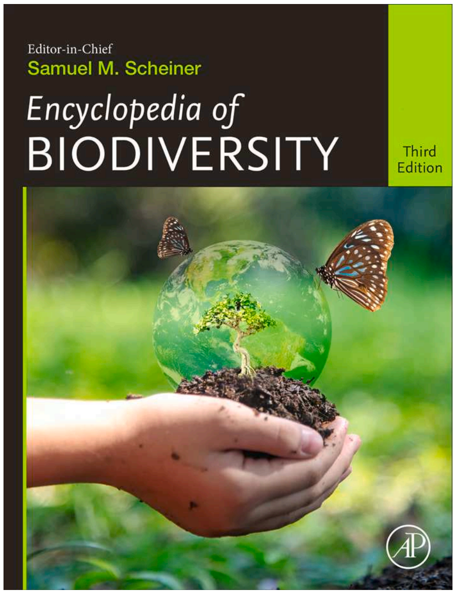

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Symbiosis: A Review of Different Forms of Interactions Among Organisms

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Abstract

Symbiosis refers to the interactions between different organisms. It is usually categorized into three main associations, which include mutualism, parasitism, and commensalism. Here, we define all types and the specialized forms that separate them from one another. Symbiosis typically involves an organism known as the symbiont residing within another organism referred to as the host. All symbionts are thought to have evolved from a free-living ancestor and were acquired through a constant interaction between the partners. The evolution of each type of symbiosis is a complex process, with multiple mechanisms resulting in the association. Understanding symbiosis is important globally given the roles these associations have not only in our ecosystems but as well as in human health.

Key Points

- The definition of symbiosis involves a symbiont and a host.
- The three main forms of symbiosis which are commensalism, parasitism, and mutualism has many different subtypes.
- Symbionts can shift from one form to another.
- Symbionts generally evolved from a free-living ancestor through different mechanisms.
- Numerous examples of each form of symbiosis are provided, which range from bacterial microbes to eukaryotic organisms.
- Symbiosis can have beneficial or detrimental effects on us on a larger scale such as agriculture and health.

Introduction

Organisms are constantly interacting with other organisms, whether it is a brief encounter or a permanent connection. These interactions can occur between individuals of the same species, or between different species. They can be as different as an elephant interacting with microbes in its gut, or those affiliated with their footpads. When these interactions are persistent, they are termed as symbiosis (Egerton, 2015). This chapter outlines the main types of symbiosis, describes their evolution, examines some model systems, and their broader impacts in agriculture and human health.

Symbiosis has existed perhaps for as long as their host organisms have been present. The relationship between herbivores eating plants and their waste products becoming fertilizer for plants could be seen as a vital type of symbiosis (Egerton, 2015). This type of symbiosis is beneficial for both organisms involved, where the herbivores gain a food source and the plants use their waste products. This beneficial symbiotic relationship between two organisms is known as mutualistic.

Not all symbiotic relationships are beneficial though. The basis of many diseases for instance are caused by microbes that benefit from their host, but harms them in the process. This is another type of symbiosis known as parasitism. The third main type of symbiosis is commensalism, where one organism benefits from another organism without harming or benefiting them. One example of commensalism is the association between Amazonian frogs and plants. Frogs from species such as *Adelphobates castaneoticus*, *Osteocephalus castaneicola*, and *Rhinella castaneotica* lay their eggs in the fruit capsules of *Bertholletia excelsa*, the Brazil nut tree (Lemes *et al.*, 2022). There is no benefit or harm done to the plant, but the frogs rely on it to complete their life cycle.

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These types of symbiotic relationships, be it parasitism or mutualism have been recorded back to antiquity. Intestinal round worms, for example, were mentioned in the Egyptian Ebers medical papyrus (Egerton, 2015). An example of mutualism that can be found in a report by the Greek historian, Herodotos around 450 BCE are Egyptian Plovers that were described to safely pick leeches from the mouths of Nile crocodiles.

In modern times, many examples of symbiosis can be found and have been well studied. One popular example of symbiosis found in many biology textbooks are rhizobia, a type of bacteria that are found on plant roots. This group is comprised of species stemming from a multitude of genera, including *Rhizobium*, *Bradyrhizobium*, *Azorhizobium*. Rhizobia provide plants sources of nitrogen as well as phytohormones, which help plants grow (Jaiswal *et al.*, 2021). Nitrogen is an essential nutrient as it is found in all amino acids and nucleic acids, making it vital for plant growth. This relationship is especially important for plants residing in nitrogen-poor soil. The types of phytohormones rhizobia provides to the plant host includes indole-3-acetic acids, lumichrome, and riboflavin which are all used for solubilizing phosphates vital to plant metabolism. The bacteria are localized to the root nodules, where signaling between the host plant and rhizobial symbionts occur (Jaiswel *et al.*, 2021).

Additional examples of symbiosis continue to be discovered. A relatively recent discovery is the symbiosis between the bacterial endosymbiont *Candidatus Azoamicus ciliaticola* and their ciliate host. The host lives in a habitat with little or no oxygen and their mitochondria, which typically generate energy using oxygen, are not functional. Instead, the endosymbionts generate energy from nitrates (Graf *et al.*, 2021). This example is interesting in that it parallels the evolution of mitochondria, which evolved from a bacterial symbiont at the origin of the eukaryotic cell.

Sometimes the classification of parasitism, commensalism, and mutualism are not always clear. It may be more accurate to view these types of symbioses as being on a continuum (Drew *et al.*, 2021). This spectrum can be visualized from the viewpoint of the host, where if the host is being harmed, then the interacting organism is a parasite (**Fig. 1**). In contrast, if there is a lack of harm or benefit to the host, then the organism is a commensal. Alternatively, if the organism provides a benefit, then it is a mutualist. There are cases where commensals can turn into parasites if given the opportunity.

Commensalism

Although there are many different forms of commensalisms, the common feature among all of them is that the host organism is not harmed or benefitted. We detail three different types: (1) commensals can hitch a ride on other organisms to find a new habitat – phoresy; (2) commensals can take up residency in a habitat created by other organisms – inquilinism; and (3) commensals can utilize an environment made suitable by other organisms – metabiosis.

