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Is biological interaction about to supplant the notion of organism?

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Résumé

Une double prise de conscience a émergé en biologie, en ce début de XXI^e siècle : les microbes sont partout, et ils tissent, au-delà des maladies ou de la décomposition, des relations vitales, à bénéfices mutuels, avec les plus gros organismes. L'ensemble des fonctions des plantes et des animaux est affecté par le microbiote qu'ils contiennent et qui influe sur leur nutrition, leur santé et leur développement (et, dans le cas des animaux, leur comportement). Ce texte est une présentation générale de la présence physique et fonctionnelle des microbiotes, et des modalités d'acquisition de celui-ci. On y discute la notion d'individu et d'organisme face à l'émergence de l'holobionte, et aussi de la force des interactions et des réseaux d'interactions dans les écosystèmes.

Abstract

Two revolutions have emerged in biology at the beginning of the twenty-first century: microbes are

everywhere, and, beyond diseases or decomposition, they weave vital relationships with mutual benefits with larger organisms. All the functions of plants and animals are affected by the microbiota that they contain and which influence their nutrition, health but also development (together with, in the case of animals, behavior). This text is a general presentation of the physical and functional presence of microbiota, and how it is acquired. It discusses the notion of the individual and organism, facing the emergence of the holobiont, and also the strength of interactions and networks of interactions in ecosystems.

Mots clés

endophyte, holobionte, interdépendance, microbiote, mycorhize, organelles, souris axénique.

Keywords

axenic mice, endophyte, holobiont, interdependency, microbiota, mycorrhiza, organelles.

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Introduction

The dominant Western view of biology since the 19th century has been based on the concept of the organism, i.e., a living entity that by and large is structurally and functionally independent (we speak of the biology of organisms). We generally approach this view through the description and naming of the species (“a rabbit”) and functional analysis in the “physiology of the organism.” The organism is imagined regardless of scale, but once we go below one millimeter we add the prefix “micro”, as if to distinguish at all costs two worlds, the visible and the invisible: on the microscopic scale, therefore, we speak of microorganisms, or microbes.

In recent years, albeit with remarkable epistemological slowness, the scientific community has belatedly and gradually come to see that the macroscopic functions of animals and plants are accomplished through interactions with microbes. One determinant in this has been the possibility, using the tools of molecular biology, of describing extremely diverse microbial communities associated with animals and plants, without the need for culture or direct observation, which long delayed awareness of the taxonomic and functional diversity of these communities. The sequencing techniques (Buermans and Den Dunnen, 2014) which simultaneously determine the primary structure of numerous mixed fragments of DNA, enable the description of the composition, even genetic, of highly diverse and complex microbial communities.

This is doubtless one reason why there is now greater recognition of the microbial diversity present in animals and plants. But a functional approach has also emerged in parallel. In the last ten years, microbial communities and their roles have been described in all large organisms, not only in the digestive tract of mammals, but also of insects, or in plant roots and flowers, and even in algae.

This is how the concept and the importance of cooperation with microbes, which is widely acknowledged among specialists in symbiosis (Margulis and Fester, 1991; Selosse *et al.*, 2004) but has long been marginalized, have finally spread to biological research as a whole.

