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An ecological and evolutionary perspective on human-microbe mutualism and disease

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Abstract

The microbial communities of humans are characteristic and complex mixtures of microorganisms that have co-evolved with their human hosts. The species that make up these communities vary between hosts as a result of restricted migration of microorganisms between hosts and strong ecological interactions within hosts, as well as host variability in terms of diet, genotype and colonization history. The shared evolutionary fate of humans and their symbiotic bacteria has selected for mutualistic interactions that are essential for human health, and ecological or genetic changes that uncouple this shared fate can result in disease. In this way, looking to ecological and evolutionary principles might provide new strategies for restoring and maintaining human health.

Nowhere in the study of human biology are basic concepts changing more rapidly than with respect to the human microbiota. Microorganisms were first shown to cause disease in humans in the 1800s, and after this finding, the popular and scientific views of the microbial world became dominated by the quest to understand, prevent and cure microbial disease. This led to millions of lives being saved through improved hygiene, vaccinations and antibiotics. However, most interactions between humans and microorganisms do not result in disease. Beneficial host–microbe interactions have been studied for more than a century, but it was not until the advent of molecular biology that the pathogen-dominated view of human-associated microorganisms began to change. Gene-sequence-based approaches have recently allowed complex microbial communities to be characterized more comprehensively and have removed the constraint of being able to identify only microorganisms that can be cultured, greatly increasing knowledge about commensal microorganisms and mutualistic microorganisms of humans^{1–12} (that is, organisms in a relationship in which one partner

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benefits and the other is unharmed, and organisms in a relationship in which both partners benefit, respectively), as well as human pathogens^{13–18}. Researchers are now finding that host–microbe interactions are essential to many aspects of normal ‘mammalian’ physiology, ranging from metabolic activity to immune homeostasis^{19–25}. With the availability of new tools to investigate complex microbial communities and the expanded appreciation for the importance of the human indigenous microbiota, this is an opportune time to apply ecological and evolutionary principles to improve the current understanding of both health and disease.

So far, the human microbiota has not been fully described, but it is clear that microorganisms are present in site-specific communities on the skin and mucosal surfaces and in the intestinal lumen. Each community contains microorganisms from certain families and genera that are found in the same habitat in many or most individuals, although at the species and strain levels the microbiota of an individual can be as unique as a fingerprint^{3,11,26}. The microbial communities of other terrestrial vertebrates mainly contain lineages that are related to, but distinct from, those in humans^{27–31}. These characteristics indicate that humans have co-evolved with their microbial partners. In this review, we examine evolutionary and ecological principles that are relevant to these relationships, and we consider microbial pathogenesis in this context.

Evolution of mutualism

In the 1960s, evolutionary biologists rejected the idea that natural selection would generally favour the good of the species (or any group), because individual types with the greatest reproductive success in a population increase in relative abundance regardless of the consequences for the population as a whole³². Since then, the evolution of traits that benefit individuals other than the trait bearer has been extensively researched, both theoretically and empirically. Although the field has been contentious at times, there is now general agreement about the conditions that promote cooperation, including mutualism between species^{32–34}.

Organisms can have traits that contribute directly to their own fitness and also incidentally benefit members of another species. When such ‘by-product benefits’ occur in both directions, the result is a no-cost mutualism³⁴. For example, plant polysaccharides that are not digestible by humans are the main substrates for microbial growth in the colon, whereas butyrate and other products of microbial fermentation are important energy sources for the host^{35,36}. Intestinal symbionts are selected to be effective consumers of available resources through direct effects on their fitness, but this also benefits the host because resource competition provides an additional barrier to colonization by potential pathogens^{37–41}.

If mutualistic by-product interactions such as the example above are possible, but not ecologically inevitable, then traits that improve the likelihood or stability of a relationship (for example, site-specific attachment molecules) might evolve in one or both partners. A species might also evolve to increase its own fitness by increasing the fitness of a mutualistic partner³⁴. For example, microbial symbionts that secrete molecules that inhibit host pathogens (known as pathogen interference)^{38–40} or detoxify compounds that harm the

host⁴² can augment the lifespan and reproductive capacity of the host, thereby giving the symbionts more opportunities to spread. Evolution to increase mutualistic benefits has been called ‘partner fidelity feedback’, and it is strengthened if the same lineages of partners interact across multiple generations^{33,34}. Unlike traits that support mutualism incidentally, traits that evolve specifically to improve mutualism, such as the production of compounds dedicated to pathogen interference, can impose a direct fitness cost, although a net benefit would be expected in the context of the evolved mutualism³⁴.

Mutualism-promoting traits with a direct cost for the bearer, however, create the potential for ‘cheating’. When organisms interact to create a shared benefit, cheaters are organisms that obtain the benefit without helping to create it. For example, a cheating microbial phenotype could result from a mutation that redirects resources towards faster growth of the microorganism itself instead of detoxification or pathogen interference. The cheater therefore increases its relative fitness in a host by avoiding costly contributions towards host fitness while benefiting from the improved host fitness that results from the mutualistic contributions of its competitors^{33,34}. Various evolutionary outcomes are possible, including the absence of costly contributions to mutualism, contributions to mutualism that are below the level that would maximize the mutualistic benefit, and the coexistence of mutualists and cheaters in the community⁴³. A possible example of this dynamic balance is that certain benefits attributed to probiotic bacterial species are characteristic of only a subset of the strains that make up the species^{38,40}. For any mutualism that is not cost free, the partners can evolve mechanisms to protect their relationship from being exploited by cheaters^{32,34,44}, and mutualism can be stronger and more stable where ecological features limit the potential for exploitation (discussed later).

