# Evolution and ecology of streptomyces.

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*Annual Review of Microbiology*

# Evolution and Ecology of *Streptomyces*

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Annu. Rev. Microbiol. 2025. 79:383–403

First published as a Review in Advance on August 19, 2025

The *Annual Review of Microbiology* is online at micro.annualreviews.org

https://doi.org/10.1146/annurev-micro-051524-032254



## Keywords

*Streptomyces*, multicellularity, antibiotics, development, experimental evolution

## Abstract

*Streptomyces* are among the most well-studied and important groups of bacteria, largely owing to their prolific production of biomedically important compounds like antibiotics and antifungals. Research over more than a half-century has elucidated the molecular and mechanistic details of *Streptomyces* multicellular development and the production of secondary metabolites. In contrast, the evolutionary and ecological mechanisms that underlie these phenotypes are comparatively understudied. Our aim in this review is to examine these aspects of *Streptomyces* biology, with a focus on the benefits associated with their complex life cycle, their multicellular architecture and development, and their production of antibiotics. In addition to highlighting existing studies, we point to clear knowledge gaps that can serve to motivate further research on these bacteria. A greater understanding of *Streptomyces* evolution and ecology is needed to improve our ability to exploit these organisms for biomedical and agricultural applications.

## Contents





## 1. INTRODUCTION AND BIOGEOGRAPHY

*Streptomyces* are one of the most recognizable and well-characterized genera of *Actinobacteria* (8). The genus includes more than 700 recognized species (91), not including the uncharacterized diversity of putative species in metagenomes. *Streptomyces* have a venerable and important history. Long viewed as a puzzling intermediate between fungi and bacteria due to their filamentous morphology, *Streptomyces* were designated as bacteria in the 1940s by Waksman & Henrici (130), who also established their importance as prolific producers of antibiotics. Since then, their taxonomy has been periodically modified to account for advances in sequencing and phylogenetic analyses, and their relationship to morphologically similar taxa has been clarified (2, 37). On the basis of whole-genome sequences, the *Streptomycetaceae* family also includes genera like *Kitasatospora* (147) and *Streptacidophilus* (69) as well as several newly defined groups (81, 88). Although these genera have significant phenotypic differences, they are broadly defined by a complex life cycle that includes a branching multicellular mycelial network and the production of durable spores (**Figure 1**). In addition to their multicellular morphology, *Streptomyces* are studied primarily for the diversity of their specialized metabolites, including antibiotics, antifungals, anticancer agents, and many others. Our aim in this review is to provide a current (selective) update on our understanding of the ecology and evolution of these bacteria, focusing on aspects of their multicellular growth and life cycle. We also refer readers to several excellent related reviews on the mechanisms of *Streptomyces* development, antibiotic production, and symbiosis (2, 8, 25, 31, 44, 48, 59, 60, 110, 113).

### 1.1. Genome Size

*Streptomyces* genomes range from 6 Mb to 12 Mb and are among the largest in bacteria (87). While all *Actinobacteria* have a single chromosome, *Streptomyces* are one of the few groups to have evolved linear chromosomes (78). The core region of the genome disproportionally contains essential housekeeping genes (13) that are syntenic with those of other actinomycetes (26) and

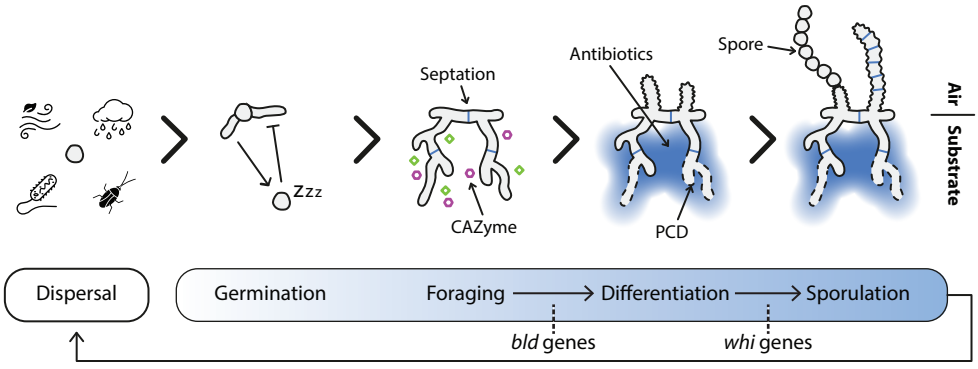


**Figure 1**

*Streptomyces* life cycle. *Streptomyces* spend the majority of their time as dormant spores inside and between soil grains subject to passive environmental dispersal (83). Development starts when spores germinate and one or more germ tubes emerge. Vegetative hyphae grow and penetrate the substrate through tip extension. Septa compartmentalize the hyphae, and enzymes are secreted to aid in foraging. Nutrient depletion triggers *bld* gene expression and the transition to differentiation, accompanied by the death and lysis of vegetative hyphae and antibiotic production. Hydrophobic aerial hyphae, coated in rodlins and chaplins, extend away from the substrate to facilitate dispersal. The *whi* gene cascade induces synchronous septation of the aerial hyphae, leading to chains of unigenomic spores. Across the entire colony, developmental steps often overlap, leading to ontogenetic heterogeneity. Abbreviations: CAZyme, carbohydrate-active enzyme; PCD, programmed cell death.

phylogenetically conserved. Increases in genome size resulted from large duplications and the accumulation of transposable elements and integrative conjugative elements. In addition, *Streptomyces* frequently carry one or more circular and/or giant (>1 Mb) linear plasmids that contribute to genome plasticity by facilitating horizontal gene transfer (HGT) and genome rearrangements (87). The left and right chromosome arms primarily encode conditionally adaptive genes, such as biosynthetic gene clusters (BGCs) and carbohydrate-active enzymes (CAZymes) (see the sidebar titled Ecology of *Streptomyces* CAZymes), which are variable within and between species (87, 90).