Phoresy is one type of commensalism where one organism known as the phoretic uses another organism known as the carrier to move into different habitats. This form of commensalism is crucial for organisms that have low mobility, yet depend on resources that may be very scattered. One example of this type of phoresy can be found in mites, a type of very small arachnid, where many species are able to latch onto larger organisms. There are a number of types of phoresy. Seeman and Walter (2023) generally defines phoresy as a temporary symbiosis between the phoretic and the carrier with the goal of dispersing the phoretic to another environment. For example, some phoretic species are parasites that feed on their host as they are being transported.

Typically, such phoresy occurs during a specific life stage. Mites become phoretic at the deutonymph or adult life stage (Seeman and Walter, 2023). There are occasions where free-living mites ride along larger organisms by chance. These are known as accidental or facultative phoretics. Examples include members of Oribatida that are sometimes found riding on birds and beetles. Facultative phoresy involving a mite from Oribatida riding on an insect was thought to be found in the earliest known case of phoresy dating back to the Carboniferous Period.

The effect of the phoretics on their carrier can range from beneficial to parasitic. *Dendroctonus frontalis*, which are referred to as the southern pine beetle are known to carry mites belonging to the genus *Tarsonemus* (Seeman and Walter, 2023). These mites spread through beneficial or antagonistic fungi. One type of symbiotic wood fungi is pathogenic yet the beetle relies on. However, the mites can also pass on bluestain fungi which are harmful to the beetle.

A second type of commensalism is inquilinism, where one organism takes up residency in another host organism's nest or dwelling place. The sea urchin, *Echinostrephus molaris* lives in intertidal zones in southern Japan where it bores pits in rocks (Yamamori and Kato, 2017). When an individual dies, other marine life can colonize the pit including non-boring sea urchins such as *Anthocidaris crassispina* and *Echinometra tsumajiro*. These non-boring sea urchins have stouter spines compared to *E. molaris*. These

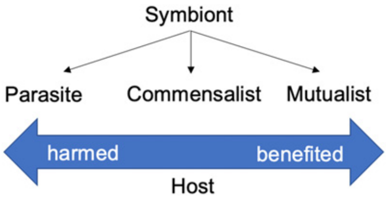

Fig. 1 Symbiosis spectrum. Organisms that cause harm to their host are parasitic. Those that provide benefit are more mutualistic. If they do not significantly harm or benefit their host, then they are commensalists.

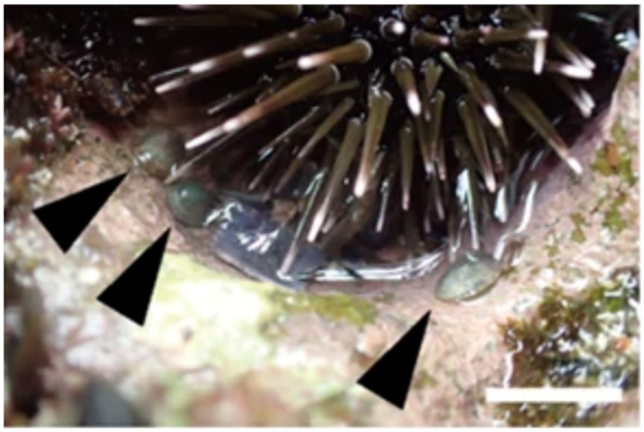

Fig. 2 Obligate inquilinism of *B. iridescens* snails (shown by black arrows) in pits with sea urchins. Reproduced with permission from Springer Nature.

thicker spines prevent them from being able to migrate deeply into the pits and from folding their spines flat against the walls of the pits. This results in a space between their spines and the pit wall, which creates a habitat for other organisms such as algal grazers and carnivores that can live both on the exterior and interior of these pits. Another inquiline in this system is the limpet-shaped snail, *Broderipia iridescen* that resides in the space between the non-boring sea urchin spines and the pit walls (**Fig. 2**). By living in between these spines, they are protected from other predatory snails. The space provided by the non-boring sea urchins were also found to house other commensals, including the alpheid shrimp *Athanas indicus* and *A. dorsalis*. Bodies of these shrimp have a color that is similar to the spines of the non-boring sea urchins. Other inquilines found living in the pit were filter feeders including gastropods, bivalves, and polychaetes. These filter feeders are susceptible to predation by muricid snails. Therefore, having these pits co-occupied with the non-boring sea urchins are thought to protect these filter feeders from predators (Yamamori and Kato, 2017).

The third main type of commensalism is metabiosis where one organism creates a suitable environment for another. Microbes that remove oxygen and reduce the oxidation-reduction potential form an anaerobic environment and subsequently permits the growth of other microbes can be classified as metabiosis. One example is the fermentation of milk into lactic acid by the bacterium *Lactococcus lactis*. Fermentation creates a suitably acidic environment for lactobacilli to thrive (Preetha and Narayanan, 2020) and further metabiosis occurs when yeasts and molds oxidize the lactic acid, raising the pH of the milk. Proteolytic bacteria are then able to grow in this modified environment. Other examples of metabiosis are fermented products such as sauerkraut and cheese. During the production of Swiss cheese, lactic acid bacteria form lactic acid out of lactose. The lactic acid is then metabolized by propionibacteria to form propionic acid, which is responsible for the flavor of Swiss cheese (Preetha and Narayanan, 2020). Additionally, metabiosis can also be found in food spoilage pathways. Lactic acid bacteria convert the amino acid arginine into ornithine, which in turn is used by enteric bacteria to form the amine putrescine which gives spoiled food their foul smell and taste.

Parasitism

When a host organism is harmed by its symbiont then the interacting organism can be categorized as a parasite. As with commensalism, there are many different forms of parasitism. Three types of parasites will be described in this section: obligate parasites, facultative parasites, and ectoparasites. These types are not exclusive and may overlap in other categories. For instance, a facultative parasite may also be an ectoparasite.