The immune system is the most conspicuous set of anti-exploitation adaptations involved in human–microbial symbiosis. The gastrointestinal mucosa is intimately associated with the most abundant and diverse microbial communities in the human body, but the gut-associated immune system neither controls the composition of the gut microbiota nor remains ignorant of it. Instead, specialized tissues and cells actively sample the intestinal contents and initiate local immune responses that help to confine the microbiota to the gut, avoiding a damaging systemic inflammatory response to the microorganisms present in the healthy gut⁴⁵. However, if host tissue is damaged⁴⁶ or if microorganisms spread to normally sterile sites⁴⁵, then there is a vigorous systemic response to clear the infection. Therefore, microorganisms are free to compete for resources in the gut, generating a robust and disease-resistant community^{37,41}, but are prevented (usually) from exploiting the host to obtain additional resources. Recent work has also shown that the normal development and activity of the ‘host’ immune system is itself a result of mutualistic interactions^{20–22,24,25} (see page 819).

Humans and their collective microbiota are segmented into many local communities, each comprising an individual human with his or her symbionts. This ecological pattern, characterized by strong interactions within distinct local communities and limited interactions or migration between them, is described as a metacommunity. Another level of metacommunity organization exists because individual humans belong to social groups that tend to share a similar microbiota^{47,48}. At both levels, the metacommunity structure

allows selection to occur between the local units (that is, between individuals or between social groups), which promotes mutualism and restrains cheating within the human–microbe symbiosis^{32,49}. Such selection occurs when a local symbiotic community succeeds or fails together, with more successful communities increasing in abundance or prevalence relative to less successful communities³². For example, a human individual or social group that carries a microbiota with strong defences against an abundant pathogen is likely to leave more progeny than those lacking such defences. If the progeny tend to carry the parental microbiota, then mutualistic microorganisms that make costly contributions to pathogen defence are favoured by selection between distinct local symbiotic communities. This community-level selection opposes the tendency for cheating non-defenders to increase in relative abundance within each local symbiotic community³². The greater similarity of the microbiota within a human family than between human families¹² (and within, rather than between, chimpanzee social groups³⁰) shows that there is, indeed, a shared evolutionary fate. The individualized microbiota of each person has a stake in his or her fitness.

Human–microbe mutualism often involves more than two partners, although the same principles apply. For example, the colonic degradation of polysaccharides that provides butyrate for the host is a cooperative microbial process^{35,36}. Extracellular enzymes from multiple species are required for complete hydrolysis of the polymers. In addition, some of the resultant sugars are consumed by strains that do not produce extracellular enzymes but provide growth factors to strains that do³⁵. Some fermenters such as *Bifidobacterium* spp. release lactate as waste. Their fermentation efficiency is increased by lactate fermenters, such as *Eubacterium hallii*, that release butyrate as waste, and this butyrate is then used by the host³⁶. Sugar-fermenting lactobacilli that produce neither hydrolytic enzymes nor growth factors could be considered cheaters from the perspective of polysaccharide degradation, but they could be considered mutualists of the entire symbiotic community if they interfere with the colonization of pathogens⁴⁰. The butyrate-producing consortium as a whole is a mutualist of the host and would be favoured by community-level selection over consortia producing less desirable fermentation products³⁶. However, selection for mutualistic functional traits such as butyrate production cannot entirely determine the composition of the microbiota, because communities of different composition can have similar functional characteristics in a given context. Not only selection on community-level traits but also competition within the community and chance colonization events affect the structure of the microbiota⁵⁰.

Human microbial communities and health

The distribution of microorganisms in and on the human body reflects adaptations to life on land, which were made about 400 million years ago. Terrestrial vertebrates developed skin, lungs, internal fertilization, and protective membranes around the embryo. The skin became relatively impermeable, and mucous membranes were confined to protected sites. Because microorganisms generally thrive only in moist environments, these adaptations to a mostly dry environment have shaped the abundance, location and phenotypes of human-associated microorganisms and have limited the exchange of microorganisms between individuals.

The current understanding of the human microbiota relies heavily on cultivation-based approaches and therefore is biased and incomplete. Although imperfect, molecular approaches that identify microorganisms from small-subunit (16S) ribosomal RNA gene sequences offer advantages over cultivation. The 16S rRNA gene is typically chosen because it is present universally and can provide a taxonomic identification ranging from the domain and phylum level to approximately the species level. However, these methods have been used to study human microbial ecology for only a decade, and the available data are limited. There are few deep surveys of microbial-community membership in any human habitat and even fewer assessments of functional potential or activity. In general, 16S rRNA gene-sequence data have been collected from one site in a few humans at one time, representing a narrow range of health and disease states^{2,5-7}, although there are studies that include several temporal or spatial samples per individual^{1,3,4,51}. Sequence-dependent approaches that are less labour-intensive but yield lower-resolution data have been applied to a larger number of individuals, at various time points and under various conditions^{8,9,11,12,52}. Even so, the microbial communities associated with only a small proportion of the diversity of human genotypes, lifestyles, diets and diseases have been investigated. One high-throughput method for obtaining information about bacterial communities is to use phylogenetic microarrays, which yield high-resolution data, but this method also depends on adequate 16S rRNA gene-sequence databases¹⁰. Like these microarray studies, metagenomic and proteomic analyses are just beginning to be published^{53,54}. Technical and ethical constraints restrict sampling from humans; therefore, model systems will continue to be important, and examples of these are listed in Table 1.

