poorer in accessing nutrients.	[13,41]
	Sulfonamide resistance	Reduced dihydropteroate synthase (DHPS) activity	Mutations in *folP* affecting DHPS result in sulphonamide resistance, but the cost is ameliorated by compensatory mutations in DHPS that allow it to function normally.	[69]
	Acquired cefotaxime resistance	Reduced ceftazidime resistance	Adaptation of the enzyme TEM-1 β-lactamase to one novel antibiotic exhibits antagonistic pleiotropy to another.	[70]
Virulence	Adhesion in virulence	Reduced biofilm stability	In uropathogenic *E. coli*, point mutations in *fimH* increase uroepithelial adhesion. The R66 mutation results in a strong advantage in bladder colonization but also reduced shear-enhanced binding properties, in turn reducing in-host survival.	[47,48]
		Survival in aquatic environments	*Pseudomonas aeruginosa* adapted to long-term chronically	[71]

Table 1. (continued)

Trade-offs Affecting:	Benefit in One Environment	Resulting Cost in Another Capability	Organisms and Properties Affected	Refs
	Adaptation to cystic fibrosis lungs		infected patients are less efficient in resisting phages and killing by protists.	
	Competitive edge in nutrient-poor environments	Fitness costs of colicin production	Colicin production by *E. coli* provides a competitive edge in nutrient-poor environments but the costs of colicin production reduce fitness in other situations.	[72]
	Competitive edge in extraintestinal environments	Reduced stress resistance and reduced antibiotic resistance	*E.coli* in extraintestinal infections reduces expression of RpoS in a number of ways to alter the stress: nutrition balance.	[66]
Resistance to Phages	Phage resistance to bacteriophage T2	Reduced competitive ability	Bacteriophage-resistant isolates of *E. coli* B show a decreased competitive ability in both the resource environment in which strains were isolated and in two alternate environments.	[10,73,74]
	Phage resistance to bacteriophage λ	Loss of ability to use maltodextrins	*E. coli* resistant to bacteriophage λ is unable to use maltosaccharides through loss or alteration of glycoporin channels.	[75,76]
	Phage T5 resistance	Loss of a means of Fe uptake	*fhuA* mutations of *E. coli* affecting a surface receptor for Fe-chelate can abolish T5 binding but can affect Fe uptake.	[77]
Resistance to Environmental Stresses	Osmotic stress, acid, oxidative stress resistance	Slower growth on many nutrients (e.g., glucose, acetate, glycerol)	*E. coli* exhibiting high levels of RpoS sigma factor is more resistant to environmental stresses but grows more slowly due to diversion of transcription away from vegetative genes.	[14,20,78]
	Detergent resistance	Growth on nutrients	*E. coli* adapts in the mouse gut in the presence of bile salts and competition for nutrients; some bacteria become more resistant to bile salts but grow more slowly.	[42]
	Yeast survival with heat, acid, and oxidative stress	Growth rate	*Saccharomyces cerevisiae* with a redistribution of resources toward stress tolerance functions shows a reduced growth rate.	[23]
	Nickel tolerance	Growth rate	*Rhizobium* symbiotic with legumes exhibits a trade-off between nickel tolerance and its ability to replicate rapidly.	[24]
Genome/ Information Maintenance	Mutator mutations increase evolvability	A high mutation rate leads to the cost in deleterious mutations	A high mutation rate in *E. coli* was initially beneficial in the mouse gut because it allowed faster adaptation, but this benefit disappeared once adaptation was achieved.	[79]
	Translational accuracy	Translational rate	The bacterial ribosome's interactions with mRNA govern its translation rate, which is controlled by trade-offs between site	[80,81]

Table 1. (continued)