**Integrative conjugative element:** mobile genetic element capable of autonomous integration, excision, and conjugation between strains

## ECOLOGY OF *STREPTOMYCES* CAZYMES

CAZymes (carbohydrate-active enzymes) are enzymes that mediate the buildup, breakdown, or modification of carbohydrates. *Streptomyces* genomes contain hundreds of CAZymes, especially glycoside hydrolases, that allow these species to degrade complex carbohydrates, like chitin and cellulose, to fuel their saprotrophic growth (87, 90). The *Streptomyces* pangenome contains more than 44,000 proteins with at least one CAZyme domain (90), reflecting the vast enzymatic capacity of the genus. However, CAZyme abundance varies significantly across habitats and species, suggesting that the CAZyme repertoire is driven by competition and nutrient availability. Across species, there are moderately more CAZymes in terrestrial than marine streptomycetes, more in plant- than in animal-associated species (87), and particularly enriched cellulolytic capacity in *Streptomyces* symbionts of herbivorous insects (16). These differences suggest that CAZyme diversity is ecologically adaptive, allowing species to exploit abundant nutrients while also facilitating coexistence by enabling them to avoid competition by partitioning resources (76). There is considerable CAZyme heterogeneity between and within species. While *Streptomyces bingchenggensis* encodes 381 CAZymes, *Streptomyces spongiicola* contains 121 (90). Additionally, CAZymes are overrepresented on *Streptomyces* chromosome arms (87), possibly leading to within-species heterogeneity and facilitating rapid adaptation to environmental change. Further study of CAZymes is needed to elucidate their crucial ecological roles and to identify novel enzymes for industrial applications.

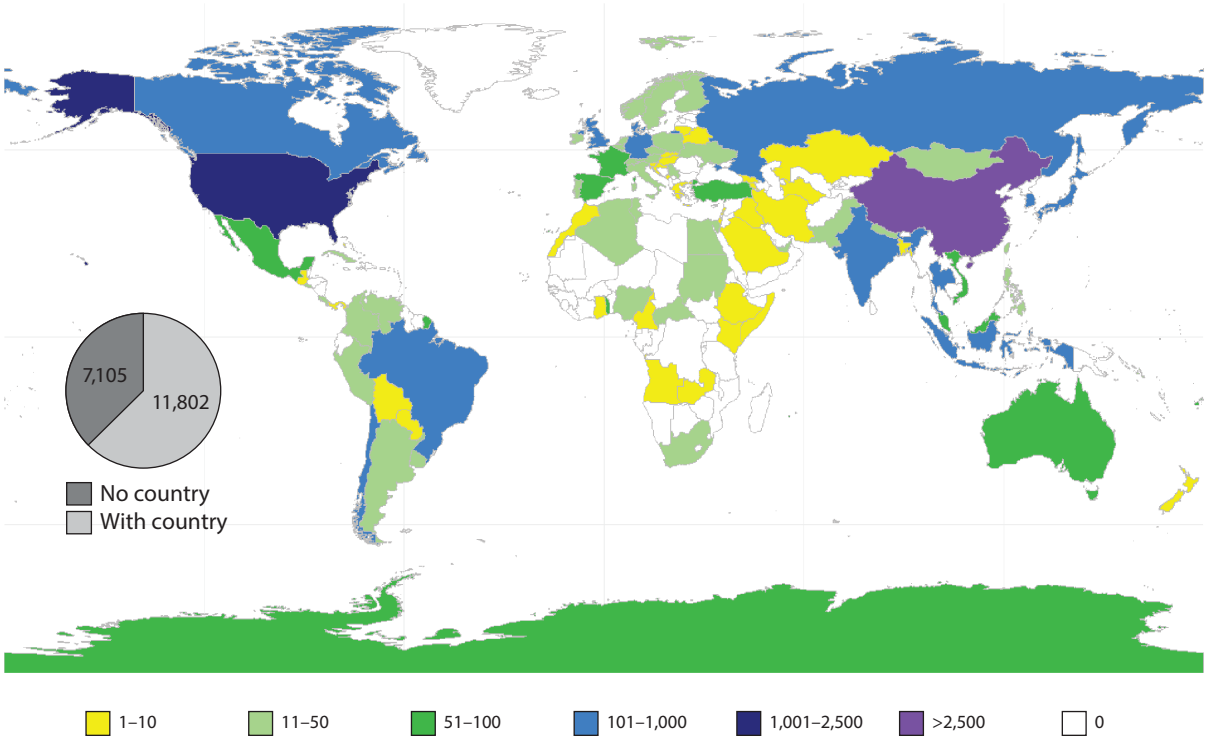


**Figure 2**

Country of origin of *Streptomyces* genomes. Sequenced strains isolated between 1910 and 2024 were collected from the National Center for Biotechnology Information (NCBI) database. We used the NCBI Datasets API to query the genomes under the taxon *Streptomyces* and retrieved their metadata summaries. The metadata were saved in JSON Lines format for further processing. More than 37% of the isolates had no country of origin.

**Biosynthetic gene cluster (BGC):** a set of colocalized genes that encode the biosynthetic machinery to produce specific secondary/specialized metabolites

**Panmictic population:** bacterial populations with high genetic diversity and limited clonality, reflecting extensive gene flow via HGT

Two factors appear to underlie heterogeneity in the chromosome arms. First, *Streptomyces* are prone to genome instability that leads to duplications and large deletions at the chromosome ends (145, 146). Second, chromosome arms experience higher levels of HGT (45). Several studies have demonstrated that these regions are recombination hot spots caused by conjugation (e.g., 121). Frequent gene flow is consistent with an essentially panmictic population genetic structure (28), although recombination in some species is constrained by habitat-driven barriers (29).

Larger genome sizes in bacteria are correlated with a broader functional diversity and ecological distribution (112), which is consistent with the large geographic range of *Streptomyces* (**Figure 2**). Although sequenced genomes come from around the globe, the distribution is highly uneven. The majority (more than 75%) of the strains in GenBank were sampled from terrestrial soils from forests, grasslands, deserts, savannahs, tundra, and caves (87, 90), where *Streptomyces* average ~5 × $10^6$ CFU/g and ~20% of culturable bacterial biomass (4, 7). In addition, ~10% of known species are host associated, as endophytes or pathogens in plants or as mutualists with some arthropods (27, 30, 110, 115). Associations with fungi are not as well-studied as are those with mammals (97). The second largest source of streptomycetes is aquatic environments, including deep-sea sediment, mangroves, coastal areas, and freshwater. While aquatic species were originally believed to be derived from runoff from terrestrial habitats, it is now clear that these species are specifically adapted to these environments, including requirements for high salinity (63) and obligate associations with algae, coral, sponges, or fish (51). *Streptomyces* have been found

in extreme environments, including the Mariana Trench (66) and Antarctica (89), and have been studied with the goal of discovering new antimicrobial, antifungal, and antitumor compounds (44).