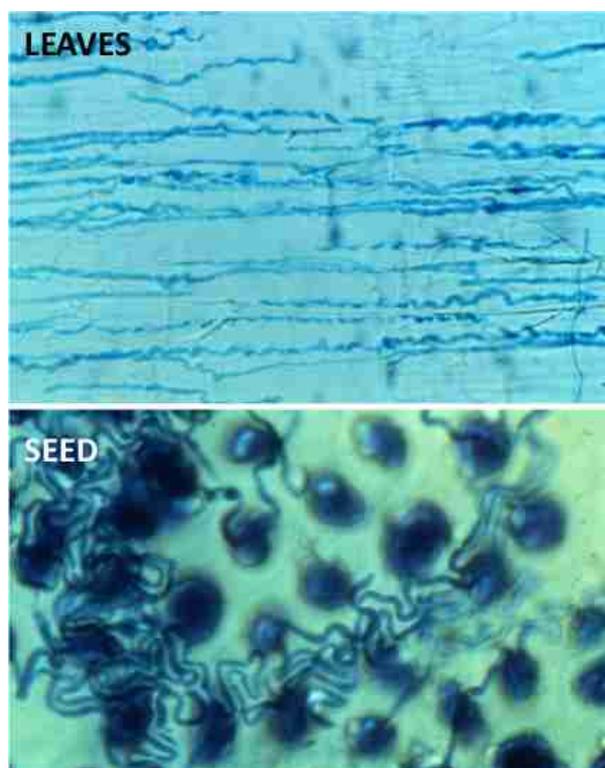


Figure 1. Kentucky 31 and its fungal endophytes Neotyphodium (stained in lactophenol cotton blue staining) in leaf tissues and in seed tissues.

Colonizing microbes shape their host's ecology and vice versa

Microbes are ubiquitous and, although their presence is discreet, they may have a major impact everywhere, as witnessed by a terrible agronomic mistake made in North America. In 1931, the University of Kentucky began a program to improve tall fescue (a grass) to enrich the pastures of the American West. After the selection of the most competitive plants, the cultivar *Kentucky 31* was marketed in 1943 (Saikkonen, 2000). Widely sown, it quickly formed dense prairies. Alas, cattle feeding on it soon developed “fescue foot:” vasoconstriction of the extremities leading to gangrene and tail loss, hooves sloughed off, stress behavior, nocturnal activity, 30 % drop in milk and meat production, and more

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frequent abortions (Bacon, 1995). *Kentucky 31* today is an invasive plant that has cost agriculture dear (Clay and Holah, 1999).

What was the cause of fescue foot? The culprit was unmasked as an ascomycetes (fungus) of the genus *Neotyphodium*, which lives within the plant and produces ergot alkaloids (figure 1). Some of these fungi are toxic for insects, others for mammals: among their mycotoxins, ergovalin is a vasoconstrictor that explains the gangrene of the extremities in cattle; lysergic acid (from which the psychedelic drug LSD is derived) alters behavior. However, and this is what led to it being overlooked, this fungus is invisible as it never “leaves” the plant and so produces no sporulating lesion: it colonizes all the plant tissues and, in particular, the seeds. It reproduces by transmission to the offspring (figure 1), and unwittingly this led to selection of the most toxic fungi, which improve plant growth because their repellent effect wards off herbivores (Tanaka *et al.*, 2005)!

Major properties (economic and ecological in this case) of large organisms sometimes result from the microorganisms that live within them. Such microbial contributions are often decisive: if the fungus in cultivar *Kentucky 31* is removed by antifungal treatment or by mild heating of the seeds, the plant becomes more palatable to herbivores and so does not become lastingly established in nature (Clay and Holah, 1999). It is the plant-fungus consortium that is competitive!

Plants and animals are therefore inhabited by microbes that shape their traits. This gave rise to the concept of holobiont (Zilber-Rosenberg and Rosenberg, 2008; Theis *et al.*, 2016) (from the Greek *holo*, whole, and *bios*, life), which designates the biological unit composed of a host (plant or animal) and all its symbiotic microbes (in the largest sense, being symbiotic does not necessarily mean mutualist interaction but rather an interaction within the gradient from parasitism to mutualism). The holobiont concept replaces the vision of isolated organisms, because all organisms, as we shall see, are accompanied. The holobiont cumulates the properties of the host organism and of its symbiotic passengers (like the alkaloids of *Neotyphodium*), all the genomes of