Despite the limited data available, analyses of the human microbiota have revealed intriguing features. Most of the phylogenetic diversity is found in shallow, wide radiations in a small subset of the known deep lineages²⁶. Specifically, there are more than 50 bacterial phyla on Earth, but human-associated communities are dominated by only 4 phyla (Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria), with 9 other phyla (Chlamydiae, Cyanobacteria, Deferribacteres, Deinococcus–Thermus, Fusobacteria, Spirochaetes, Verrucomicrobia, and the candidate phyla TM7 and SR1) found in some sites and individuals (Fig. 1). In contrast to the paucity of phyla represented, the human microbiota contains an abundance of species and strains. Uniform probabilities of speciation and extinction over time would result in an exponential increase in the number of lineages throughout evolution. However, in humans, there is a marked excess of phylotype diversity at the species and strain level compared with the trends in more inclusive taxa (Fig. 2); there are similar patterns in other vertebrate hosts²⁶. This finding might reflect a long history of stability in the types of microbial niche associated with terrestrial animals, together with factors (such as host heterogeneity and metacommunity structure) that promote diversification among organisms in similar niches. In contrast to the remarkable diversity of bacterial species, a striking but unexplained finding is that the only Archaea found frequently in humans are several species of methanogens. *Methanobrevibacter smithii* is abundant in the colon of some humans^{3,53}. Also, *Methanobrevibacter oralis* and close relatives can be found within the subgingival crevice in the human mouth but only in the setting of moderate to severe disease⁵⁵. Overall, the human microbiota is similar to that

of other mammals at the phylum level, but most bacterial families and genera seem to be distinct (Fig. 3).

Multiple samples of the microbiota that are taken separated in time or space from a single body habitat within one individual are generally more similar to each other than they are to samples from the same habitat in another individual^{3,9,11}, although temporal variation in the skin microbiota of an individual is as great as the variation between individuals⁴. In addition, the bacterial communities at a given site are more similar between human family members than between unrelated individuals¹², but more studies are necessary to distinguish the effects of genetic relatedness and a shared early environment⁵⁰. Antibiotics can markedly affect the composition of the microbiota in the short term, with most (but not all) families and genera of gut microorganisms returning to typical levels within weeks of exposure^{51,56}. However, pathogens can exploit the reduced competitiveness of a community disturbed by antibiotics, thereby establishing themselves in the host^{39,57}. The degree to which the unique bacterial communities of an individual are re-established after antibiotic treatment is unclear, but particular antibiotic-resistant strains that colonize or evolve during treatment can persist for years^{58,59}.

A human infant acquires its microbiota from the environment. In humans, symbionts are not vertically transmitted (that is, transmitted through the germ line), as they are in some invertebrate animals. Colonization, succession and diversification occur within characteristic windows of time in the various microbial habitats in the body, ranging over the first weeks, months or years of life^{10,60,61}. The composition of faecal communities in early infancy, for example, is dynamic and reflects opportunistic environmental exposures, especially to the mother. The introduction of solid foods then begins the transition to an individualized, adult-like microbiota¹⁰. The assembly of bacterial communities on tooth surfaces also follows a consistent pattern as teeth emerge⁶², as well as after the removal of pre-existing biomass (that is, plaque)^{52,60}. The horizontal transfer of microorganisms to every human generation favours strains that are locally abundant at that time (for example, those present in parents and kin), but colonization remains somewhat stochastic⁵⁰. The mixing of lineages from different sources that occurs during community assembly is analogous to the reassortment of parental alleles during sexual reproduction⁴⁹, and it promotes the adaptation of community composition to local conditions and the rapid spread of beneficial strains. However, strains that become locally abundant by cheating can also spread.

Competition for niches within the human microbiota is ubiquitous and occurs together with the selective forces that promote mutualism in the community as a whole. Microorganisms can even compete and cooperate simultaneously. For example, *Bacteroides thetaiotaomicron* and *M. smithii* facilitate each other's growth by complementary energy metabolism, while competing for nitrogen⁶³. Cooperatively crosslinked biofilms containing multiple species promote the colonization of tooth surfaces, even while the constituent species compete with each other for individual binding sites⁶⁴. Symbionts that are highly prevalent and abundant probably have effective mechanisms for competing for resources: for example, *B. thetaiotaomicron*⁶⁵ and *Bifidobacterium longum*⁶⁶ have a wide variety of inducible genes encoding factors involved in the binding, uptake and degradation of plant- and host-derived polysaccharides. Competition within the human microbiota involves not only

resources but also interference; that is, the direct inhibition of one strain by another in a resource-independent manner. In some cases, the metabolic byproducts of one species (such as lactate or short-chain fatty acids) inhibit other microorganisms. In other cases, dedicated compounds are generated solely because of their inhibitory effect: for example, reactive oxygen species and the peptide antibiotics known as bacteriocins^{39,40}. The immediate fitness costs and context-dependent benefits of dedicated interference compounds result in selection for diversity: for example, the capacity to produce and resist bacteriocins evolves rapidly among closely related strains^{67,68}. Both resource competition and interference competition contribute to the resistance of the intact microbiota to colonization by pathogens^{37–40}.

Microbial evolution and human disease

Microbial symbionts occupy a complex adaptive landscape. Many traits affect fitness, and many different trait combinations can generate a local optimum fitness (that is, a fitness peak). Natural selection generally acts on subtle phenotypic differences to move microorganisms ‘uphill’ towards a fitness peak, but larger changes can move an organism onto the slope of a different fitness peak (Fig. 4). The fitness of a symbiont depends on environmental features that can change, such as the coexisting microbiota, the diet of the host, and which species and even particular individual is the host. Thus, the adaptive landscape is dynamic.

Changes in the genotype or environment of a non-pathogenic symbiont can result in the invasion of host tissue. The usual outcome is then an immune response that eliminates the infection. This high rate of microbial mortality imposes a strong selective pressure: the rare changes that enable a symbiont to survive such a challenge would involve avoiding immune recognition or circumventing immune control, at least until some progeny have been transmitted to a new host. Alternatively, changes that increase the opportunities for a non-pathogen to be transmitted to a new host reduce the dependence of the microorganism on the fate of the current host. In this case, the selective pressures on the fitness of the symbiont are less constrained by the need to preserve host fitness as well. In either case, the microorganism can begin adapting towards a fitness peak as a pathogen.