## 1.2. *Streptomyces* Biogeography

An understanding of *Streptomyces* biogeography depends on the scale of inquiry. While macrobiogeographic patterns reflect global diversity, resource heterogeneity or ecological interactions between strains occurs at the micrometer scale. At the broadest spatial scales, several studies have found evidence for regional endemism (107, 125). Using a biogeographic sampling scheme, Andam et al. (1) uncovered a negative latitudinal gradient in *Streptomyces* diversity in North America that was interpreted as driven by postglacial demographic expansion and dispersal limitation. Similar research in New Zealand found that *Streptomyces* diversity was best explained by pH, temperature, and plant community richness, but not latitude (58). The same research group found that species diversity scaled positively with altitude (0–3,000 m) and that geographic differences between closely related strains varied as a result of thermal tolerance, consistent with the idea of habitat preferences or local adaptation (32, 55).

Recent studies using whole-genome sequences have also found evidence for habitat-specific population genetic structure and local adaptation (132). Focusing on *Streptomyces albidoflavous*, Li et al. (79) sequenced 30 strains from terrestrial, marine, or insect-associated environments and found strong phylogenetic partitioning between free-living and host-associated strains. Although certain functions (e.g., the ability to utilize sialic acid for growth in the free-living strains and the production of the catechol-like siderophore griseobactin in the host-associated stains) were habitat associated, no functions were habitat specific, reflecting continued gene flow between these environments. More differentiation was found between free-living and insect-associated *Streptomyces olivaceus*, which suggested incipient speciation driven by ecological divergence (132). Both of these studies (80, 132) highlight the growing importance of whole-genome studies in characterizing population genetic structure and the biosynthetic and metabolic pathways that drive speciation.

In addition to global biogeographic patterns, it is crucial to understand diversity at a more local scale, where the distribution of species and strains is driven by local biotic interactions. Davelos et al. (40) sampled streptomycetes from small (1 $m^2$) soil grids to characterize the diversity of inhibitory and resistance phenotypes. They found 93 distinct phenotype groups among 153 sampled strains. A follow-up study using Biolog plates to examine resource use diversity reported 453 unique resource use phenotypes from 459 strains, with huge variation in their ability to use the different carbon and nitrogen sources in these phenotype arrays (106). Both of these studies found that closely related strains had more similar phenotypes. More striking was that most strains were phenotypically unique, even though they were sampled from a small area. This finding likely reflects the patchy nature of the soil environment and the discretely structured resources, like chitin and cellulose, on which *Streptomyces* grow.

More recent studies measured interactions between strains isolated from single grains of soil. This is arguably the most ecologically relevant scale for bacteria, where cells live on soil microaggregates of <250 μm with an average intercellular distance of ~10–20 μm (96). Vetsigian et al. (126) sampled streptomycetes from single grains of soil (~1 mg) and recovered 64 different strains that varied both functionally, in terms of inhibitory patterns, and phylogenetically, indicating that diverse strains can coexist and compete at this smallest of spatial scales. Using a similar sampling scheme, Tidjani et al. (121) identified surprisingly high genetic diversity among coisolated strains of *Streptomyces olivochromogenes* from French forests. They also confirmed that coexisting strains frequently engaged in HGT driven by integrative conjugative elements. Chromosomal changes due to recombination were disproportionately observed at the chromosome ends, and in several cases the horizontally transferred genes were associated with antibiotic production.

**Endophyte:** a microorganism that lives within plant tissues without causing harm and possibly providing benefits

**Regional endemism:** a pattern of biological diversity where species are confined to a specific geographic location

**Siderophore:** an iron-chelating molecule secreted by microbes essential for iron uptake

## 2. DEVELOPMENT AND HETEROGENEITY ACROSS THE LIFE CYCLE

A central feature of *Streptomyces* multicellularity is the coordination between developmental timing and environmental cues (54). In addition, *Streptomyces* can experience environmental conditions that vary across different sections of their mycelial bodies. Fitness is maximized by coordinating different spatial responses across the colony, ensuring that some areas continue feeding and growing while others initiate sporulation (60). Different regions of the same colony, while genetically identical, are therefore ontogenically distinct.

### 2.1. Spores

Spores vary in germination timing and germ tube growth (139). Germination is thought to be stochastic but is also affected by heat shock, resource concentration, neighboring spores, and mechanical disruption (15). Spores contain very little water but high concentrations of mRNA, hydrolases, saccharides, and calcium, which are necessary to initiate germination (15). Moreover, much like asynchronous seed germination in plants that arises via bet-hedging, a portion of spores can remain dormant to protect strains from extinction (15). To maximize fitness, spores balance the ability to survive, disperse, and germinate, and these attributes that affect spore size, number, and viability may trade off with one another. Size typically correlates with higher durability but decreased dispersal. Interestingly, a harsh environment could promote both extremes: highly durable spores that endure and highly dispersible spores that escape.

To facilitate dispersal in wind and water, the surface of *Streptomyces* spores is composed of a striated pattern of pairwise aligned rodlin and chaplin proteins (35) that confer varying degrees of hydrophobicity (101). Surface structures vary markedly across species and mediate attachment to arthropod exoskeletons through attraction between hydrophobic surfaces (101). In addition, recent studies found that the ubiquitous *Streptomyces* volatile compound, geosmin, promotes attraction and dispersal by springtails (10). Across smaller distances, hydrophobic spores can hitchhike on the flagella of motile bacteria (85). Alternatively, strains with hydrophilic spores cannot attach to hydrophobic surfaces but are much more efficiently transported by water (101), which allows them to disperse across long distances. During sporulation, the rodlin sheath that covers aerial hypha can remain smooth or differentiate into spines, hairs, or warts (123). While these physical decorations can mediate physical attachment to animals, they can also inhibit movement through soil pores and the hydrophobic interactions necessary for attachment to arthropods (101) or bird feathers (105). However, these assumed connections between spore morphology and dispersal remain untested. Also unknown is whether a colony can produce multiple spore phenotypes, although it is known that traits like glycogen storage, and therefore germination timing, can depend on the growth environment (15).