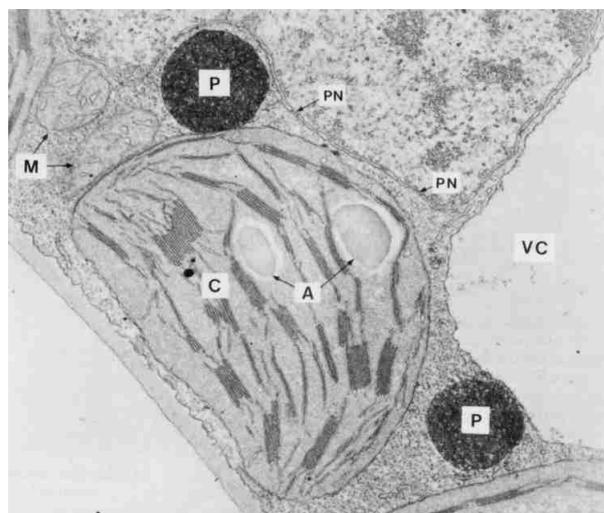


Figure 2. A plant cell with mitochondrion (M) and chloroplast (C), two organelles of endosymbiotic origin.

which the host assembles. Emergent properties also occur. It is often asserted that the holobiont has an evolutionary dimension (i.e., a new entity subject to natural selection), but while it is clear that the holobiont contributes to the success of its members as a target for selection, it is not itself fully reproduced (see below) and this evolutionary approach is debated (Douglas and Werren, 2016). The holobiont leads to the notion of hologenome, which extends the genome of the organism by adding those of its microbes. How are the associations that structure holobionts set up? How and via which functions do they modify the host? We shall see that biological interactions between the host and its microbes act powerfully on the evolution of both.

Inherited microbes and hitchhiking microbes

A holobiont teems with microbes. A recent reassessment of the quantity of microorganisms carried by humans suggests that the human body has as many microbial cells as human cells: if we ignore the non-nucleated and abundant red blood cells, there are ten microbial cells for every human cell (Sender *et al.*, 2016). And this inventory does not include

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mitochondria! Some of these microbes are inherited, while others are transient. Some, like *Neotyphodium*, are inherited and persist from generation to generation without leaving the host. Far from being the most frequent, these microbes are often interlinked with holobiontic functions so closely that they may be discovered late in the history of science, as with *Kentucky 31*. For example, mitochondria, which are responsible for respiration and numerous biosyntheses in eukaryotes, are bacteria that have lived in our cells for aeons (figure 2).

Although early observers guessed that this was the case, because mitochondria divide in two like bacteria, the idea took a long while to catch on. The elucidation, in the early 20th century, of the biochemistry of respiration revealed close ties between respiration and the rest of cellular metabolism, and this functional unity tended to marginalize the idea that mitochondria are of bacterial origin (Margulis, 1970). The discovery that mitochondria contain DNA and a reduced bacterial genome firmly established their bacterial nature after the 1970s, driven by the overarching vision of Lynn Margulis (Margulis, 1970). Respiration and the eukaryotic cell are therefore holobiontic states that cannot, in evolutionary terms, be reduced to one organism with a single origin.

The same is true for photosynthesis: algae and plants photosynthesize using plastids (figure 2), cellular organelles that also contain a reduced bacterial genome and which are, in fact, intracellular photosynthetic cyanobacteria. Some vital cellular properties therefore are those of microbes that long ago became heritable. These microbes remain because within the cell they acquired two properties: division in the cell and transmission to host daughter cells – notably, the reproductive cells, spores or gametes (often the ovule). So, plastids and mitochondria are intracellular bacteria, though their extreme dependence on the cell host and their status as organelles lead some authors to consider that they are no longer bacteria. This is naturally a question of definition, but it also ignores that all organisms are dependent (so, dependence is not itself a criterion). Here, and for heuristic reasons

(Pallen, 2011; Selosse, 2011), we shall consider the bacterial nature as being of phylogenetic origin (eubacterial) – the bacteria can be more or less free or dependent and become organelles when they import some or all of their proteins.

Insects contain bacteria in advanced states of dependency. Their hereditary interactions with microbes have enabled the diversification of ecological niches, through feeding on a wide variety of foods (Moran *et al.*, 2008). The 4000 species of aphids, for instance, have become feeders on plant sap thanks to the heritable bacteria *Buchnera*, which complete the nutritional needs of aphids by synthesizing tryptophan, leucine, and vitamins absent or in too low amounts from sap (Jiang *et al.*, 2013).