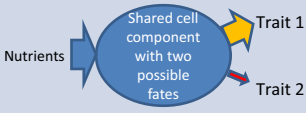
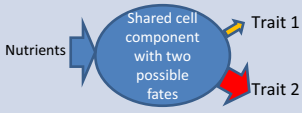
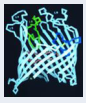
Trade-offs Affecting:	Benefit in One Environment	Resulting Cost in Another Capability	Organisms and Properties Affected	Refs
			accessibility, RNA unfolding, and sliding at upstream standby sites.	
	Accuracy in promoter selection	Stability to mutation	Transcription factor binding sites are subject to a trade-off between specificity, which is greater in long binding sites, and robustness to mutation, which is greater in short binding sites.	[82]
	Fitness through reduced genome by loss of biosynthetic genes in rich media	Low fitness in minimal media, smaller niche	Selective advantages can explain the prevalent loss of biosynthetic genes in *E. coli*, *Shigella*, and *Acinetobacter baylyi*, but with loss of prototrophy.	[36,37]
	Chemosensory information processing	Energy consumption	Chemotaxis information processing for cellular regulatory functions has a cost in terms of energy use.	[83]
	Hydrogen peroxide resistance	Fidelity of DNA repair	A *mutS* mutation in *E. coli* results in the elevated secretion of catalase but reduces the capacity for DNA repair.	[84]
	Horizontal transfer and stability of integrons	Fitness cost of maintaining functional integrases	Insertional inactivation of the integron IntI1 increases fitness but prevents integration of genes. This provides an explanation for the frequent observation of inactive integron-integrases in bacterial populations.	[85]
	Informational exchange, recombination	Lower growth rate	High mating efficiency in yeast *S. cerevisiae* carries a cost in terms of growth rate.	[86]
Biofilm Formation and Motility	Biofilm-mediated adaptation	Bacterial survival in culture	Biofilm-inherent bacteria have a stark fitness trade-off that reduces growth in free culture.	[87]
	Local competition	Dispersal	Extracellular polysaccharide (EPS)-producing *Vibrio cholerae* has an advantage in competition against an EPS-deficient strain. The bacteria, however, have an ecological cost in dispersal to new locations.	[88]
	Hyperswarmers	Biofilm formation	*P. aeruginosa* hyperswarmers outcompete the ancestral strain in swarming competitions, but are strongly outcompeted in biofilm formation.	[49]
Phage Biology	Phage offspring production	Phage survival quality	A comparison of 16 phages infecting *E. coli* showed that their mortality rate is negatively correlated to their multiplication rate in the bacterial host.	[89]

characteristics. As shown in the groupings in Table 1, trade-off effects impact on metabolism, motility, biofilm formation, virulence, DNA repair, evolvability, and resistance to phage, antibiotics, or environmental stresses. So just about every important characteristic of bacteria is constrained by trade-offs. It is worth noting that the examples in Table 1 are not truly comprehensive and that some linked traits may well have been overlooked or undoubtedly remain to be discovered. Table 1 also contains further information on the specific organisms and cell components involved.

A particular aim of this review is to present the proposal that all the trade-offs in Figure 1 and Table 1 involve at least one of three underlying molecular mechanisms. These three mechanisms are quite distinct and provide a means of understanding the basis of trade-offs. Historically, most trade-offs have been characterized on the basis of ecological, whole-cell effects (e.g., survival-multiplication), but we can now explain some trade-offs in fundamental detail. This is important because these mechanisms at the molecular level may reveal trade-offs not identified in physiological or ecological studies. In subsequent sections, a means of classifying these trade-offs is presented.

A Molecular Approach to Understanding and Classifying Trade-offs

The three identifiable processes resulting in trade-offs are, namely, resource allocation, design constraint, and informational processing. Their properties and differentiating features are compared in Figure 2. Because of space limitation, only one trade-off in each of these classes is shown in Figure 3 to provide a fuller picture of how each of these mechanisms operates in bacteria. In addition, a few brief illustrations of each mechanism are described, using the cases, in Table 1.

Trade-off mechanism	General requirement	Trait 1	Trait 2
Resource allocation	Shared cell component with two possible fates	Shared intermediates are directed to a branch of metabolism or macromolecular synthesis 	Shared intermediates directed to another branch of metabolism or macromolecular synthesis 
Design constraint	Protein with alternative or overlapping functions changed by mutation or modification	Protein structure specific for a substrate or function  e.g., antibiotic, phage or substrate specificity (Trait 1)	Structure altered by mutation or modification  Gain of new function (Trait 2) but with reduced original activity
Information processing	Transfer of sequence information from one macromolecule to another	Accurate information transfer (Trait 1):  Slow, expensive, maintains information integrity	Inaccurate information transfer (Trait 2):  Faster, cheaper, results in mutations or mistranslation

Trends in Microbiology

Figure 2. A Summary of the Mechanistic Underpinnings of Trade-offs. Shown are the correlations between two traits (Trait 1 and Trait 2), one of which is high when the other is low. The properties of the three discussed mechanisms are tabulated, focussing on the different bases of the three mechanisms.