Obligate parasites cannot complete their life cycles without their host. *Cuscuta campestris*, for example, is a parasitic plant that cannot complete its life cycle without infecting their host plant (Bernal-Galeano *et al.*, 2022). These parasitic plants, known as dodders, are not photosynthetic, which is a typical characteristic for this group of parasites. Dodders also lack roots and expanded leaves, making them dependent on the host plant. Dodders use a special organ called the haustorium to colonize the stems of their host, allowing them to gain nutrients and water from the host plant. Individuals begin as seeds that germinate in soil, producing a thread-like outgrowth. During this seedling stage they search for a host to colonize since they have limited resources. Once finding a host, the parasitic seedling coils around the host stem with the thread-like outgrowth, which from there the haustorium begins to develop. The haustorium penetrates the epidermis and cortex of the host and continues to elongate until it encounters the host vascular elements. The parasite is then able to withdraw carbon from its host through the haustorium. Molecular studies on *Cuscuta* spp. have shown that they exchange macromolecules such as proteins, mRNA, and microRNAs. Some of the microRNAs excreted into the host affect expression of genes controlling colonization. Besides water, sugar, and minerals, host plants also provide a cytokine to the parasite, 6-benzylaminopurine (BA), that can induce haustoria formation.

Organisms that complete their life cycle without the need of a host, but can parasitize them if an opportunity arises are known as facultative parasites. One example is *Acanthamoeba castellanii*, which is a free-living amoeba that resides in soil and water environments. *A. castellanii* are quite ubiquitous and can be found from extreme environments such as thermal springs and under ice, to more mundane places including air ducts and bottled water. These protists obtain their nutrients by feeding on bacteria and other microbes. However, they can infect humans, thus making them facultative parasites (Niederkorn, 2021). *A. castellanii* exists primarily in two stages, trophozoites, or a more dormant stage known as cysts. The cyst stage is smaller than trophozoites in size and is resistant to harsh environmental conditions such as ultraviolet irradiation. Human infection begins with trophozoites that are carried usually on contact lenses, which are then transmitted to the epithelial surface of the cornea when the lenses are worn causing *Acanthamoeba* keratitis (AK). AK can lead to radial keratoneuritis which is often associated with extreme pain. Wearing contact lenses induces the expression of mannosylated proteins on the corneal epithelium, allowing the trophozoites to bind to the surface more readily. This is initiated by the trophozoite cell membrane releasing mannose-induced protease 133 (MIP-133) in response to binding to the mannosylated proteins. MIP-133 signals apoptosis and cytolysis of corneal epithelial cells, which allows trophozoites to infect these areas. If trophozoites encyst, they can induce inflammatory delayed-type hypersensitive (DTH) and IgG antibody responses. Cysts of *Acanthamoeba* are therefore immunogenic and antigenic. Inflammation induced by these cysts is generally the cause of chronic scleritis that is found in 10–18% of patients diagnosed with AK.

Ectoparasites are parasites that reside on the outside of their host's body. *Varroa destructor* is an ectoparasitic mite of the domesticated Western Honey Bee, *Apis mellifera* (Nazzi and Conte, 2016). Their original host was *A. cerana*, a wild bee native to southern and eastern Asia. *V. destructor* then spread to domesticated bees in the early 20th century. This ectoparasite, which causes varroosis, has led to large economic losses in the beekeeping industry. The life cycle of *V. destructor* takes place entirely in the nests of *A. mellifera* either on immature or adult bees and is tightly synchronized with the life history of the host. *V. destructor* has two phases, a phoretic phase where it resides on an adult bee and a reproductive phase that takes place in a bee brood cell (**Fig. 3**). When inside the brood cell, the mite feeds on the bee's hemolymph and oviposits on the cell wall surface. When the adult bee emerges from the cell, so will the newly hatched mites, which will then transition into the phoretic phase on the adult bee. *V. destructor* seems to have a preference for drones over worker bees; queen bees are rarely parasitized. This preference may be due to larger amounts of attractants found in drone larvae or in the food of drone brood cells. Queen cells, on the contrary, contain octanoic acid, which is a repellant of varroa mites.

Mutualism

When interactions between two organisms are beneficial to each other, the relationship is known as a mutualism, of which there are number of different forms. Just as there is obligate parasitism, there is also obligate mutualism, such as the interaction between fig wasps (*Eupristina altissima*) and fig trees (*Ficus altissima*). Fig trees rely solely on fig wasps for pollination, and wasps needs fig trees to deposit and develop their eggs. This is also a form of dispersive mutualism as the fig wasp helps transfer fig tree pollen. Unlike typical pollinator-plant systems, the mutualism between fig wasps and fig trees are very specific (Dunn, 2020). The fig wasp pollinates only

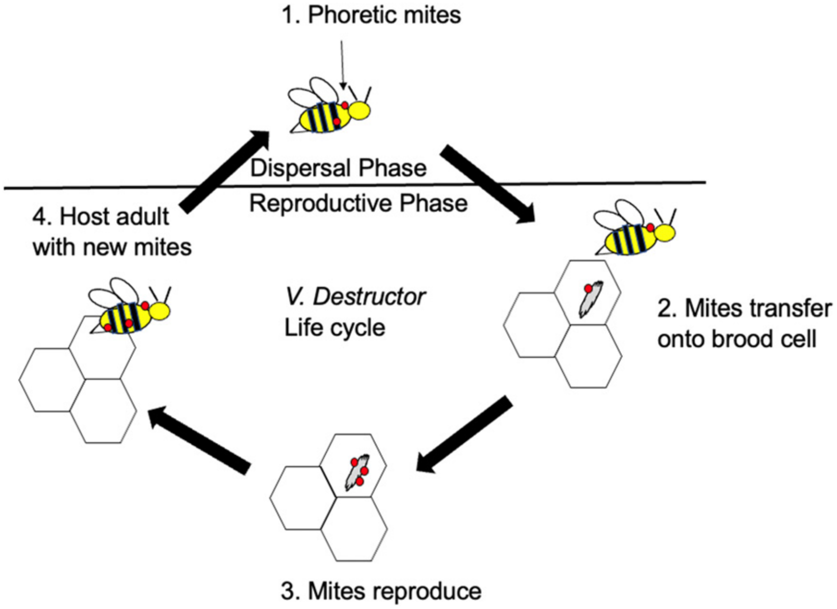

Fig. 3 Life cycle of *V. destructor* in the brood next of honey bees. The mites (shown as red dots) are present in both larval and adult stages of the bee.

fig trees, and fig trees are only pollinated by fig wasps. Thus, the benefits to both partners are reciprocated; wasps provide pollen to the plant whereas the host plant provides nutrients, shelter, and an egg depository for the wasp in the form of a fig.