All human microbial symbionts must be able to establish themselves in new hosts. The adaptations of mutualistic or commensal microorganisms towards this end can facilitate a pathogenic lifestyle as well. For example, the biochemical mechanisms for sensing host environments, interacting with host surfaces and even communicating with the host are often the same in human pathogens, commensal microorganisms and mutualistic microorganisms^{15,69–71}. Not surprisingly, many common human pathogens are closely related to non-pathogenic symbionts: examples are found in the genera *Staphylococcus*, *Streptococcus*, *Neisseria* and *Enterococcus*, and in the family Enterobacteriaceae^{13–18}. It is not coincidental that these taxa tolerate the aerobic environment between hosts, whereas the more abundant, but less aerotolerant, taxa of the colon have fewer known pathogens as close relatives. The greater ability of aerotolerant taxa to be transmitted to a new host weakens the selection for mutualism in the current host^{33,34}. In general, the pathogenic phenotypes in taxa that contain abundant non-pathogenic symbionts have multiple evolutionary origins^{13–18}, emphasizing that pathogenicity is not necessarily a

considerable evolutionary barrier for microorganisms. By contrast, other pathogens have originated only once^{72,73}, but the continued emergence of new diseases is a reminder that there might be many unoccupied pathogen fitness peaks at present.

The evolution of pathogen virulence has received considerable attention, largely centred on the paradox that pathogens both harm and depend on their hosts⁷⁴. The view that highly virulent pathogens originated recently, with selection inevitably reducing virulence over time, has been supplanted by the realization that there is an optimal level of virulence (for the pathogen) that depends on the biology of its host interactions^{74,75}. For example, if pathogen transmission is inherently damaging to the host (as occurs with *Salmonella enterica* serovar Typhimurium⁷⁶), then selective pressure on the pathogen balances the benefit of higher transmission against the loss of host viability as a result of higher virulence. By contrast, pathogens with environmental reservoirs (for example, *Vibrio cholerae*), transmission vectors (for example, *Plasmodium falciparum*) or environmentally resistant propagules (such as spores; for example, *Clostridium tetani*) might be able to afford a higher level of virulence than those that depend on direct transmission⁷⁷. For pathogens that depend on normal host activity for transmission, such as sexually transmitted pathogens (for example, *Chlamydia trachomatis* and *Treponema pallidum*), low virulence and/or long latency can promote the spread of pathogen. In host populations with a reduced potential for pathogens to encounter new hosts, the optimal virulence is reduced to allow the host to survive long enough to ensure pathogen transmission⁷⁸.

The observed level of virulence for a pathogen, however, does not necessarily correspond to its evolutionary optimum. Many pathogens are zoonotic (that is, transmitted from animals to humans)⁷⁹ and can be adapted to a low-virulence niche in their primary host; an example is enterohaemorrhagic *Escherichia coli* in cattle⁸⁰. Unless transmission by humans contributes to the evolutionary success of the pathogen, excessive (or suboptimal) virulence in humans exerts no selective pressure on the microorganism. Competition between different strains of a pathogen (as a result of co-infection, as occurs with *Plasmodium* spp., or in-host evolution, as occurs with human immunodeficiency virus) can affect virulence, because an optimally virulent pathogen (as measured by transmission success) might not be the best competitor during mixed infections in a single host⁸¹. A rapidly replicating, excessively virulent strain might kill the host or provoke a successful immune response before transmission of a co-infecting, less virulent strain, even if the latter strain is optimally virulent when infecting a host alone⁸¹. Competition between pathogens can also decrease virulence. The production of extracellular iron-scavenging molecules (known as siderophores) contributes to the virulence of many bacterial pathogens, but cheating lineages that consume siderophores without producing them reduce virulence, thereby benefiting the host⁸². The diverse biology of host–pathogen and pathogen–pathogen interactions precludes simple predictions about the effect of interpathogen competition on virulence^{81,83}.

The importance of opportunity for the origin of pathogens is emphasized by a recent analysis of the 25 infectious diseases that cause the most human death and disability⁸⁴. The preferred host of a pathogen is thought to change most easily to a species closely related to the current host⁸⁵. Indeed, although primates constitute only a small proportion of all animal species on Earth, they are the origin of a large proportion of these serious human diseases.

However, an even larger proportion of these diseases originated from domestic animals, reflecting greater opportunities for the symbionts of domesticated species to be transmitted to humans⁸⁴. With the advent of agriculture, changes in human populations simultaneously created a new niche for deadly pathogens. Ten of these 25 major infectious diseases could have arisen only after urbanization, because they depend on human–human transmission and quickly kill infected individuals or leave them with lifelong immunity⁸⁴. Such ‘crowd’ diseases could not have survived in the small dispersed human societies present before agriculture. Common pathogens derived from human mutualistic microorganisms have also exploited these changes in the human population, with many clonal lineages being disseminated globally^{13–18}.

Urbanization and global travel have eroded some of the barriers to microbial transmission between social groups that contribute to the metacommunity structure of the human–microbe symbiosis. The diminished fidelity of host and symbiont lineages to each other (both within and between generations) and reduced opportunities for community-level selection between human social groups have reduced the strength of selection for mutualism. Microbial cheaters that allocate resources to their own growth and dissemination instead of pathogen interference or other costly contributions to host fitness can now spread globally, instead of merely within a tribe. Symbionts that colonize an infant who resides in an urban area include many microorganisms that are not derived from the infant’s relatives, much less from an extended kin group with a consistent lifestyle and geographic range over generations. This disruption of co-evolved mutualism between humans and human microbiota, as a result of changes in human ecology, contributes to the increasing prevalence of chronic and degenerative disease in industrialized countries^{21,47}.