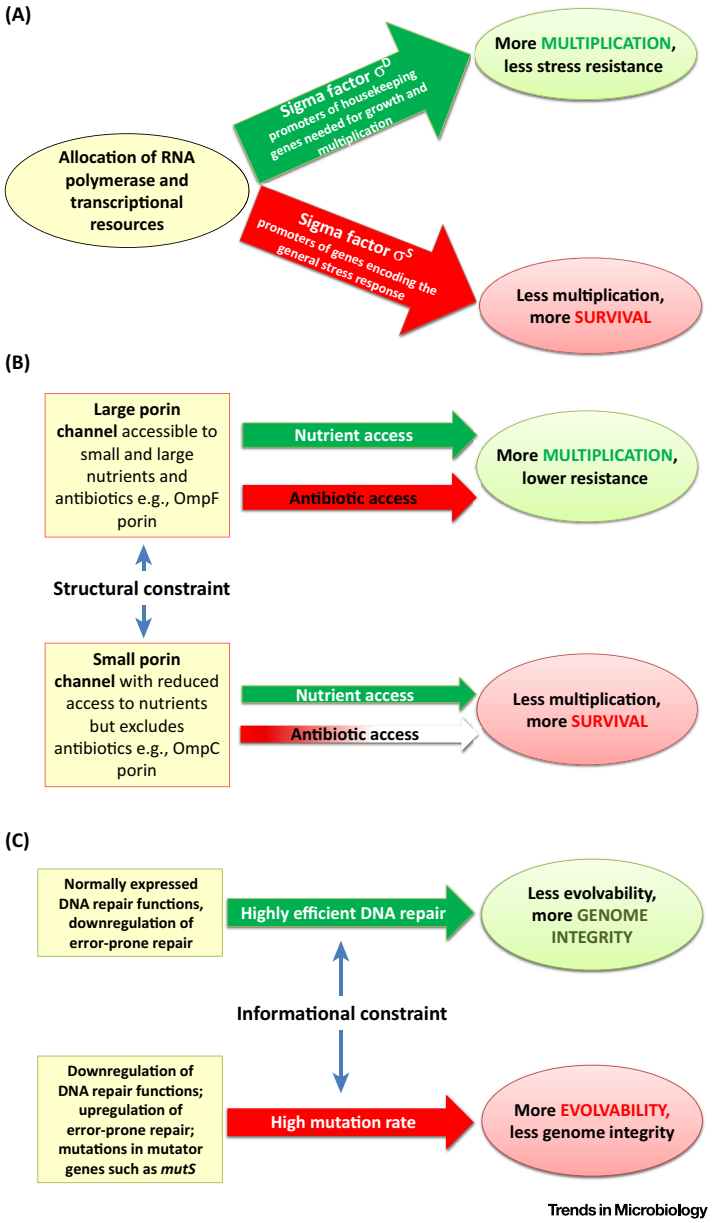


Figure 3. Three Examples of Trade-offs with Different Mechanisms. (A) Resource allocation in *Escherichia coli* between growth and stress resistance (ecologically a multiplication-survival trade-off). Limiting nutrients are channelled to different purposes by cellular controls governed by the intracellular concentration of the RpoS/σ^S master regulator of the general stress response [21]. Bacteria with low RpoS levels multiply rapidly because they divert resources into making proteins needed for metabolism and growth through σ^D. When cells have high levels of σ^S, the bacteria devote nutrients to making protective resistance mechanisms that stop them being killed, but devote less to growth and multiplication. Polymorphisms in *rpoS* in natural populations [90] result in altered amounts of RpoS in cells [91] and hence altered settings of the resource allocation. (B) An example of a structural constraint underpinning a multiplication-survival trade-off in *E. coli* between growth and antibiotic exclusion. Large-channel porins in the outer membrane permeate limiting concentrations of nutrients more rapidly than do small-channel porins [92]. Bacteria expressing mainly OmpF (larger channels) are more competitive in nutrient-poor environments, but a switch from OmpF to OmpC (smaller channels) makes them less nutrient-competitive but more tolerant to detergents and antibiotics [13]. Mutations reducing OmpF pore size or abolishing expression have the same effect. Mutants lacking both OmpF and OmpC are the most antibiotic resistant [41]. (C) An informational processing trade-off between evolvability and genome integrity. The mutation rate in species *E. coli* is not constant; a few percent of isolates exhibit very high mutation rates due to mutator mutations [67]. Strains with normal DNA repair can still show elevated stress-induced mutagenesis under conditions stimulating the general stress response and