Other insects can feed on blood because although it is poor in vitamins of the B group (thiamine, folate, thiamin precursors, etc.) these are produced by inherited bacteria: *Wigglesworthia* in tsetse flies, *Riesia* in fleas, and *Wolbachia* in bedbugs. Some insects that feed on dry, vitamin-poor foodstuffs benefit from food complements synthesized by yeasts. Examples are the coleoptera called drugstore or bread beetles (*Stegobium paniceum*) and cigarette beetles (*Lasioderma serricornis*). In the latter, yeasts detoxify nicotine, which is normally insecticidal (Dowd, 2007).

The bacteria involved in these endosymbioses have extremely reduced genomes, 5 to 30 times smaller than that of *Escherichia coli*. The genome of *Carsonella*, an endosymbiont of the sap-sucking hemiptera *Psylla*, is reduced to 160 kb (180 genes) (Moran and Cutcheon, 2011). What with specialization in a metabolic function and regression of functions associated with living independently, these bacteria have lost many genes and have become closely dependent: like cellular organelles, certain endosymbiotic bacteria import some of their proteins (Nakabachi *et al.*, 2014). Here we have reached the point where mitochondria and plastids have acquired the full status of organelles. Inherited bacteria have therefore contributed to the extensive evolutionary diversification of insects.

The heritable part of the holobiont, the inherited

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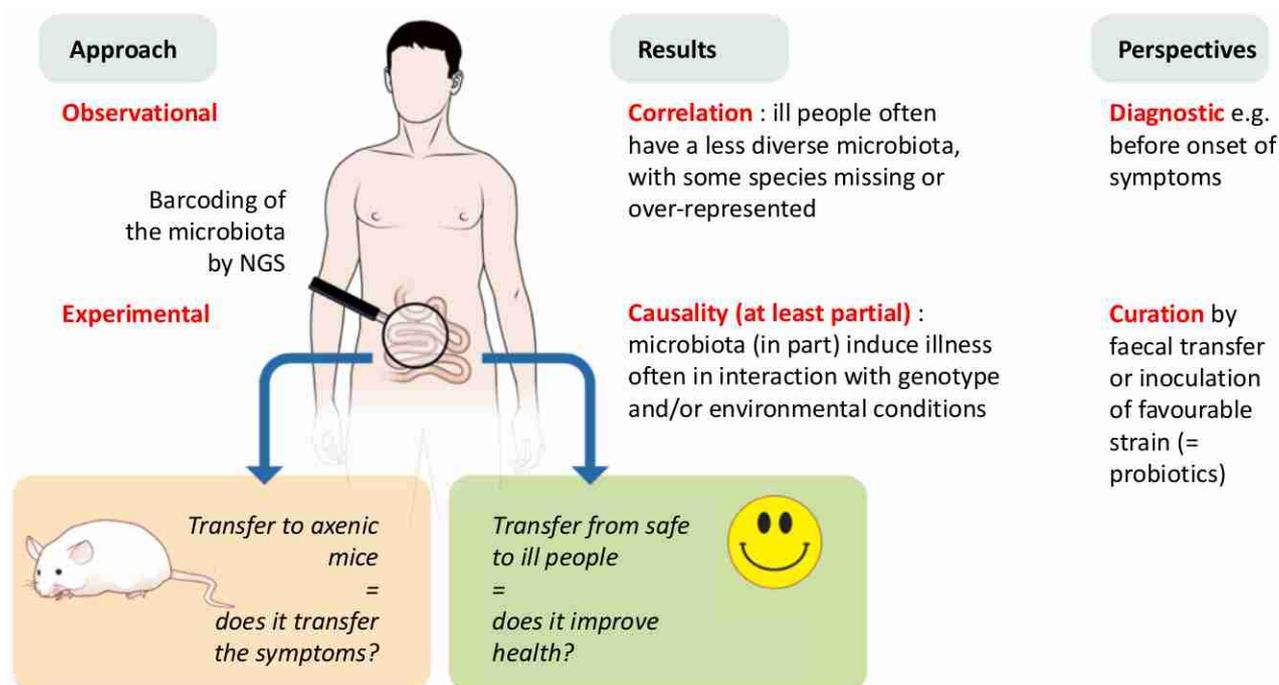