Paths forward

Researchers have only just begun to describe the microbial communities that are associated with humans and the extent of the interactions between host and microbiota. Understanding this symbiotic ‘landscape’ will require research that spans the biological hierarchy from molecules to communities and is informed by ecological and evolutionary theory. Only with an integrated approach will it be possible to comprehend the complex ecology of human health and the many ways in which interactions between humans and microorganisms can go awry.

The first step in improving our understanding is to describe the composition of microbial communities in each habitat of the human body and how this varies over time, among individuals and with respect to variables such as diet, host genotype and health status. This project is now in its early stages, with the first successful forays having laid the groundwork for more ambitious studies, such as the Human Microbiome Project (see page 804).

Several recent studies highlight remarkable examples of how a co-evolved microbiota can markedly affect host biology at the molecular level^{19–25}, and these findings call for a complete re-examination of human physiology and immunology⁴⁴. Attributes that were assumed to be human traits have been shown to result from human–microbe interactions.

Although human studies are essential, the technical and ethical limitations of carrying out experiments and obtaining samples from humans mean that experimental model systems also need to be used. These two approaches offer complementary information. The relevance of human studies is clear. But experimental model systems have two main advantages: they highlight evolutionary conserved features that are likely to be crucial for function, and they show diversity (how a single ‘goal’ is accomplished differently), thereby exposing the essence of a characteristic. Models for the study of symbioses range from binary relationships between an invertebrate and one microbial species to complex vertebrate systems involving consortia of microorganisms (Table 1). For models with complex consortia, gnotobiotic techniques are used to manipulate the symbiosis experimentally. By contrast, using simpler consortia facilitates the molecular dissection of interactions in the intact natural setting. The genetic tools available for some model hosts allow the identification of genes and proteins that control host responses and manage the consortia.

From the microbial perspective, the host is simply a complex environment — the distinction between human health and disease is important only as far as it affects microbial fitness. To think that we can intervene effectively in human–microbe relationships without considering microbial ecology and evolution is folly, as demonstrated by the spread of antibiotic-resistant microorganisms^{13,14,16,17,58,59} and by the connections between some modern diseases and alterations in the human microbiota^{21,47}. The principles and mechanisms that underlie microbial community structure and host–symbiont relationships must become incorporated into our definitions of human health. It will be crucial to consider the role of microbial communities, and not just individual species, as pathogens and mutualists⁵⁵. Moreover, one of the goals of medical intervention during disease should be minimizing damage to the health-associated homeostasis between humans and their microbiota. Medical and general educational curricula will need to be modified accordingly.

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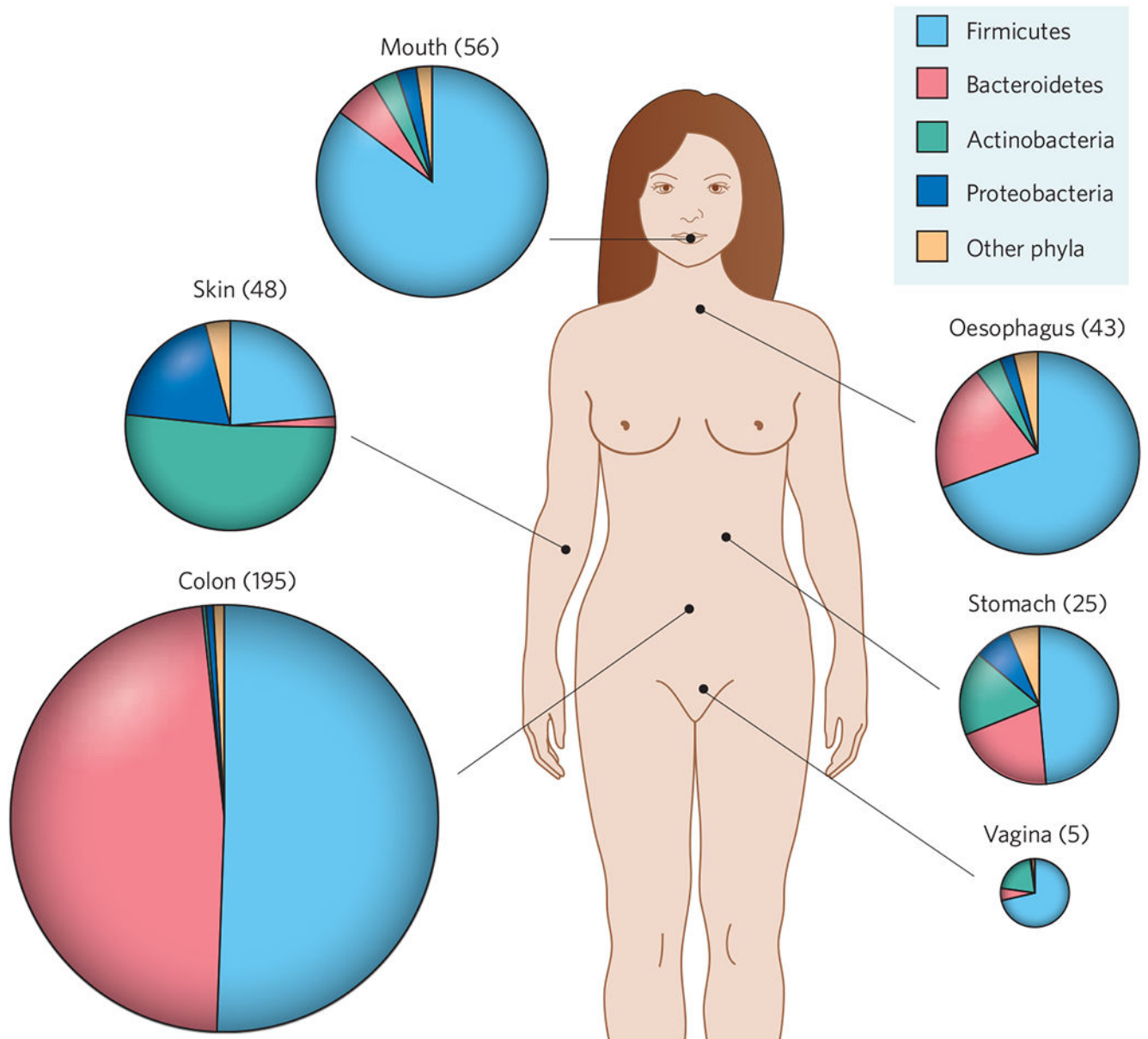


Figure 1 | Site-specific distributions of bacterial phyla in healthy humans.