A single fig tree flower ovary which is within an enclosed inflorescence known as the fig fruit typically can house only one wasp larvae. This causes the ovary to swell, forming a "gall." This gal however prevents seeds from being produced as the larvae feeds on the flower endosperm. Therefore, seed production occurs in ungalled flowers. Female wasps enter figs through a thin tunnel that leads to the cavity of the fig known as the lumen. The wasp will lay her eggs there, while at the same time transferring pollen onto the flower styles.

Mutualisms do not always have to be dependent on one another. This non-obligatory relationship is known as facultative mutualism. Seagrasses and bivalves, for example, can survive without each other, but they can form a mutualistic partnership. Seagrass beds trap suspended organic matter which helps them grow. However, the organic matter that builds up can decompose into sulfide from sulfate-reducing bacteria, which can be toxic to the seagrass. Lucinid bivalves contain sulfide-oxidizing bacteria that can reduce the amount of toxic sulfur surrounding the seagrass (Cardini *et al.*, 2022). Thus, bivalves and their bacteria benefit from the sulfide food sources in addition to oxygen released by the seagrass.

Symbiosis between seagrasses and lucinid bivalves also have a positive effect on sediments by increasing the redox potential. The seagrass *Cymodocea nodosa* enriches water in the sediment pores with dissolved organic carbon, which can be a nutrient source for sulfate-reducing bacteria (Cardini *et al.*, 2022). The presence of lucinid bivalves increases the biomass of *C. nodosa* seagrass most likely as a result nitrogen cycling, enabling more efficient uptake of nitrogen by the seagrass. This symbiosis allows them to persist in polluted environments. *C. nodosa* by themselves are very flexible and are able to resist polluted environments. *Loripes orbiculatus* bivalves, on the other hand, are susceptible to polluted environments without their seagrass partner. They are, however, able to persist in polluted environments in the presence of their seagrass partners.

In some facultative mutualisms, one partner can offer protection to the other, whether it would be from predators or other harm in the exterior environment. *Lagria villosa* beetles can harbor *Burkholderia* bacteria, which protects the beetles as well as their eggs from fungal infections (Florez and Kaltenpoth, 2017). *Burkholderia* symbionts are transmitted vertically by the adult female and are found on eggs and inside some of the compartments where the larvae live. Males carry them only in the larval stage and most likely lose them during metamorphosis. This preference for protection of female adults and larvae may be due to a balance of cost and benefits for symbiosis. Female adults pass the symbionts onto the next generation via vertical transmission; males cannot pass on these microbes through this mechanism.

Multiple strains of *B. gladioli* can also be found co-existing on their beetle hosts. Having more than one strain is thought to help inhibit the growth of antagonistic fungi by having a diverse array of secondary metabolites being produced by the different strains The co-occurrence of multiple *Burkholderia* strains is also found on hosts other than beetles such as stinkbugs, bordered plant bugs and in legume root nodules, but little is known as to what beneficial attributes are present in these associations. Additionally, defensive mutualism is not unique to beetles alone. *Enterococcus* symbionts have been shown to protect hoopoe bird eggs and adults from predators. Bryozoans have microbial symbionts that protect them in both adult and larval stages through the release of anti-predator toxins. These toxins are in the family of bryostatins and are produced by symbiotic bacteria known as *Candidatus* Endobugula sertula (Sharp *et al.*, 2007).

The Evolution of Symbiosis

How these three forms of symbiosis evolved likely differs depending on the organisms being studied. For microbial symbionts, what is common among the three forms is that all are derived from free-living microbes (Drew *et al.*, 2021). In most cases, free-living microbes evolve to become facultative symbionts, or in some cases, obligate symbionts. Horizontal gene transfer is one mechanism where free-living microbes become symbionts. These genes are typically involved in exploiting or benefiting the host, and include traits such as evading the immune system, fixing nitrogen, and producing bioluminescence.

Many mutualists are descended from parasites by evolving to become less harmful to their host, possibly driven by a lack of alternative hosts or an increase in parasite transmission linked to an increase in host fitness (Drew *et al.*, 2021). Some parasites may even develop mutations that are beneficial to their host. For example, the gut bacterial parasite *Enterococcus faecalis*, was experimentally evolved to develop mutations that increased the production of reactive oxygen species (ROS). The ROS were then used by their nematode host to suppress growth of the pathogen *Staphylococcus aureus*.

Some mouse experiments have shown how pathogenic bacteria can evolve from being parasitic to commensal. *Listeria monocytogenes* is a parasitic microbe that causes listeriosis (Cho *et al.*, 2021). *L. monocytogenes* has a surface protein called internalin A (InlA) that binds to the host small intestinal epithelial protein cadherin (E-cad) after an oral infection. This binding allows *L. monocytogenes* to move through the small intestine epithelium, leading to infections in internal organs. However, some mice can survive infections by an immune response of *L. monocytogenes*-specific $CD8^+$ T cells along with protection from gut microbiota through a process called "colonization resistance." Mice that are able to resist this late phase of infection by *L. monocytogenes* can still persist as a commensal in the lumen rather than penetrating the intestinal epithelium. *L. monocytogenes* also downregulates genes associated with virulence in response to host $CD8^+$ T cells. The pathogenic fungi *Candida albicans* can also undergo an evolutionary shift from parasitism to commensalism in mice. *C. albicans* completely loses its virulence genes unlike *L. monocytogenes*, where virulence genes are only downregulated (Cho *et al.*, 2021).