Figure 3. Investigations on gut microbiota.

endosymbionts, are, however, less diverse than the symbionts that "climb aboard" at each generation. At germination or at birth, a microbial horde colonizes the organism, in particular on the surfaces where the organism feeds. There are often-overlooked resemblances between roots and the gut, not only in nutritional function, but also through the great microbial diversity recruited at each generation (Mommer *et al.*, 2016). The soil surrounding the root, the rhizosphere, is enriched in dead cells and secretions and attracts myriads of fungi and bacteria – from 100 to 1,000 millions per gram of soil. The root takes up mineral resources and emits molecules that create conditions that filter a specific community from the soil (Müller *et al.*, 2016). The gut also harbors an abundant microbial community: each human being harbors more than 1,000 species of bacteria and yeasts (more than one kilogram) and has as many bacteria as body cells (Sommer and Bäckhed, 2013). This represents a tremendous diversity of genes: the microbiome (i.e., the sum of the genomes of the microbiota) in humans exceeds by 100 times our own coding capacity. Nourished by ingested foodstuffs, the intestinal

community is also filtered from the environment by feeding behaviors, the conditions (anaerobiosis and the presence of enzymes) and the immune system, which determines which microbes thrive.

Vertical and horizontal transmission have their advantages

Microbial passengers are either acquired at each generation, or ever-present heritable partners: which most favor the host? All depends on the criteria used. Inherited microbes are less varied (no choice of partner in this case) than those recruited at each generation, which are of such variety that they can adapt to different environments and new food. Our gut microbiota, for example, adapt us to our diets: Asians have bacteria that oxidize a toxin of soybeans (daidzein, a natural endocrine disruptor) (Gaya *et al.*, 2016); the Japanese have others that digest the walls of the red algal cells that are characteristic of their cuisine, such as the edible seaweed nori (Hehemann *et al.*, 2012).

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However, an inherited microbe is reliable, whereas a recruited microbe might be scarce in some places. The germination of orchids depends on soil fungi that feed the seedling and anyone who has tried to sow orchids in their natural milieu will have failed in many places because of a lack of suitable fungi (Hehemann *et al.*, 2012). This is doubtless why some orchid species are rare (McCormick and Jacquemyn, 2014).

Microbes present for the duration and microbes that hitch a ride also differ in the mechanisms that avoid unfavorable partners. Microbes inherited long ago tend to be more favorable to the host: their reproduction depends on that of the host, so those that favor their host are, of course, selected because they reproduce more (Sachs and Wilcox, 2006). Vertical transmission, if strict, favors the emergence of mutualism. This selects mitochondria, plastids, or the fungi of *Kentucky 31* that are favorable for the host (a variant of this is the pseudo-vertical transmission (Wilkinson, 1997), where environmentally acquired microbes are these from the parents that are around the offsprings).

The environment, on the other hand, can be a source of good and bad, such as a root parasite or an intestinal illness. On the one hand, the locally available microbes are more likely to be adapted to the site where they occur, and thus resent a novel source of adaptations. On the other hand, microbes that hitch a ride can take advantage of resources provided by the host, to which their future is not definitively tied. To counter this, the host deploys the "carrot and stick" strategy.