### 2.2. Germination and Growth

Colonies commit to multicellular growth after spore germination. Although this may not be the stage where *Streptomyces* spend most of their time (that stage appears to be as spores; 84), it is when they are active (and arguably most interesting). One or more germ tubes grow and eventually specialize in different activities. Vegetative hyphae specialize in foraging but are transient. Their death during starvation is hypothesized to fuel the formation of aerial hyphae that specialize in spore creation (119). Due to their different roles, these two types of hyphae grow differently. Vegetative hyphae grow radially from the colony center and penetrate the substrate (49) to maximize their direct interaction with nutrients. To enhance resource acquisition, vegetative hyphae secrete CAZymes and secondary metabolites. Live imaging has shown that the Tat secretion system is localized directly behind the hyphal tip. This finding points to a localized release of enzymes like

surfactants to aid in movement and CAZymes to degrade complex carbon sources (20). However, further research is required to elucidate how metabolites are spatially distributed and how this distribution influences the availability, uptake, and transport of liberated metabolites. When vegetative hyphae exhaust local nutrient sources, they can potentially transport resources throughout the mycelium. After vegetative hyphae lyse, competitors can exploit the newly available nutrients in the substrate; it has been argued that hyphae produce antibiotics to protect these resources (119).

## 2.3. Growth and Development

Colonies transform their local environment by secreting metabolites and CAZymes, leading to spatial gradients whose concentrations are used to organize and compartmentalize development. In a solid homogeneous environment like an agar plate, colonies grow radially outward. The center matures earlier and is the first area to differentiate into aerial hyphae (143). Recent research has clarified that activation of developmental pathways radiates in a wavelike pattern that can be disrupted by physically disturbing metabolic gradients underneath the colony. In *Streptomyces coelicolor*, this disturbance arrests the production of aerial hyphae. However, differentiation can be partially restored if the substrate is supplemented with siderophores (143). Interestingly, the failure to develop caused by substrate homogenization is reminiscent of growth in liquid, where many species grow as hyphal pellets but are frequently unable to differentiate or produce spores (82). It is tempting to speculate that this deficiency may arise from the absence of spatially regulated metabolic cues in such well-dispersed environments. If so, it remains unclear how liquid-sporulating strains overcome this limitation.

Certain triggers may even radically override the colony developmental program. A novel development mode, termed exploratory growth, has recently been reported in many species of *Streptomyces* (64). Driven by environmental cues, including those elicited by other species, *Streptomyces venezuelae* invests in a rapidly expanding vegetative mycelium that grows nearly 10 times faster than typical hyphae (64). Exploration, caused by enhanced growth and surfactant secretion, fundamentally alters the multicellular architecture of the colony (114). Depending on the media, this process can coincide with the repression of sporulation, substrate alkalinization, and promotion of exploration in neighboring strains (64). The explorer phenotype may be an ecological strategy that allows *Streptomyces* to rapidly colonize, and possibly monopolize, distant resource patches and sporulate far from the point of inoculation. The fact that this phenotype has been found in many but not all natural isolates (64, 114) suggests that different species may have evolved different ecologically relevant cues to induce this dramatic response.

## 2.4. Sporulation

The developmental journey culminates in the transformation of aerial hyphae into spore chains. This transformation requires a complex interplay among cell division, genome segregation, and cell wall–remodeling mechanisms (33, 48, 135). Like other transitions, sporulation occurs asynchronously across the colony and can differ between clonal colonies. In *S. venezuelae* grown in liquid culture, this asynchrony can manifest as successive sporulation waves (D.M. Norte, unpublished data). Although species-specific mechanisms coordinate the temporal regulation of spore synthesis, this regulation should complement their overall life-history strategy. Therefore, the selective pressures (and mechanisms) that shape developmental programming are likely to also shape sporulation dynamics and developmental timing. For example, artificial selection on development speed significantly alters sporulation efficiency after a few hundred generations (D.M. Norte, unpublished data). The heritability of the new developmental program confirms that sporulation timing is one of many ecological strategies on which selection can act.

## 3. BENEFITS OF FILAMENTOUS MULTICELLULARITY

**Saprotroph:** an organism that feeds on and derives nutrients from dead or decaying organic matter

*Streptomyces* display several hallmark features of multicellularity, including terminal morphological differentiation, division of labor, programmed cell death, and intercellular cooperation (34). Enormous advances have been made in understanding their development genetic regulation (17, 33, 49, 143). However, we lack a clear understanding of how these bacteria benefit from multicellular growth.

### 3.1. Benefits for Resource Access and Transport

Growth of long multichromosomal hyphae occurs at the tips without subsequent cell division. Periodic branching leads to a large mycelial network (8) of filaments compartmentalized by semipermeable cross-walls. This arrangement mimics that of filamentous fungi (80) that share the same saprotrophic lifestyle and habitat (8). The similarity between the two groups is a striking example of convergent evolution (117); however, the benefits of this filamentous growth are largely unclear. One advantage is the ability of filamentous colonies to forage on patchy resources, together with their potential to transport material throughout the mycelium (86). Using a mathematical model, Heaton et al. (56) argued that environments with poor and hard-to-digest resources, like soil, are better exploited by hyphal osmotrophs, whereby a network of interconnected cytoplasm enhances nutrient transport and CAZyme utilization. When local resources are depleted, the benefit of searching and foraging over a large area appears to outweigh the transport costs of moving resources throughout the mycelium. Filaments may also benefit from their ability to weave through soil grains or penetrate large, insoluble resources like chitin or cellulose (138). In areas with low moisture, the air-filled pores between soil grains can create significant dispersal barriers for unicellular organisms (128). Although filaments lack motility, they can bridge the air between soil grains. Once resources are localized, in analogy to fungi, *Streptomyces* hyphae may provide opportunities for resource transport across the network. Extracellular transport of molecules is more expensive and unreliable compared with the intracellular cytoplasmic highway of filaments (9). Current research on transport between *Streptomyces* compartments is limited, but cross-walls and membranes are at least permeable to small proteins like green fluorescent protein (19) and to plasmids (120). In addition, preliminary data from our lab (E. van de Velde, D.E. Rozen & J. Willemse, unpublished data) found evidence for short-range transport of a fluorescent glucose analog. Although these findings are promising, it remains unclear how far nutrients can travel within the mycelial network or how *Streptomyces* controls compartment permeability. For example, fungi vary in septation and have evolved active mechanisms to plug septal pores (118). These properties allow them to control the intracellular movement of solutes and minerals and to quarantine threats (109), especially in the apical compartment, which is the first to encounter danger.