The area of the chart for each site represents the average number of distinct phylotypes (approximate species-level taxa, based on 16S rRNA gene-sequence analysis) per individual. (The mean number of phylotypes per individual is shown in parentheses; 3–11 individuals were studied per habitat.) The coloured wedges represent the proportion of phylotypes belonging to different phyla. More than 50 bacteria phyla exist, but human microbial communities are overwhelmingly dominated by the 4 that are shown. The relative abundance of these phyla at most sites tends to be consistent across individuals: for example, in almost all humans studied so far, Bacteroidetes and Firmicutes predominate in the colon. By contrast, the composition of the vaginal microbiota is more variable; most women have a preponderance of Firmicutes with few other representatives, whereas a minority of women

have a preponderance of Actinobacteria with few other representatives. An estimated 20–80% of human-associated phylotypes (depending on habitat) are thought to have eluded cultivation so far. Data taken from refs 1–7.

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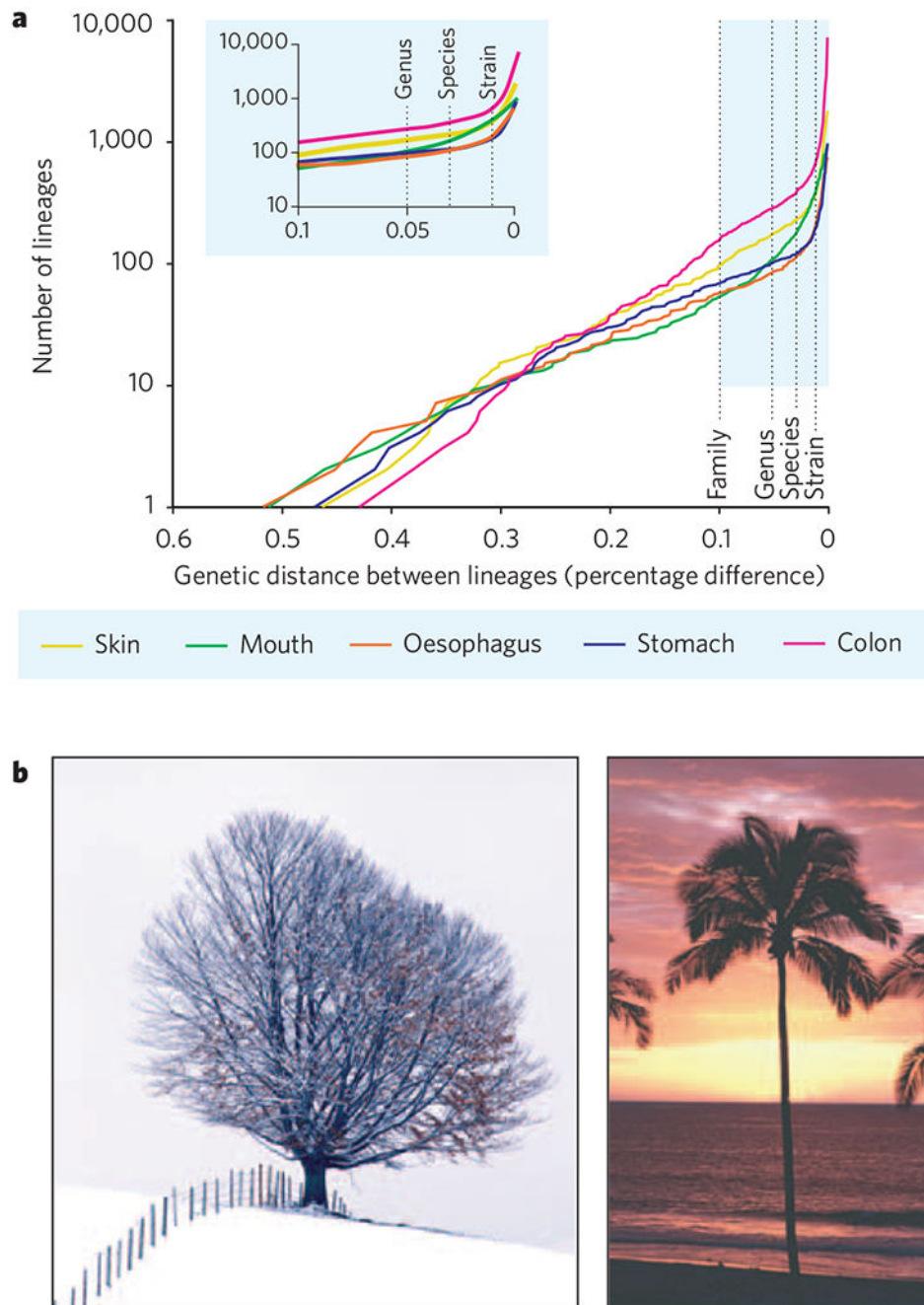


Figure 2 |. Patterns of human-associated microbial diversity.