Resource Allocation Trade-offs

This is the mechanism alluded to in the Goethe quote and has been a cover-all ecological explanation of trade-offs whose mechanisms were otherwise unexplained [8,16]. In general, trade-offs are possible through the allocation of shared resources between alternative fates, such as when a nutrient, intracellular metabolite, pathway, or transcriptional output has branched, alternative end-points (Figure 2). Additional resource allocations are possible with more complex organisms, such as those with organs or subcellular compartments [8,16]. If these end-points have alternative roles in an organism, then there is an inevitable functional trade-off in channelling resources to one or other function.

The alternative fate of resources underpin several of the trade-offs in Table 1. In particular, Figure 3A shows an example of a survival-multiplication trade-off. The two alternative end points of allocated resources in Figure 3A promote either improved survival under stress or more rapid vegetative growth. Bacteria cannot achieve both simultaneously [17]. In bacteria such as *Escherichia coli*, the general stress response is by far the most costly and large-scale bacterial protection mechanism, and hundreds of cell components (proteins and stress-protectant metabolites) accumulate to counteract environmental challenges [18,19]. The regulation of the general stress response is centrally controlled at the transcriptional level; resource allocation is determined by whether the bacteria commit RNA polymerase to make one set of proteins or another (Figure 3A). The concentration of the transcriptional regulator RpoS (or σ^S) acts as the resource allocator, shifting cellular resources from vegetative genes (dependent on RpoD) to stress-response genes (Figure I in Box 1 and [14,20]). Certainly, *in vitro*, changes in the relative concentrations of RpoS and RpoD determine the transcription balance between vegetative genes to stress genes [21]. The concentration of RpoD in cells is relatively constant, so it is the concentration of RpoS that is the main variable [22]. A model such as Figure 3A can be studied in depth by artificially fixing the cellular concentration of RpoS at different levels, and this has permitted the analysis of a wide range of intermediate trait values such as x_2–x_4 in Box 1, allowing a better understanding of trade-offs in synthetic organisms and their role in coexistence [14].

The RpoS/RpoD trade-off is not unique, and resource allocation trade-offs often arise when global transcriptional patterns shift towards either of two alternative end-points. In principle, any shift between sigma factors should result in trade-offs. Many forms of stress tolerance or resistance are through diverting cellular resources to expressing expensive protective functions instead of growth functions. Table 1 contains some traits additionally affected with different organisms and a variety of stresses. For example, in *Saccharomyces cerevisiae*, a redistribution of resources toward stress-tolerance functions shows a reduced growth rate [23]. Likewise, *Rhizobium* symbiotic with legumes exhibits a trade-off between nickel tolerance and bacterial ability to replicate rapidly [24].

Several examples in Table 1 are based on resource allocation in metabolism rather than transcription. The commitment of a shared metabolic intermediate to branching metabolic pathways with different end-points is common in metabolism. One physiologically important example is the choice between high-throughput inefficient pathways and pathways that are slower but more energy efficient [25,26]. In the presence of excess glucose, a wasteful pathway in many organisms is glycolysis leading to excreted acetate or other incompletely metabolized products [27]. The alternative is the channelling of glucose metabolism and glycolytic intermediates to respiratory metabolism in times of nutrient limitation [28]. Adaptation to faster, wasteful growth may be

RpoS and/or the SOS response [55]; this state exists in stressed bacteria. The low, 'normal' mutation rate is exhibited in the presence of expressed DNA repair functions and the absence of the SOS response; this is the regulated state in exponentially growing, unstressed bacteria.

competitively beneficial in a rich environment but altered resource allocation to improve yield is better in another. Table 1 includes further instances of alternative metabolic flows with *E. coli* and other organisms that influence ecological capabilities [25,26,29–32].

Resource allocation can also affect the ability of bacteria to scavenge nutrients. Putting bacterial resources into expensive transport systems to scavenge nutrients reduces growth yields, but provides an ecological advantage in nutrient-poor settings [33–35].