### 3.2. Extracellular Metabolism and Competitive Overgrowth

Although *Streptomyces* grow slowly, their filamentous growth allows them to encounter and exploit different resources in different regions of their extended bodies. Moreover, at least on petri plates, their branching filaments can cover a large area, in terms of distance traveled, and occupy space with densely grown hyphae. Nature, however, is not a petri dish. Whereas resources in a laboratory environment are at high concentrations and uniformly distributed, food in the soil is patchy. In addition, while *Streptomyces* in the lab grow on simple sugars that can be directly transported for growth, *Streptomyces* in nature specialize on recalcitrant resources that require CAZyme secretion to degrade insoluble resources into simpler oligomers and monomers. Multicellularity, which necessarily entails higher cell densities, may be particularly beneficial in this context. Secretion in unicellular organisms can be inefficient because of the diffusive loss of CAZymes and the products

of their degradation (73). By contrast, CAZyme secretion in multicellular species can significantly increase local CAZyme concentrations that, in turn, increase the efficiency of these public goods. Experiments with yeast (74) showed that unicellular yeast were unable to grow in low sucrose concentrations, while strains that were engineered to grow as multicellular clusters were able to do so. A subsequent study even found that yeast grown in low sucrose concentrations evolved de novo multicellularity via mutations that impaired cell division (73). Undifferentiated multicellular aggregates in these experiments benefited in two ways. First, they could locally produce high enough concentrations of the invertase needed to degrade sucrose to offset loss caused by diffusion. Second, multicellular organization provided a type of structural defense against "cheaters" by allowing them to privatize their catabolic output. By analogy, multicellular filaments in *Streptomyces* might benefit from increased efficiency of CAZyme secretion and resource privatization in heterogeneous and low-resource environments. The multicellular architecture that allows *Streptomyces* to reach complex carbohydrates is complemented by an arsenal of metabolically expensive digestive CAZymes (8). In addition, these resources are further privatized via production of antibiotics, which can protect the resources degraded by CAZymes from opportunistic microbes.

### 3.3. Division of Labor

Multicellularity allows tasks to be spatially segregated among cells of the same organism, which in turn allows specialization, via a division of labor, that increases organismal efficiency. In contrast to other multicellular bacteria that form via aggregation (e.g., myxobacteria), multicellular *Streptomyces* colonies are initiated from growth of a single spore. Accordingly, colonies are clonal, creating conditions where altruistic behaviors can arise and be maintained due to kin selection. Clonality, moreover, is associated with obligate multicellularity, larger size (more cells), and an increase in the number of cell types (a proxy for division of labor) (61). Different types of labor division can occur in *Streptomyces*: spatial and temporal, reproductive, and antibiotic production. Spatial and temporal patterning provides evidence for division of labor in developmental timing and antibiotic production that relies on spatially explicit gradients (143). Different sections of the same colony can even show some level of localized differentiation. For example, the side of a colony adjacent to a competitor developed differently and produced more antibiotics than the side opposite to the competing colony (104). Better known is the reproductive division of labor between vegetative cells and spores, which is analogous to the germ–soma division in eukaryotes. The process of "offloading" reproductive capabilities to a subset of hyphae necessarily accompanies the partitioning of the colony into multiple cell types via spatial and temporal developmental patterning. At the same time, spore production creates a second scale on which natural selection can act. Thus, while vegetative hyphae specialize on foraging, as outlined above, spores can specialize on durability and dispersal into environments that are more favorable for germination and colony growth. The fact that *Streptomyces* spend most of their time as spores speaks to the importance of spore durability. Although this hypothesis has not been explored, local dispersal can also increase local genetic relatedness and provide conditions for cooperative defense and feeding.

Another type of division of labor arises as a consequence of the surprisingly high genetic instability of *Streptomyces*, whereby a proportion of spores have large deletions and duplications, primarily in the terminal regions of their linear chromosome. This inherent genomic instability has long been observed (127), but its evolutionary effects remain puzzling. Organisms go to great lengths to maintain genome integrity; however, *S. coelicolor* seems to benefit from genome damage in part of the colony, at least to a certain degree. While cells with large genomic lesions grew more slowly and produced markedly fewer spores, these same cells produced higher titers of antibiotics (145, 146). Results suggest that this division of labor may shift the high cost of producing antibiotics to a subset of progeny whose reproductive potential was already low. Moreover, the

fraction of cells that adopt this fate is partly dependent on the competitive environment (43). Because antibiotics are public goods, this trade-off appears to benefit the whole colony. Genetic instability, thereby, leads to a division of labor where an effectively sterile caste of antibiotic producers lowers the total cost of production for the rest of the population, which can specialize in sporulation.

### 3.4. Experimental Evolution Is a Tool to Study Benefits of Multicellularity

Experimental evolution can provide valuable insights into the origins and benefits of multicellularity. In the best-studied example, Ratcliff et al. (95) used gravitational settling to select for multicellular yeast clusters, producing elaborate snowflake-like phenotypes with enhanced fitness, a complex life cycle, and a reproductive division of labor. Spontaneous evolution of multicellular organization in wild-type yeast was also observed when cells were grown in environments that required extracellular degradation of sucrose, which increased resource use efficiency (73). Selective pressures like predation and aggregation-driven motility also drive multicellular evolution (57, 144). While these studies have provided key insights into de novo multicellular evolution, similar dynamics cannot be fully replicated in *Streptomyces* because they are already multicellular. However, their multicellular growth may offer other advantages in elucidating the benefits of multicellular organization, cell–cell interactions, and spatial differentiation within mycelial colonies, including mechanisms that mediate phenotypes like hyphal growth and filamentation, spores, and explorer cells.