Carrot-wise, the host actively attracts favorable microbes. A plant root, for example, emits strigolactones (hormones also involved in interactions with fungi after secretion in soil) and these are recognized by favorable soil fungi, which colonize the roots of 90 % of plants thereby forming a mixed organ called the mycorrhiza (Gough and Bécard, 2016). These soil fungi exchange sugars for mineral salts and water collected by the root from the soil. Legumes have roots that emit flavonoids, which attract rhizobia, soil bacteria that colonize the roots by producing nodules where they transform atmospheric

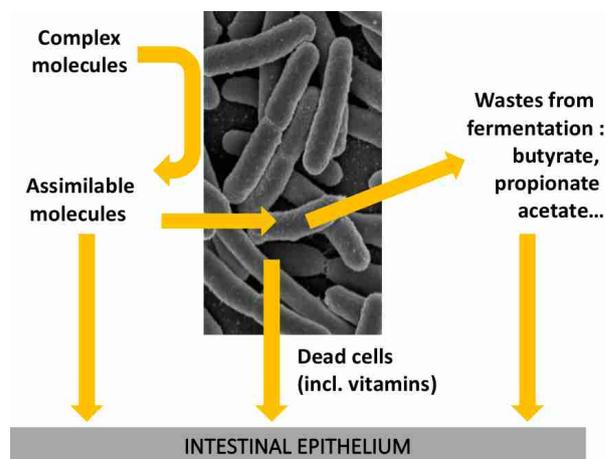


Figure 4. A summary of the roles of gut microbiota in digestion.

nitrogen into nitrogen resources for the legumes (Long, 1996). As some of this nitrogen is released, on the death of the plant for instance, or in exudates, this turns the legumes into "green manure," even if nitrogen fixation is, in fact... holobiontic. In humans, maternal milk favors the colonization of the infant's gut by bacteria, which aid digestion and protect against diarrheal agents. Human milk contains oligosaccharides composed of three to five monosaccharide residues whose concentration (15 g/L) makes them the third constituent of breast milk, after lactose and lipids, but well ahead of proteins. As the infant cannot digest these oligosaccharides, they were omitted from formula milk. They are, however, easily digestible by appropriate bacteria, like certain *Bifidobacteria*, which are highly specialized in their use (Ward *et al.*, 2006).

Stick-wise, immune reactions reject the pathogens that harm tissues while mechanisms sort the best partners. For example, on roots, not all fungi able to form mycorrhiza are also favorable to a given plant, which therefore risks nourishing partners that are of little or no use. After the plant has formed mycorrhizae with various partners, it selectively feeds those fungi that supply it with more mineral nutrients, like phosphorus and nitrogen, and feeds less those fungi that prove useless (Selosse and Rousset, 2011). More generally, in the rhizosphere, root

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secreted molecules (mainly phenolics like salicylate, coumarins or derivatives of hydrodynamic acid) strongly contribute to shape microbiota, by excluding some species (Hu *et al.*, 2018; Voges *et al.*, 2019). Hence, a long coevolution with microbes has shaped, in animals and plants, mechanisms optimizing the use of microbes, which adapted to their hosts: the holobiont therefore is the outcome of reciprocally influenced evolution, otherwise called coevolution.

The microbiote plays various roles in the host organism

Over the course of evolution, longstanding and temporary partners have ended up assuming multiple roles in the holobiont. In recent decades, plants grown in sterile soil and rodents raised without any exposure to microorganisms (i.e., germ-free or axenic) have enabled eloquent comparisons that reveal varied roles which, once again, are similar in the animal gut and in plant roots (figure 4).

Feeding is a holobiontic affair. Mycorrhizal fungi lower mineral salt levels in the soil around the root, bacteria solubilize iron and phosphate or, like rhizobia, mobilize atmospheric nitrogen... to the point that many plants, like pines, grow little or poorly in sterile soil (Van der Heijden *et al.*, 2015). In the intestine, bacteria help digestion *via* their enzymes and produce vitamins (K and B12) and other essential molecules (figure 3): deprived of bacteria, germ-free mice require, for the same growth, 25 % more food (Wostmann *et al.*, 1983). Microbes that offer protection to the host, which provides them with room and board, have been selected. They keep pathogens at bay through local competition and at the price of an antibiotic war that rages in the gut and around the root. For example, *Staphylococcus lugdunensis* of the human microbiote synthesizes an antibiotic peptide that destroys *Staphylococcus aureus* (Zipperer *et al.*, 2016), which 10 to 30 % of healthy human carry and which, when uncontrolled, can produce skin diseases, even septicemia. But the protective effect of microbes also involves modification of the host: germ-free

mice have a less developed immune system, both in the gut (fewer lymphocytes, attenuated expression of immune system genes) and in the rest of the body (Thaiss, 2016). Likewise, plants devoid of root microbes react more slowly and less aggressively to parasitic attack and so suffer increased damage (Martinez-Medina *et al.*, 2016).