Chomicki *et al.*, 2020 found a number of pathways to mutualism. As the two species become dependent on each other, traits in each that promote the mutualism are selected for. For example, flowers with long styles become dependent on pollinators with long beaks or tongues. Additionally, other traits can be lost, which further selects traits that enhance the mutualism. One example is the mutualism between the ant, *Philidris nagasau* and the epiphyte, *Squamellaria*, which exists in the nests of their hosts. *P. nagasau* lost the ability to form their own nests, making them dependent on the plants to provide a suitable nesting place.

The extreme is when a mutualistic partner can force another to become dependent on it by restricting the partner's means of obtaining resources. For example, in the mutualism between the Central American ant and acacia plants, ants feed on the plant's nectar which contains enzymes such as chitinase and invertase. The ants also produce invertase, which cleaves sucrose, allowing them to harness energy from the sugar. However, the chitinase from the plant's nectar prevents the ant from producing invertase. The ant then becomes dependent on the plant's nectar for their source of invertase (Chomicki *et al.*, 2020).

One evolutionary outcome of mutualism is the prevention of exploitation. The ant-epiphyte mutualism provides a good example. The two partners co-evolved to become dependent on each other. The plant makes the ant more dependent by producing more rewards for the ants in the form of sugar. The sugar, however, can be exploited by other, non-mutualistic ants. The plant has therefore evolved a mechanism to prevent this by concealing the sugar so that only the specific mutualistic partner ant can access it. Another example of host driven evolution are legumes that prevent nonfunctioning nitrogen-fixing bacteria from colonizing their roots by blocking resources to those bacteria. Additionally, legumes can also reward beneficial fungi with extra carbohydrates. The host prevents parasitism from arising, while at the same time promoting mutualism.

Once dependency is lost, the mutualism can then cease to exist. This loss can happen in a number of ways, such as by reversion to a free-living life style, the extinction of one partner, or partner switching. For example, *Cecropia* plants host ants that are specific for those hosts. However, *Cecropia* can lose them in some parts of their range – higher elevation or islands – where the ants are not present. The extinction of a partner is more profound in obligate mutualisms. Corals, for example, are dependent on their zooxanthellae symbionts. As temperatures increase due to climate change, their symbionts are expelled, leading to the death of the corals.

Mutualists can also evolve to become parasites, although this is uncommon. The bacterium *Parachlamydia acanthamoeba* is normally a symbiont of the amoeba *Acanthamoeba*. Recent data experimentally evolved this species to become parasitic to its host over multiple generations. Traits that allowed parasitism to evolve were linked to machinery for host cell manipulation such as the type III secretion system (Drew *et al.*, 2021). Conversely, commensals can also evolve to become parasites. *E. coli* typically act as commensals in the guts of mice. Previous evidence demonstrated that older mice with inflamed guts had strains of *E. coli* with mutations connected to stress and virulence (Drew *et al.*, 2021). For humans, mobile genetic elements can cause *E. coli* to become enteropathogenic (EPEC) and enterohemorrhagic (EHEC) pathogens (Croxen and Finlay, 2010). Another example are cheater fig wasps that evolve from mutualistic fig wasps to become parasites; they feed within the figs of their plant host without providing the benefit of pollination (Chomicki *et al.*, 2020).

Current Model Systems

There are a number of model systems that researchers use to study aspects of coevolution in symbiosis. From these studies, we can gain a better understanding of how organisms interact with each other and their evolutionary life history patterns. One such model is the interaction between the bacterium *Xenorhabdus nematophilus* and its host nematode *Steindernema carpocapsae*. This type of symbiotic model system is useful since it involves both mutualistic and parasitic characteristics (Koch and McFall-Ngai, 2018). *S. carpocapsae* juveniles are able to infect a number of arthropod species. *X. nematophilus* are then released from the juvenile hosts, and invade the arthropod as parasites that release toxins that kill the arthropod (Koch and McFall-Ngai, 2018). Mutualism between the bacterium and the nematode subsequently take place as both feed upon the arthropod carcass for its nutrients (Stilwell *et al.*, 2018).

This is an ideal model system because the host nematode is small and transparent, allowing visualization of the organ where the bacterial symbiont resides through the use of fluorescent proteins (Stilwell *et al.*, 2018). Additionally, both host and symbiont are easy to culture, and their genomes are fully sequenced (Koch and McFall-Ngai, 2018). Having these model systems is vital because they can provide information on many different processes general to symbiosis such as signaling, recognition, persistence, host development, and nutrient exchange. Nematodes and other bacterial symbionts have also been used as model systems to study other aspects of symbiosis. These include entomopathogenic nematodes and gammaproteobacterial symbionts, the marine nematode *Laxus oneistus* and their *Wolbachia* bacterial symbiont, and *Caenorhabditis elegans* nematodes with their diverse array of microbial symbionts.

Another model system that has been studied for more than 30 years (Koch and McFall-Ngai, 2018) is the interaction between bobtail squids (Cephalopoda; Sepiolidae) and their symbiont, the bioluminescent bacterium *Vibrio fischeri*. The squid is a nocturnal predator and is able to harness their symbiont's bioluminescence for a process called counterillumination as shown in **Fig. 4** (Jones and Nishiguchi, 2004). What makes the squid-*Vibrio* symbiosis an ideal model system is that both the host and symbiont are culturable, and their genomes have been sequenced to allow the investigation of symbiosis related genes in both organisms (Koch and McFall-Ngai, 2018).