Our lab has developed this approach in two contexts: The first builds on the results of Ratcliff et al. (95) on size, and the second focuses on the evolution of the *Streptomyces* life cycle (**Figure 3**). Experimental evolution of mycelial size has significantly shifted multicellular architecture, leading

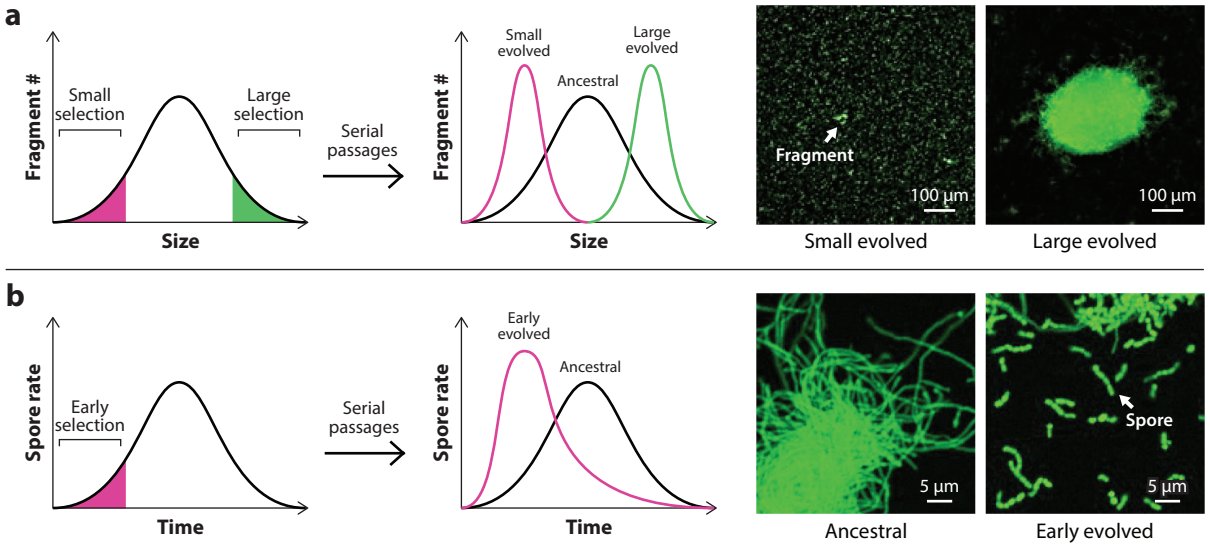


**Figure 3**

Experimental evolution of size and development in *Streptomyces venezuelae*. (*a*) Selection of small or large mycelial pellets using filtration and serial passage led to the evolution of strains that vary markedly in size. These changes dramatically altered multicellular architecture and life-cycle regulation. (*b*) Selection for faster development by serially passing the first set of produced spores (early populations) led to evolved strains with faster and more synchronous sporulation. These evolved responses led to changes in mycelial architecture, fragmentation, and size and displayed trade-offs with vegetative growth and biomass.

in extreme cases to the loss of multicellularity entirely (L.A. Avitia-Dominguez, unpublished data) (**Figure 3*a***). Interestingly, size selection radically disrupted the life cycle, such that some strains lost the ability to sporulate. In a related experiment, we examined the evolution of the life cycle by selecting for faster development (D.M. Norte, unpublished data) (**Figure 3*b***). The evolved strains in this experiment had faster and more synchronized sporulation, and they also increased the proportion of biomass allocated to reproduction. This change in developmental speed and efficiency was accompanied by dramatic morphological changes and came at the expense of vegetative growth and biomass. Although both experiments are still at an early stage, they demonstrate the potential to uncover trade-offs between multicellular traits in *Streptomyces* and the mechanisms that regulate these evolved shifts.

**Polyketide synthases:** modular enzymes that combine acyl-CoA units to produce bioactive polyketides, including pharmaceutically important drugs like erythromycin and avermectin

**Nonribosomal peptide synthetases:** modular enzymes that synthesize biomedically important bioactive molecules (e.g., penicillin, vancomycin, and daptomycin)

## 4. ANTIBIOTIC DIVERSITY AND FUNCTIONS

### 4.1. Biosynthetic Gene Cluster Diversity

One of the most extensively studied attributes of *Streptomyces* is their capacity to produce secondary metabolites via encoded BGCs. *Streptomyces* are exceptionally prolific producers of BGCs, and their metabolites have unrivaled human relevance, accounting for more than 50% of the antibiotics used in medicine and agriculture (41). Online tools such as antiSMASH and BiG-FAM have identified more than 80 distinct BGC types in *Streptomyces* and around 30,000 gene families involved in specialized metabolism (14). The different types of BGCs are based on the metabolic pathways they encode and the chemical classes of secondary metabolites they produce, including several associated with antibiotic production (e.g., type I and II polyketide synthases, nonribosomal peptide synthetases, and ribosomally synthesized and posttranslationally modified peptides). In addition to antibiotics, BGCs encode pigments, siderophores, surfactants, and signaling molecules that serve a variety of functions (6). *Streptomyces* genomes contain between 8 and 83 BGCs; the number typically scales with genome size (12). At the same time, significant variation in BGC composition and diversity exists within and between species (12).

The factors underlying BGC diversity are likely as diverse as the BGCs themselves. Mechanistically, the modular nature of some BGCs can facilitate innovation through iterative biosynthesis (131). Such innovation enables variability and evolutionary tinkering, where mutations within modules create chemical diversity. Additionally, swapping and recombination of modules between BGCs produce hybrid metabolites that expand molecular and functional diversity. Vertical inheritance maintains metabolite differentiation by ensuring lineage-specific conservation of key biosynthetic traits that adapt over evolutionary timescales via gene gain, loss, duplication, and divergence (24). At the same time, HGT can enhance biosynthetic diversity by transporting BGCs between species (28). Thus, entire pathways can be acquired and integrated, or partial BGCs can be recombined into existing pathways. HGT is widespread in *Streptomyces* and is evident when the distribution of BGCs does not correspond with the species phylogeny (1).

Biome-specific BGC composition is evident, with many gene clusters biased to particular habitats (50). For example, terrestrial species typically harbor more BGCs than their marine counterparts (87). While *Streptomyces* from unique and extreme environments, such as high-altitude soils or deep-sea sediments, can contain novel biosynthetic pathways, considerable diversity can also be found in urban microbiomes like Central Park in New York City (23). Soil composition, pH, and latitude have been found to correlate with BGC diversity (22, 77). However, because the same factors can also influence microbial diversity more broadly, it remains possible that BGC diversity is simply a correlated response to selection acting on other ecological traits. Biotic interactions, discussed in more detail below, may also affect BGCs through cooperative or antagonistic interactions.