Resources can also be channelled to multiplication by shutting down unused microbial pathways or expensive properties. This is evident in the mutational loss of pathways or even significant genome reductions in organisms that lose a capability that is not needed in a particular environment. For example, selective advantages can explain the prevalent loss of biosynthetic genes in *E. coli, Shigella*, and *Acinetobacter baylyi*, but resulting in the loss of prototrophy [36,37]. Of course, the ecological down-side to these organisms is the decreased fitness in environments where the eliminated genes are useful.

Design Constraint Trade-offs

Design constraints are intrinsic to many biological processes, as indicated in Figure 2, in which enzymes or proteins are involved. In catalysing transformations, enzymes in general exhibit an inherent trade-off between enzyme accuracy (selectivity and specificity) and speed (turnover rate and processivity) [38]. Another common characteristic of proteins is a basic trade-off between protein stability and activity [38]. Both of these trade-offs can constrain adaptation. Therefore it should not be surprising that bacterial phenotypes can be affected by trade-offs in which a protein with a particular combination of characteristics is altered to be better at one function than another.

Several of the trade-offs shown in Table 1 are indeed due to constraints at the level of individual proteins. A survival-multiplication trade-off explained by a structural constraint is illustrated in Figure 3B. The basis of this trade-off is that the outer membrane of bacteria is evolved to exclude toxic compounds [39] but at the same time needs to provide access to nutrients [13]. The diffusible access of nutrients is through channel-forming proteins called porins [39]. The general permeability into *E. coli* of various structurally diverse polar nutrients and antibiotics is determined by the type of porin protein expressed in cells [39–41]. The major porins of *E. coli*, OmpF and OmpC, act as molecular sieves, and OmpC channels are the more restrictive and better at excluding antibiotics [39,40]. Indeed, in clinical pathogen isolates, a contributing factor to drug exclusion is the mutational loss of OmpF or, in more extreme cases, both OmpF and OmpC [41], so the trade-off is shifted towards resistance. Besides antibiotics, bile salt (detergent) resistance in *E. coli* is also altered by changes of porin in the intestinal environment. *E. coli* adapts in the mouse gut and becomes more resistant to bile salts but grows more slowly [42]. On the other hand, OmpF channels are better at accessing nutrients. The cost of making OmpF or OmpC is the same because they are similar-sized proteins made in similar amounts, so the trade-off is not determined by differences in resource cost. The fitness cost of exclusion changes has been evaluated systematically across the species *E. coli* to show how this design constraint differentially affects competition for nutrients and antibiotic susceptibility [13,43]. Growth-fit bacteria indeed tend to be the most susceptible to antibiotic.

Another structural constraint leading to improved survival involves amino acid substitution(s) in a phage receptor (LamB protein of *E. coli*; Table 1) that results in the same quantity of protein but resistance to phage. The trade-off cost in bacteria with resistant LamB is that the protein change results in a lesser ability to use substrates like maltosaccharides channelled through wild-type receptor protein [44]. This is because the binding sites for phage and sugars overlap, and a change in one affects the other [45]. Thus the structural constraint results in a trade-off between

phage resistance and sugar utilization. The conclusion from comparing similar ecological trade-offs (i.e., survival-multiplication) in Figure 3A and 3B is that they can have very different underlying molecular mechanisms.

Structural constraints affect varied trade-offs in Table 1. These include fosfomycin resistance through a structural change in CpxA, with the altered protein reducing the ability to use sugar phosphates [46]. Another is a structural change in uropathogenic *E. coli* that can increase fimbrial FimH-dependent adhesion but reduce in-host survival [47,48]. So diverse phenotypes can be influenced by structural constraints and probably many more exist but have not been deeply considered.

Some trade-offs are more complex and involve structural as well as resource allocation changes. A trade-off between swarming and biofilm formation in *Pseudomonas* (Table 1) is due to the state of a regulator protein which can be mutated to overproduce flagella that improves swarming. Hyperswarming may be better in one environment but biofilm formation is better with fewer flagella, hence the trade-off [49]. The structural constraint in this instance is the structural state of the FleN regulator protein fixed in a particular mode [49]. In this example, the structural constraint may not be the complete cause of the trade-off. There is a secondary involvement of resource allocation, because of the additional ingredients needed to synthesize many flagella in hyperswarming. Indeed, a general secondary effect of regulatory protein mutations is a changed pattern of gene expression and thus resource allocation. Negative correlations between some traits can sometimes involve combinations of mechanisms, in this case resource allocation plus design constraint. Other trait trade-offs involve combinations of information processing plus resource allocation, as described below.