As with nematodes, each stage of colonization of the squid can be visualized by microscopy. This symbiotic model system was the first to reveal the function of symbiont microbe-associated molecular patterns (MAMPs) in the morphogenesis of squid host

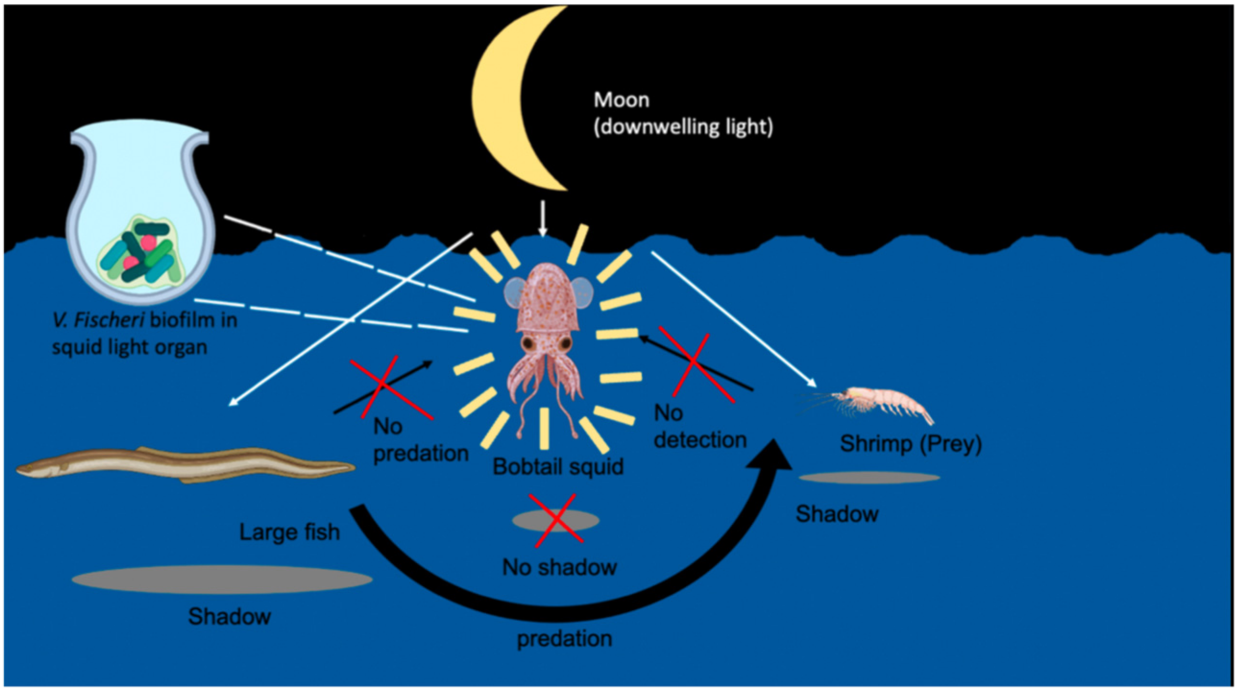

Fig. 4 The process of counterillumination camouflages bobtail squids from both predators (large fish) and the squid's prey (shrimp). The light produced by their *Vibrio* symbionts matches downwelling moonlight, which prevents the squids from casting a shadow below, allowing them to disguise themselves when out hunting at night.

tissues during colonization (Koch and McFall-Ngai, 2018). This model also led to the discovery of how symbionts influence host circadian rhythms, and how genetic changes in the symbiont effects the range of hosts they can infect (Chavez-Dozal *et al.*, 2014).

The squid-*Vibrio* model system usually involves studies of the light organ in which the *Vibrio* symbionts reside. However, bobtail squids also have another organ that is useful for studying symbiosis. Females of sepiolid squids have an organ called the accessory nidamental gland (ANG), which is responsible for producing the outer coat of the eggs during deposition. Bacteria from the ANG are also deposited in this coat, providing anti microbials/fungals that help protect the eggs from biofouling. Results from cultured ANG bacteria demonstrated that these bacteria were found to produce secondary metabolites through genomic and chemical analyses. Therefore, the squid-*Vibrio* system can be used as a model to study both binary and a consortium of symbionts (Koch and McFall-Ngai, 2018).

Other aquatic organisms such as fish are also good models for studying symbiont consortia. Zebrafish have been used as a model to study vertebrate microbiome processes such as tissue development and function (Zhong *et al*, 2022). Zebrafish larvae are also transparent, which allows for visualizing the dynamics of bacterial colonization. Zebrafish have high fecundity and develop outside of the uterus. These two features allow researchers to have a large pool of microbe-free animals that can be infected with a controlled set of microbes, thus identifying the bacterial strains and proteins needed for development, including pancreatic beta cell mass and intestinal inflammatory tone.

Symbiosis between the sea anemone *Nematostella vectensis* and its microbiota is used to study colonization during host development. This sea anemone has three developmental life stages where the microbiota changes with each developmental period. Interactions between bacteria during host colonization have uncovered specific interactions that coincide with the developmental stage of the host. Another model cnidarian, the sea anemone *Aiptasia pallida* and their algal symbionts are useful for modeling symbiosis between stony corals and reefs. Most stony corals are difficult to culture in the lab and often endangered. *A. pallida* are easy to rear and have the same algal symbionts as corals (Bosch *et al.*, 2019). For example, this symbiotic model found that the algal symbionts produce the osmolyte floridoside, which scavenges oxygen. Floridoside production was shown to be correlated with an increase in salinity, whereas reactive oxygen species leakage was reduced. This finding was confirmed to occur among corals during coral bleaching in warming ocean waters.

The symbiosis between *Hydra vulgaris* and its microbiome provided new findings in evolutionary immunology (Bosch *et al.*, 2019). The epithelium of *H. vulgaris* is covered with a number of symbiotic microbes, which are important for maintaining homeostasis of their tissues and their overall health. Both the epithelium and parts of the innate immune system work together in selecting the particular microbiota. Earlier studies hypothesized that host-specific antimicrobial peptides evolved as a result of pathogens, but work on *H. vulgaris* and their microbiome instead suggests that these peptides may have evolved to control beneficial microbes. Even though the epithelium is the main regulator of the microbiome of *H. vulgaris*, this model provides information on how other organ systems can regulate symbionts. For example, the *H. vulgaris*-microbiome symbiosis showed that the nervous system has a role in controlling beneficial bacteria through the use of neuropeptides. These microbes were shown to control *H. vulgaris'* behavior by interacting with their neuronal receptors.