## 4.2. Diverse Ecological Roles of Antibiotics

**Minimum inhibitory concentration (MIC):** lowest concentration of an antibiotic that inhibits the growth of a given strain

**Minimal selective concentration (MSC):** lowest concentration of an antibiotic capable of generating a competitive advantage for resistant strains

Although *Streptomyces* antibiotics have been exhaustively characterized in molecular, chemical, and functional terms, their diverse ecological roles have been comparatively understudied. BGC activation, and therefore antibiotic production, is intricately linked to environmental cues and developmental stages, with many compounds like actinorhodin and streptomycin synthesized during the late growth/stationary phase (124). This timing of expression coincides with the shifts from growth to sporulation and from resource acquisition and growth to specialized metabolism. Because this timing also corresponds to nutrients released from lysed cells, it is often argued that antibiotic production is used to protect these resources (133). However, not all antibiotics follow this temporal pattern. Fosfomycin in *Streptomyces fradiae* (100) and lincomycin in *Streptomyces lincolnensis* (142) are produced in the late exponential phase; in *S. coelicolor*, early-stage antibiotics like CPK are produced before the metabolic switch from growth to sporulation, while undecylprodigiosin (red) and actinorhodin are produced later on. This variability in antibiotic timing highlights finely tuned strategies that likely reflect antibiotics' (unknown) roles during dynamic interactions with competitors (11). The fact that all *Streptomyces* encode multiple antibiotics raises questions about the spatial and temporal regulation of these compounds as well as the correspondence between specific BGCs. For example, *Streptomyces clavuligerus* coproduces the β-lactam antibiotic cephamycin C and the β-lactamase inhibitor clavulanic acid, which enhances the efficacy of cephamycin by neutralizing resistance in competing microbes (21). Whether the co-occurrence of such complementary pathways reflects selection for synergy, or whether it is due to other factors specific to their biotic environments, is currently unclear.

## 4.3. Antibiotics in Soil

The role of antibiotics in soil environments has been challenging to ascertain because their concentrations, at least in bulk samples, are quite low (39). These subminimum inhibitory concentrations (sub-MICs) elicit a variety of responses in bacterial species, including increased motility, biofilm formation, increased mutation rate, and HGT. This finding has led to arguments that antibiotics function as signals between cells (141). However, bulk concentrations do not reflect the local concentrations of antibiotics next to producing colonies, where these compounds exert their effects. In addition, this idea neglects the fact that even sub-MICs can strongly select for antibiotic resistance, as reflected in the concept of minimal selective concentration (MSC) (3). Both in *Streptomyces* and in other species, the MSC can be 10- to 1,000-fold lower than the concentration needed to kill or inhibit growth (53). In addition, the effects of antibiotics are strongly spatially dependent, and our work has provided evidence that antibiotics can confer benefits by allowing strains to both maintain territory (defense) and invade new territory (offense). For example, when *Streptomyces griseus* and *S. coelicolor* are cocultured, *S. griseus* uses streptomycin production to invade susceptible populations of *S. coelicolor*, even when the invading strain is as rare as a few cells (134). However, these benefits at low frequencies were observed only in spatially structured environments. These spatially dependent benefits reflect the fact that concentrations of antibiotics are highest adjacent to producing cells and suggest that (*a*) even if antibiotics are produced at sub-MICs, they are sufficient to provide direct benefits, and (*b*) it is potentially misleading to interpret the role of antibiotics according to their concentrations in soil.

Most evidence supports the idea that *Streptomyces* antibiotics act as chemical weapons, rather than signals, that kill or inhibit competitors. Associational studies have provided evidence that *Streptomyces* are better at inhibiting coevolved competitors than strains from other locations (108). This finding supports the idea that antibiotic production and resistance coevolve, reflecting local adaptation and highlighting that antagonistic behavior is a crucial attribute of ecological success

(70). Accordingly, the capacity of *Streptomyces* for antibiosis varies even in strains from nearby locations and is tied to local nutrient availability and type (107). In *S. coelicolor*, high glucose concentrations trigger carbon catabolite repression, which inhibits the production of antibiotics through regulators like *DasR* and *AtrA* (99). But this response can vary across species, where the same resources can both increase and inhibit antibiotic production. In *S. clavuligerus*, glucose represses cephamycin C production, while glycerol enhances clavulanic acid production (103). In contrast, glucose in *Streptomyces noursei* boosts nystatin production by increasing biomass, but glycerol improves specific yields (103). Meanwhile, in *Streptomyces lividans*, glucose suppresses actinorhodin production, whereas glycerol does not have this effect (103). Reciprocally, in soil and in vitro, subinhibitory concentrations of antibiotics can alter nutrient usage (62). The changes in nutrient use can increase niche partitioning and promote coexistence, helping to shape microbial communities and minimizing competition (47). A phylogenetic analysis has also revealed that antimicrobial activity in *Streptomyces* correlates with soil organic matter, showing both site-specific and lineage-dependent variations in antibiotic production (72).

**Niche partitioning:** division of resource use among organisms that can reduce competition and enable species coexistence

Extensive research has uncovered evidence that interactions with other microbes can elicit or inhibit antibiotic production. Coculturing *Streptomyces* with other species can induce cryptic BGCs or increase production of expressed antibiotics (111). Metabolomic analyses using nano-DESI (nanospray desorption electrospray ionization) and MALDI-TOF MS (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) revealed that secondary metabolite production in *S. coelicolor* is highly dynamic and interaction specific (122). Several factors can modify antibiotic production during coculture. While phylogenetic relatedness is a strong predictor of antibiotic elicitation, cell damage during competition, as predicted by the idea of "competition sensing" (36), is not a universal trigger (134). Siderophores produced by neighboring strains triggered the production of a family of unknown compounds in *S. coelicolor*, including a suite of at least 12 different desferrioxamines (122). Quorum-sensing molecules, like the γ-butyrolactones or butenolides, that regulate secondary metabolite production and morphological differentiation can also trigger antibiotic production in other species (5). For example, avenolide in *Streptomyces avermitilis* acts as a signaling molecule to induce antibiotic biosynthesis in other species (71). Interestingly, interactions with different taxa, under the same conditions, can lead to different outcomes and different responses. Predation of *S. coelicolor* by *Myxococcus* triggers both actinorhodin production and aerial hyphae formation, while interactions with *Bacillus subtilis* induce a less intense production halo (92). Other interactions vary: No effect is visible with *Micrococcus*, *Klebsiella pneumoniae* induces aerial hyphae formation without antibiotic production, and *Bacillus megaterium* triggers only antibiotic production. Clearly, while interactions with likely competitors can modify how and which antibiotics are produced, thus far no generalizable pattern of elicitation has been found.