a. Lineage-by-distance analysis of 16S rRNA gene-sequence data from human microbial communities in specific habitats. The x axis shows the percentage difference threshold (Olsen correction), over 1,241 unambiguously aligned positions of near full-length 16S rRNA gene sequences, for delineating separate lineages. The y axis shows the number of distinct lineages that exist at the distance threshold. If speciation and extinction occur with constant probabilities as 16S rRNA gene sequences diverge, this would result in an exponentially increasing number of lineages with diminishing evolutionary distances

between them (a straight line on a semi logarithmic plot). Such a pattern seems to hold from the phylum level (largest distances between lineages) to approximately the species level. However, relative to this trend, all sites have an excess of recently diverged lineages. The excess lineages accumulate in the range of 16S rRNA gene divergence that is typically associated with species and strains. The inset depicts a portion of the same data at a larger scale. Samples were taken from 3–11 individuals, depending on the site. Data taken from refs 1–5. **b**, When displayed as a dendrogram, 16S rRNA gene-based patterns of microbial diversity in soil and aquatic environments generally resemble the tree shape on the left, with new branches arising at all distances from the root. Patterns of diversity in vertebrate-associated communities resemble the tree shape on the right, with few branches arising close to the root and many branches arising close to the branch tips.

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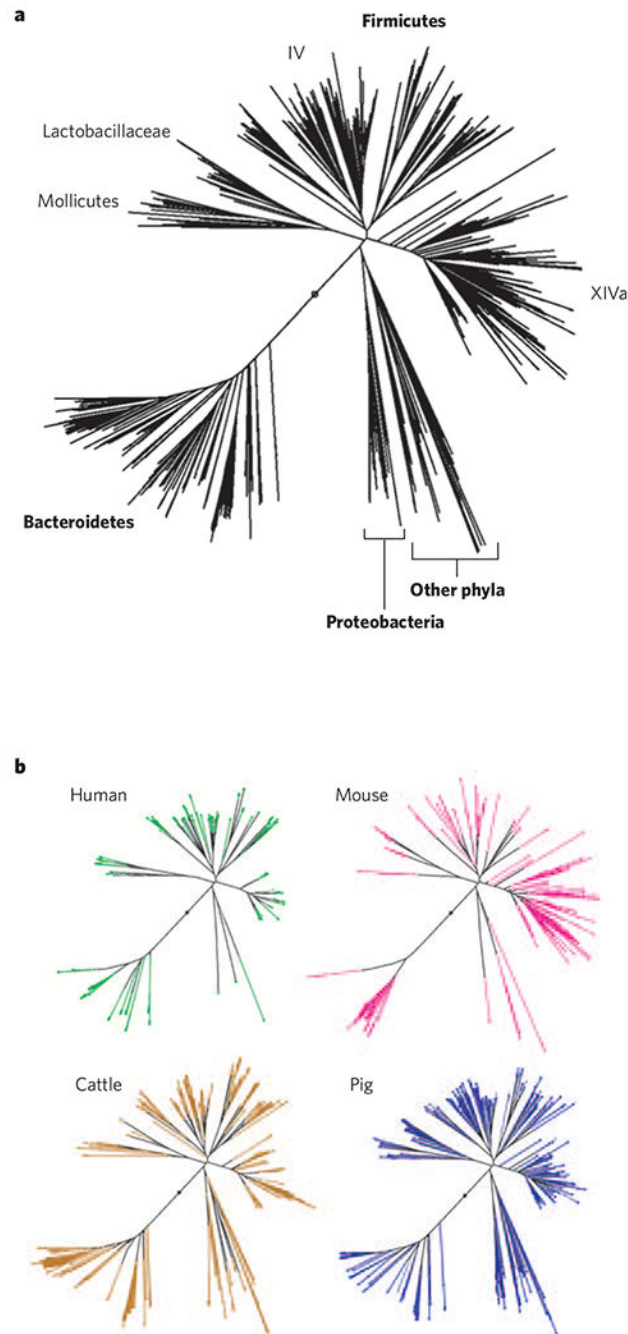


Figure 3 |. Relationships between bacterial 16S rRNA gene sequences from the intestinal microbiota of animals.

A set of aligned, high-quality, full-length sequences was obtained from Greengenes⁹⁵. Sequences derived from one human stool sample and caecal samples from one mouse family were chosen to obtain approximately the same number of sequences as obtained from multiple studies of the bovine rumen and pig caecum and colon (range 617–748 sequences per host species). **a**, A neighbour-joining tree was created from 1,241 unambiguously aligned positions in all 2,735 sequences, with selected taxa indicated. Mollicutes, Lactobacillaceae and *Clostridium* clusters IV and XIVa are within the Firmicutes⁹⁶. **b**,

Host-specific trees were created with the same topology as the entire tree, shown in part **a**, but they depict only the sequences derived from the indicated host species. Branches shared with at least one other host species are shown in black, and branches specific to a single species are coloured. The same phyla and classes predominate in these animals (evident from the overlapping tree topologies and shared branches), although their relative abundances vary. By contrast, most genera and many families are specific to a single host species (coloured branches).