Emerging Models

Other model systems are also being developed. One emerging model for studying coral symbioses is the upside-down jellyfish, *Cassiopea xamachana* and its algal symbiont, *Symbiodinium microadriaticum*, which is also a symbiont of corals. Unlike corals, *C. xamchana* reproduces daily, which allows for readily available single-cell embryos for study. Polyps can be maintained as immortal lines in the lab and symbiont-containing scyphistomae can live indefinitely as long as they are well maintained under constant conditions. Dinoflagellates within the amoebocytes regulate photosynthesis as long as their jellyfish host are in shallow water receiving sufficient sunlight. Much of the fixed carbon needed to satisfy the energy requirements of the jellyfish may be derived from this process implemented by the symbiont. *C. xamachana* can switch between asexual polyps known as scyphistomas and the sexual stage known as the medusa. Scyphistomae reproduce asexually by budding or strobilation. Symbiotic dinoflagellates, a type of unicellular algae is needed to start the process of strobilation. After the scyphistomae finds a surface to settle on, they metamorphize into polyps and form a mouth and endodermal digestive cells known as the gastrodermis where uptake of the symbiotic dinoflagellates occurs from the surrounding water (Medina *et al.*, 2021).

The symbiosis between sponges and their microbial symbionts is used to study host-microbial interactions among basal metazoans (Pita *et al.*, 2016). Many sponges from the phylum Porifera house a diverse microbiome in their mesohyl matrix, including more than 40 microbial phyla of which the most numerous are *Proteobacteria*, *Chloroflexi*, and *Crenarchaeota* (Pita *et al.*, 2016). Certain sponge species are easily accessible, especially those that are found in shallow water and collected by snorkeling, including *Amphimedon queenslandica. Rhopaloides odorabile*, and *Cymbastela concentrica*, which are all found in the Great Barrier Reef. Some sponges that can be kept in the lab for long-term studies including *Aplysina aerophoba, Ircinia strobilina*, and *Mycale laxissima*. Many species of sponges can create clonal populations thanks to gemmulation or budding. Sponge fragments therefore can be used generate clones that have the same genetic background in smaller sizes with many replicates.

Aposymbiotic animals are also crucial for comparative studies when performing research on symbiotic relationships. Even though the microbiota on sponges seems to be resistant to antibiotics, which are generally used to create aposymbiotic animals, there are sponges that are naturally aposymbiotic. Such species allow natural comparisons of host growth and reproduction with and without a symbiont. The Mediterranean sponge *Petrosia ficiformis* typically contains its cyanobacterium symbiont, *Synechococcus feldmannii*. Aposymbiotic *P. ficiformis* can also be found in the wild, particularly in caves where there is a lack of light. Another candidate is the Caribbean sponge *Xestospongia muta*, which loses its symbionts following cyclic bleaching. Studies in sponges have revealed a number of pattern-recognition receptors (PRRs) that have an important role in sensing symbiotic microbes. PPRs can induce responses ranging from defense against parasitic microbes, to upregulating microbiota homeostasis. The vast range of symbiosis in sponges make them an ideal candidate for studying phylogeography and co-evolution of host-microbial symbiosis.

Another emerging model for studing vertebrate gut microbiomes is the cardinalfish, *Siphamia tubifer*, and its bioluminescent symbiont *Photobacterium mandapamensis* (Gould *et al.*, 2022). Cardinalfish live in coral reefs ranging from East Africa to French Polynesia. They are also easy to collect as they reside in shallow waters and can be maintained with their symbionts and as aposymbiotic animals. Mitogenomic analysis suggest that *S. tubifer* diverged from the cardinalfish family, Apogonidae, around 50 Mya. The symbiosis with its bioluminescent bacteria is thought to have a role in this divergence.

Implications of Symbiosis

Beyond the obvious individual-level effects, symbioses can have much broader effects. Parasitism unsurprisingly can have devastating effects on agriculture. Plant parasites can become invasive when they are transported around the world on agricultural products. Plant-parasitic nematodes are known to cause problems in growing vegetables such as cucumbers, green peppers, carrots, eggplants, basil, and celery. Overall, nematodes are known to result in crop loss worth billions of dollars every year (Tileubayeva *et al.*, 2021). The most common type are root-knot nematodes (RKNs) of the genus *Meloidogyne*. They are ubiquitous in Spain, leading to yield loss of 85% of cucumbers, 59% of tomatoes, 40% of zucchinis, 36% of watermelons, and 29% of lettuce. Yield losses are further exacerbated by secondary infections caused by the transmission of fungal and bacterial pathogens. Understanding how beneficial bacteria contribute to the health of the nematode will allow the development of molecular methods to reduce nematode fitness and the dependence of pesticides used to kill this agricultural menace.

Teasing apart symbiotic associations can have positive insights as a source of new innovations such as antibiotics (**Table 1**; Gogineni *et al.*, 2020). Antibiotic resistance usually results from mutations or horizontal gene transfer, which allows for the acquisition of resistant genes. Cases of antibiotic resistant pathogens have been increasing over the past 60 years. Projected outcomes of this resistance are that by 2050 around 10 million people could die due to antibiotic resistance in microbes.

A good source of novel antibiotics are symbionts of marine sponges, which harbor a vast number of microbes from diverse lineages. A little over half of a marine sponge's dry weight can be symbiotic microbes. 80% of antibiotics currently derived from marine sources come from various species of *Actinomyces* that inhabit sponges. Some examples of antibiotics produced from

Table 1 List of hosts and their symbionts that have been the sources of antibiotics