Informational Processing Constraint

Storing information has a cost, such as the storage of digital photos when compressed at the cost of resolution. Biological information is also associated with costs, such as the resource allocation in maintaining large microbial genomes. In this regard, genome size is a variable within bacterial species, and genome reduction is a selectively advantageous possibility when biosynthetic genes are not needed. The trade-off is of course the loss of information, genetic flexibility, and in some cases auxotrophy [36].

Transferring and processing information accurately also has a price for the cell. The trade-off between accuracy and rate of information transfer and correction is inherent to polymer synthesis based on genetic sequence information. An example with macromolecular synthesis is that translational accuracy and rate are constrained at the level of ribosome function ([50,51], Table 1). Transcriptional accuracy is more difficult to study but is affected by RNA polymerase mutations [52]. Likewise, the accuracy and speed of transcriptional gene regulation is affected by the length of DNA binding sites recognized by regulator proteins (Table 1). The rate–accuracy trade-off affects macromolecular processing generally and is likely subject to environmental selection because translational accuracy is not constant within a species [53].

Perhaps the most interesting informational processing trade-off occurs in the transmission of information accurately from generation to generation, through DNA replication and repair. Accuracy in these processes results in genetic integrity, but at a price. Aside from the resource allocation to multiple repair processes, an inevitable consequence of high fidelity is the lack of mutations and genetic diversity in a population. Conversely, a high mutation rate has a cost in terms of frequent deleterious mutations. The consequence of this fidelity-mutation availability relationship in Figure 3C can be considered to be a trade-off between short-term fitness with few

mutations as against long-term evolvability. Informational constraints dictate that genetic diversity and optimum fidelity are mutually exclusive traits.

The way bacteria get around this fidelity–evolvability trade-off is by changing the accuracy of informational processing between good and bad times. Genetic diversity is essential for generating rare beneficial mutations, and these are most useful when growth is limited by an environmental constraint [54–56]. Stress-induced mutagenesis (SIM) is a means of shifting the trade-off towards mutations, without permanently bearing the cost of high deleterious mutation rates. Indeed, SIM is a highly regulated process [55,56] but 'SIM breaks the trade-off between adaptability and adaptedness, allowing rapid adaptation to complex environmental challenges without compromising the population mean fitness in a stable environment' [57]. Further implications and mechanisms of SIM are described in other reviews [54,58].

A second common natural phenomenon affecting the DNA fidelity and evolvability trade-off in Figure 3C is the emergence of hypermutators in rapidly evolving populations, caused by mutations in mutator genes [59]. Common, for example, are *mutS* mutations, which decrease a key component of the methyl-directed mismatch repair pathway (MMR pathway) and result in a ~100-fold increase in mutation rate [60]. Hypermutators carry a fitness cost due to an increased number of lethal deleterious mutations (estimated to be ~1% [61]). But a hypermutator bacterium has a much higher probability of generating a beneficial mutation than does a *mutS*$^{+}$ [62]. If the hypermutable cell generates the next beneficial mutation that sweeps through the population, then the hypermutator (*mutS*) will 'hitchhike' along with it because the two mutations must remain linked without sex-based recombination. Mutator and non-mutator bacteria frequently coexist in, for example, pathogen populations [63], so organisms with different levels of fidelity and mutation rate exist in such populations.

Consequences of Trade-offs and How They Lead to the Immense Diversity of Bacteria

A simple explanation of bacterial diversity can be offered, based on trade-offs. It should be noted that trade-offs are not the sole contributors to diversity and coexistence in bacteria; at least four other ecological mechanisms can contribute to diversity [64]. As the extensive examples in Figure 1 and Table 1 indicate, it is, however, one of the most generally important ones.