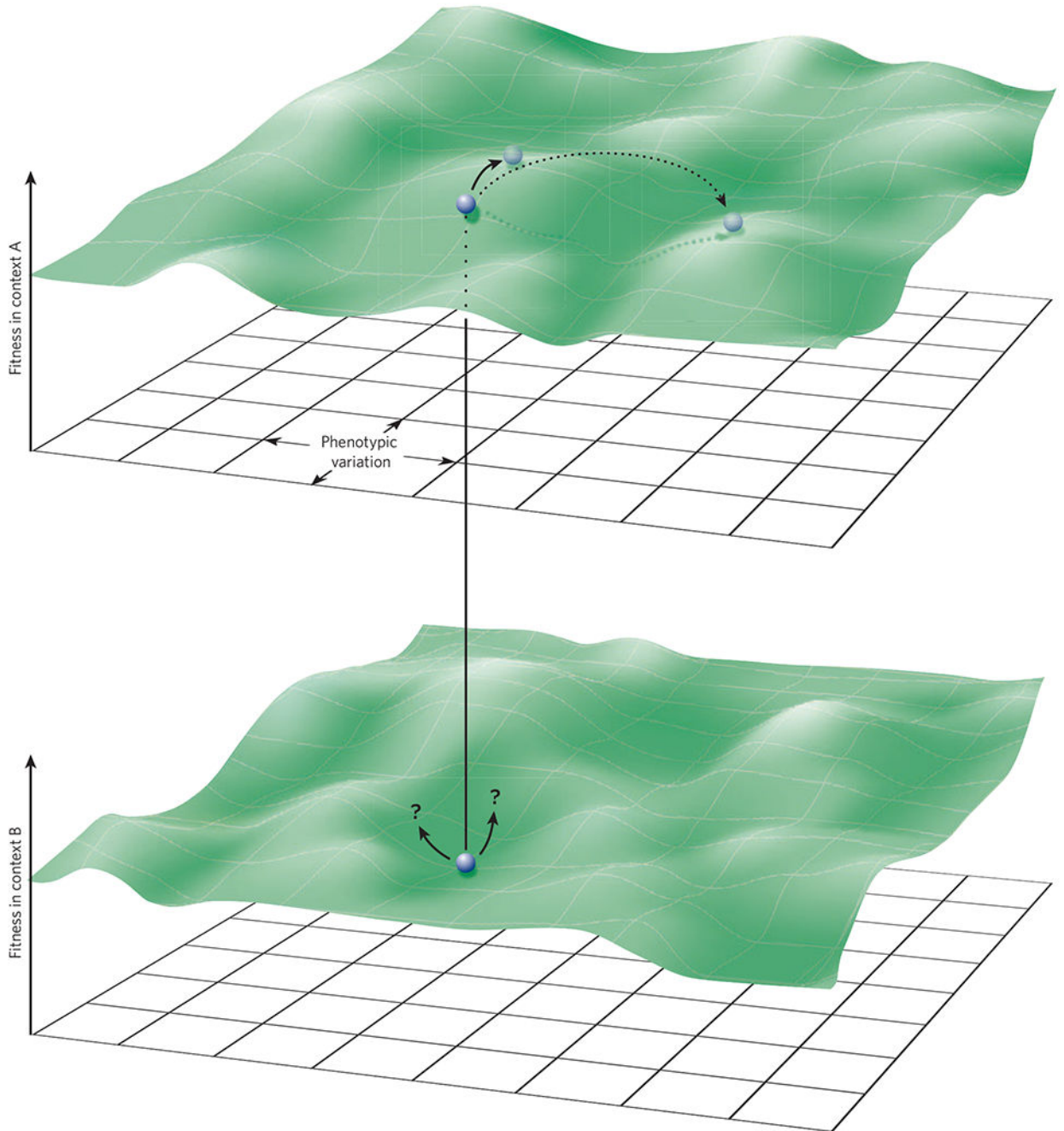


Figure 4 | Adaptive landscapes.

The plane is a conceptual representation of the multidimensional phenotypes that are available to a microorganism. The height of the surface above the plane represents the fitness of the corresponding phenotypes in a given ecological context, including biotic and abiotic components of the environment. In a given environment (context A, upper panel), for mutations that have a small effect, a phenotype (circle) under natural selection will tend to evolve along the steepest path uphill towards higher fitness (solid arrow), eventually moving the mean phenotype of a population to a local fitness maximum. Mutations that have a large

effect, such as horizontal gene transfer, can shift a phenotype to the slope of a different fitness peak (dashed arrow). This can markedly alter the outcome for the host; for example, it can result in pathogenesis instead of mutualism. The valley separating the peaks represents phenotypes of low fitness, such as those that are likely to elicit an immune response but lack the adaptations necessary to survive it. For a given phenotype, a change in context (for example, a change in host diet, alterations in coexisting microbial populations, or transfer to a different host or host species; context B, lower panel) can have subtle or marked effects on fitness. A phenotype near a fitness peak in context A might be in a valley of low fitness in context B. If the microorganism survives, the subsequent course of evolution might depend on the direction of phenotypic change caused by the next mutation.

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Table 1 |

Model systems for animal-microbe symbioses

Type of symbiosis	Specific system (Host/symbiont species)	Host phylogenetic affiliation	Host tissue colonized	Reference
Highly complex consortia (10 ² -10 ⁷)*	<i>Mus musculus</i> (mouse)	Vertebrate chordate	Intestine	19
	<i>Danio rerio</i> (zebrafish)	Vertebrate chordate	Intestine	86
	<i>Microcerotermes</i> spp. and <i>Reticulitermes</i> spp. (termites)	Insect arthropod	Hindgut	87
Relatively simple consortia (~2-25)*	<i>Hirudo medicinalis</i> (leech)	Oligochaete annelid	Intestine	88
	<i>Lymantria dispar</i> (gypsy moth)	Insect arthropod	Larval midgut	89
	<i>Drosophila melanogaster</i> (fruitfly)	Insect arthropod	Intestine	90
	<i>Hydra oligactis</i> and <i>Hydra vulgaris</i>	Hydrozoan cnidarian	Not determined	91
Monospecific (1)*	<i>Euprymna scolopes</i> (sepiolid squid)/ <i>Vibrio fischeri</i>	Cephalopod mollusc	Light organ	92
	<i>Eisenia fetida</i> (earthworm)/ <i>Acidovorax</i> spp.	Oligochaete annelid	Excretory tissues	93
	<i>Steinernema</i> spp./ <i>Xenorhabdus</i> spp. and <i>Heterorhabditis</i> spp. / <i>Photorhabdus</i> spp.	Entomopathogenic nematodes	Gut-associated vesicle or region	94

* Number of bacterial-symbiont phylotypes found reproducibly.