Host	*Symbiont*	*Secondary Metabolite*	*Target Organism*
Algae	*Phaeobacter inhibens*	Roseochelins B	*Emiliania huxleyi*
Algae	*Aspergillus tennesseensis*	Diphenyl ethers	*Bacillus subtilis*, *Gaeumannomyces graminis*, and *Cochliobolus heterostrophus*
Brown algae	*Trichoderma asperellum*	Tricholumin A	*Glomerella cingulata*
Palythoa haddoni	*Cochliobolus lunatus*	Resorcylic acid lactones	*Phytophthora infestans* and *Plasmopara viticola*
Sponges	*Micromonospora*	Manzamines	*Plasmodium berghei*, *Leishmania*, and *Mycobacterium tuberculosis*
Hymeniacidon perleve	*Pseudoalteromonas piscicida*	Norharman	Various microbes
Aplysina aerophoba	*Bacillus subtilis*	Surfactins, iturins, and fengycins	*Agrobacterium tumefaciens*, *Proteus vulgaris*, *Staphylococcus aureus*, *Clavibacter michiganensis*, *Escherichia coli*, *Bacillus megaterium*, *Paecilomyces variotii*, and *Candida albicans*
Cold-water corals	Actinomycetes	Anthracimycin	Gram-positive bacteria
Seaweed *Ulva* sp.	*Streptomyces althioticus* MSM3	Desertomycin G	*Mycobacterium tuberculosis*

Note: Gogineni, V., Chen, X., Hanna, G., Mayasari, D., and Hamann, M. T. (2020). Role of symbiosis in the discovery of novel antibiotics. The Journal of Antibiotics. 73, 490–503.

marine symbionts include mandelalides, which are made from *Verrucomicrobia* bacterial symbionts of the ascidian *Lissoclinum*. The fungus *Cochliobolus lunatus*, which is a symbiont of the sea anemone *Palythoa haddoni*, produces resorcylic acid lactones that have inhibitory effects on pathogenic fungi. One such lactone is zeaenol, which is known to have powerful anti-fungal effects against crop pathogenic fungi including *Phytophthora infestans* and *Plasmopara viticola*. Actinomycetes from the genera *Micromonospora* are known sponge symbionts that produce manzamines, which have anti-protozoan activities against the malaria-causing parasite, *Plasmodium berghei*. This compound also has antibiotic activity against *Leishmania* and *Mycobacterium tuberculosis*, the causative agents of leishmaniasis and tuberculosis.

On a broader scale, symbiosis also plays an important role in ecological restoration. Symbiotic associations in coastal habitats has been used to help restore important keystone species (Farrer *et al.*, 2022). These areas are important reservoirs of biodiversity and offer vital ecosystem services. Coastal habitats are facing stresses such as degradation in salt marches and sand dunes due to global warming, industrial and agricultural pollution, and oil spills. Symbiotic microbes can help plants grow under these stressful conditions. For example, microbial endophytes that reside in plant seeds can raise their rate of germination and mycorrhizal fungi help plants with establishment. Rhizobacteria stimulate plant growth via nitrogen fixation, nutrient acquisition, and supplying plant growth hormones. Additionally, competitive symbionts may help reduce the presence of the pathogenic fungi known to devastate plants in coastal areas.

Restoration efforts through inoculation of microbial symbionts may be one mechanism of conserving key species. Inoculation can vary as this may include a consortium of microbes from soil, to a single taxon of microbes. The type of inoculum will depend on the plants residing in the coastal areas of interest. Some plants such as pines, oaks, birches, and eucalyptus contain only ectomycorrhizal symbionts. Rhizobacteria that promotes plant growth are typically generalists, but their growth promoting activity is linked with plant genotype. Therefore, it is probably conducive to use soil inoculum from plants of similar habitats for restoration efforts rather than from commercial inoculum.

Conclusions

We presented many different examples of symbiosis. All three types – commensalism, parasitism, and mutualism – are found in virtually all forms of life including humans. Therefore, studying different symbiotic systems in other organisms can give insight as to how humans interact with our symbionts. Commensalism, where one partner benefits and the other is neither harmed or benefited is found in a wide variety of organisms, including our microbiota within our guts as well as on our skin. Some forms of commensalism include phoresy, inquilinism, and metabiosis. Parasitism, where one partner benefits and the other is harmed, includes obligate, facultative, and ectoparasites. Studying parasites is key to understanding pathogens in general as well as those that cause inherit harm to their host. Ectoparasites are an interesting case as these involve eukaryotic organisms including humans. On the other end of the symbiotic spectrum is various types of mutualism – obligate, facultative, and defensive – where both partners benefit from the interaction. Mutualism, especially those that are obligate, are vital for host organisms to live. Some of them such as corals are highly dependent on their symbionts.

The three main types of symbiosis discussed are fluid in that symbionts in some cases can switch from one form of symbiosis to another. This has been observed in the opportunistic pathogen *C. albicans* that can change from a commensal to a parasite depending on certain environmental conditions. This change in one type of symbiosis to another gives clues in how certain forms of symbioses have evolved. Although all forms of symbioses can arguably be derived from a free-living ancestor, many cases involve evolving from one form of symbiosis to another. This includes evolving from a mutualist to a parasite, or vice versa.

The subcategories of each symbiosis presented here are not the only types but may also have multiple or slightly different definitions. This includes phoresy and metabiosis. Some definitions of phoresy overlap with parasitism. Metabiosis in some cases refers to living off an environment created by another organism that has passed away. Therefore, when studying and using these terms, one should be mindful of the context.

Symbiosis can be a difficult to study, particularly when the symbionts are difficult to culture in the lab. Thus, model organisms that can be grown in the lab are useful for discovery of novel genes and pathways. Some of the current model organisms include the nematode-*Xenorhabdus*, squid-*Vibrio*, and sea anemone-algal symbiotic systems. *Hydra* is a good current model organism for studying symbiosis with symbiotic microbiomes. Yet even these current models have drawbacks and limitations. Fortunately, new models are emerging that will allow us to study other aspects of symbiotic systems, such as the upside-down jellyfish – algal symbiosis for exploring coral reef symbiotic systems, or the use of the cardinalfish to study symbiotic systems involving vertebrate gut microbiomes.

Symbiosis is an important field to area of study as virtually all living organisms have symbionts, that affect their hosts in multiple ways. The diversity of these associations, and the extent to which each partner benefits or suffers demonstrates the broad spectrum of specific ecological niches that have driven the evolution of each interaction. Knowing more about the variation across systems and the degree to which host and symbiont are intricately tied to one another will help shed light on how microbes have shaped the diversity of life on Earth.

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