For trade-offs to contribute to diversification, all that is required is that free-living bacteria are frequently under selection for one or other trait of the many in Table 1 that are affected by a two-way trade-off. Such selections occur, for example, in environments that require more emphasis on the stress resistance component of the survival-multiplication trade-off on one hand or a period of rapid growth selecting for rapid multiplication on the other. The problem for free-living microbes with traits subject to trade-offs is that there is no single optimal trade-off setting that can satisfy fitness in all environments, including extremes (except with ecological specialists that have evolved to high stress resistance and do not compete on the basis of growth fitness). For most generalists like *E. coli*, there is often conflicting selection in many environments (e.g., when stress and nutrients are both present), and perhaps intermediate trait settings (like those in Box 1) are best for fitness.

Organisms with intermediate trait settings are also nonuniform in a species affected by a trade-off because selection will fix any random mutation that sets the concentration of a trade-off controller (such as RpoS or the structure of a porin or a mutation rate in Figure 3) to a level appropriate for fitness in that situation. An additional complication is that the shape of a trade-off matters in coexistence; if convex, the extreme trait values are fittest [2,14]. So not just the existence but also the shape relationship needs to be known for trade-offs to predict organismal fitness. Box 1 and Figure I in Box 1 within this illustrate the importance of trade-off shapes in determining the co-existence of strains with intermediate trait values; these considerations apply

to all trade-offs irrespective of mechanism and have long been known to influence coexistence and heterogeneity in a species [2,5].

There is now a strong indication that many organisms with intermediate trait values of trade-offs are common in nature. The evidence is that bacterial phenotypic properties subject to trade-offs in Figure 1 are very heterogeneous and contains a continuum of properties. Here again, for space reasons, we focus on the natural heterogeneity of settings and traits in Figure 3.

In the RpoS resource allocation trade-off, studies have shown that the RpoS protein level is strain-specific in *E. coli* and that the stress and multiplication properties are also isolate-specific and form a continuum across the species [20,64]. Laboratory studies also show that RpoS levels drop through mutations selected in environments where growth is paramount, so shifting the trade-off towards multiplication and lower stress resistance [64,65]. It is likely that these mutational shifts in the trade-off reflect the diverse types in nature. Evidence for this indeed comes from the emergence of RpoS heterogeneity during infections of patients with *E. coli* [66].

A similar, broad spread of phenotypic characteristics was found to occur in *E. coli* when porin-dependent traits were investigated. By testing growth fitness based on permeability and antibiotic susceptibility, neither property was found to be constant across 72 isolates tested. Some natural isolates were fitter for growth but more susceptible to toxic compounds, others were more resistant but less growth-competitive [13]. Mutations can rapidly reset the porin-based resistance-multiplication trade-off when bacteria are selected either for rapid growth or for decreased antibiotic susceptibility [13,43]. Here too, a re-assortment of trade-off settings is likely to be a cause of intraspecies phenotypic diversity.

The informational constraint trade-off is similarly subject to species-level heterogeneity. When diverse clinical *E. coli* isolates were tested for their ability to generate rifampicin-resistant mutants, it was found that mutation frequencies differed by several orders of magnitude between isolates [67]. Natural isolates clearly do not minimize mutation rates, and the heterogeneity observed in strains is most easily explained by fluctuating selection for fidelity and rapid change in times of stress. The occurrence of mutators in evolving clinical and laboratory populations also points to heterogeneity in information replication in natural populations.

Heterogeneity in informational processing is also seen in translational accuracy in different strains of *E. coli*. Ribosomes purified from different natural *E. coli* isolates vary over 10-fold in mistranslation rates [53], implying that various levels of translational fidelity are optimal in nature. It is not clear if or how trade-offs affect this heterogeneity.

Concluding Remarks

No doubt many other traits in Figure 1 and Table 1 are also subject to a wide range of phenotypes dependent on trade-offs. Strain-to-strain variations in motility, virulence, and biofilm formation are commonly observed but need explanation (see Outstanding Questions). Yet many other microbial characters remain to be analysed within a trade-off framework. Based on the considerations in this review, it can be predicted that other diverse characteristics of bacteria are also caused by the re-allocation of trade-off costs. Microbiologists need to consider how the properties they study are subject to ecological costs and benefits and how they influence the rich intra- and interspecies diversity of microbes.

Outstanding Questions

Are there further important microbial traits constrained by trade-offs?

Are there further general mechanisms that explain trade-offs?

Can we integrate mechanisms into theoretical treatments of trade-offs and use mathematical models to predict evolution and coexistence?

Is it possible to manipulate trade-offs to overcome challenges such as industrial productivity or to combat virulence and drug resistance?

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