Beyond direct antagonism, there are several alternative functions for antibiotics. Some studies have explored the capacity of *Streptomyces* to prey on other species via the production of lytic enzymes and the synthesis of antifungal compounds like pentamycin, filipin III, and cholesterol oxidase to destabilize cell membranes (140). Antibiosis might also provide defense against protists. For instance, antiamoebic indolocarbazole metabolites have been isolated from *Streptomyces sanyensis* cultures, though no direct evidence of such function in soil environments has been reported (18). Finally, several recent studies have provided strong evidence that some *Streptomyces* metabolites, such as aminoglycoside antibiotics, can have antiphage properties by interfering with phage DNA or protein synthesis (75, 75). Anthracyclines like doxorubicin and daunorubicin, known for their anticancer effects, can also block phage replication by intercalating into phage DNA (67). Because most of these studies were carried out under in vitro conditions, it will be

important to extend this research to the highly diverse and competitive environments in natural soils.

### 4.4. Roles of Antibiotics During Interactions with Eukaryotes

While *Streptomyces* were initially studied mostly as soil saprotrophs, research from the last two decades has recognized the fundamental roles of these bacteria with other species. Several excellent reviews have detailed different aspects of these interactions (27, 30, 110, 115), so we provide only a brief overview here. We note that these studies have focused primarily on the benefits of *Streptomyces* to their eukaryotic hosts, while the reciprocal benefits to *Streptomyces* from these interactions remain less well-explored.

**4.4.1. Terrestrial invertebrates.** Symbiotic relationships between streptomycetes and invertebrates were first detected in fungus-gardening insects. In ants (38), termites (137), and beetles (52, 93), insect cuticles harbor bacterial strains that produce antifungal compounds which prevent the growth of parasitic fungi but do not antagonize the mutualistic fungi the insects cultivate (27). Other strains permanently colonize the insect's gut and infuse its feces with antifungal compounds (93). Beewolf digger wasps cultivate their own population of *Streptomyces* in specialized antenna glands (74). Bacteria are injected into the cocoon of their offspring to provide pathogen protection. Coevolution with arthropods has strengthened the antimicrobial arsenal of *Streptomyces*, diversifying and reinforcing inhibitory effects against drug-resistant fungal pathogens (30). Accordingly, most known symbioses hinge on the production of bacterially specialized metabolites to promote arthropod well-being (113).

**4.4.2. Interactions with plants.** *Streptomyces* are commonly found in association with decaying plant material as saprotrophs (8). However, they are also among the most common species isolated from the rhizosphere (7, 113). As suggested in the "cry for help" hypothesis (116), plants recruit *Streptomyces* to act as probiotics, which can benefit plants through the production of antibiotics and antifungals (46, 94). This protection can also act against arthropods, such as the insecticidal activity of endophytic streptomycetes against fruit flies (42). Antimicrobial protection can occur at all steps of the plant life cycle, from seeds (83) to adulthood (65). Some strains can even travel from the rhizosphere to flowers through the stem (68). Plants tissues provide shelter, food, and seed dispersal to *Streptomyces* in return for resistance to abiotic and biotic stress (98). These symbioses have also selected for increased CAZyme activity in *Streptomyces* (16). Thus, plant-associated *Streptomyces* provide immense potential for increased yield in agriculture and offer a rich enzymatic source for biotechnology (16, 129).

**4.4.3. Interactions with marine invertebrates.** Marine organisms have served as a valuable resource for *Streptomyces* bioprospecting. Many novel species have been isolated from marine sponges (136) and mollusks (102), providing unique secondary metabolites of interest. These symbiotic relationships, like terrestrial ones, are also likely driven by the metabolic potential of *Streptomyces* and the benefits they provide. Unfortunately, experimental challenges limit our knowledge about the nature of these interactions (110). What is clear is that marine invertebrates can maintain stable symbiotic bacterial communities that are a valuable source of new isolates and chemistry (110). Probing the details of their behaviors in the marine ecosystem will require new tools and model systems and may be difficult to imitate in the laboratory.

## 5. CONCLUDING REMARKS

*Streptomyces* have been studied for more than a century and remain one of the most important sources of antibiotics, antifungals, antihelminthic agents, and anticancer drugs. Insights from

whole-genome sequences have broadened our understanding of the evolution of the genus, particularly the origin and development of BGCs. However, many gaps remain in our understanding of fundamental aspects of *Streptomyces* biology. We have focused on a necessarily narrow set of topics in this review, with the aim of highlighting key unknowns and pointing to research objectives for the future. Among many possibilities, questions remain about the origin of *Streptomyces* multicellular diversity and the molecular mechanisms underlying it. Why do individual *Streptomyces* strains and species produce so many antibiotics with apparently redundant functions, and how does this diversity vary between biomes and hosts? How does the regulation of antibiotics and CAZyme secretion (and other public goods) intersect with the coordination of the multicellular life cycle, and how does this coordination vary between species with distinct morphologies? Despite the power of genomics technologies to address these questions, we strongly advocate for an increased emphasis on detailed experimental models to test hypotheses and to more effectively replicate conditions in natural populations. These should, in particular, move toward inclusion of increased resource diversity and complexity to better reflect the heterogeneous landscapes in which these saprotrophic bacteria evolved. In addition, experimental models should increasingly include greater microbiome diversity to reflect the competitive environments where antibiotics and other specialized metabolites function. Finally, laboratory models should, where possible, be validated in the field, leveraging the power of new omics tools to evaluate *Streptomyces* behaviors in situ, including the biology and physiology of nonmodel species. These approaches are needed to broaden our understanding of the fundamental features of this uniquely important bacterial group and to improve our ability to exploit *Streptomyces* for biomedical and agricultural applications.

## DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

## ACKNOWLEDGMENTS

We apologize to authors whose work we were unable to include for lack of space. We thank Rita Rosário for help illustrating multiple figures. We acknowledge grant support from the Dutch Research Council (OCENW.M.22.076) and from the German Research Foundation (DFG-SPP2389, TS 325/4-1).

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