This shows that microbes play a part in host development. Their colonization induces maturation of the host immune system (Selosse *et al.*, 2014), not just an immune reaction at all, but a capacity to react more effectively that is not acquired without them; this phenomenon in plants is also termed 'defense priming' (Mauch-Mani *et al.*, 2017). Immunity is not only activated, but is also completely modulated and reprogrammed: some of its components are repressed, such as lymphocytes involved in inflammation, the natural killer T cells in mice (Olszak *et al.*, 2012). The current explosion in the Western world of allergies and auto-immune diseases, in which the immune system reacts disproportionately or inappropriately or both, may be the result of a life that has become overly sanitized, where microbial diversity arrives too late in a child's development to play this role of maturation (Fujimura and Lynch, 2015). Allergies are less frequent in rural settings where exposure to microbes is more frequent and can be prevented by the addition of targeted bacteria to infant foods. An example of such "virtuous" exposure is the effect of the presence at home of a dog, which increases the diversity of the child's microbiota and correlatively reduces the risk of asthma by 13 % (Gupta, 2017).

Lastly, germ-free mice show behavioral alterations: increased activity, reduced timidity and anxiety, poor memorization (Luczynski *et al.*, 2016). Their nervous system differs from that of holobiontic mice, notably in the functioning of the synapses and in the expression of major genes. These traits return to normal after microbial colonization, but only when the animals are young and still developing (Diaz Heijtz *et al.*, 2011).

So, in a way yet to be elucidated, the presence of bacteria also induces the correct development

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of the nervous system. There is a complex dialogue between the nervous system and the microbes that persists in the adult, whose behavior can be affected by these microbes. For example, bacteria alter mood in rodents and humans. *Campylobacter* species seem to favor depressive states (Marshall, 2009); *Lactobacilli* and *Bifidobacteria* reduce depression and stress: they partially mimic the effects of anxiolytics on behavior and also, in rodents and humans, on brain activity (Bharwani *et al.*, 2017). One day, maybe, chosen bacteria will heal us. In the meantime, we wonder at so many intrusions in functions that we (wrongly) imagine are independent.

Microbes even have a say in reproduction. When we sterilize elderflower (a fragrant species used in various flavored drinks), it stops synthesizing certain compounds that attract pollinators, notably volatile terpenes, which decrease three-fold (Penuelas *et al.*, 2014). In animals, microbial interference even affects the choice of sexual partner. When fruit flies fed on molasses are mixed with others fed on starch, they prefer to mate with those fed the same food. After antibiotic treatment, this mating preference disappears; it returns in axenic flies re-contaminated either by their initial food and its bacterial components, or by *Lactobacillus plantarum*, a bacterium found in flies grown on starch and sufficient to trigger preference for partners containing the same bacterium (Sharon *et al.*, 2010). A bacterial signal can therefore determine the sexual choice in flies. *Lactobacilli* favored by eating starch seem to modify sexual pheromones, which attract partners during mating.

The evolution of interdependence

Why are there these microbial intrusions in so many processes that could be independent? We have proposed two simple mechanisms to explain this evolution toward dependence (Selosse *et al.*, 2014). We should not forget that germ-free plants and animals are laboratory creations useful for investigating and understanding the role of microbes. In nature,

microbes are always around, diverse and countless. On the one hand, evolutionary innovation, like a new floral fragrance or a supplementary food for an insect, can be based on one of these ever-present microbes. On the other hand, if microbes perform a function also performed by the host, they can supplant the host's function by, for instance, synthesizing a vitamin or replacing a stimulus in a developmental process (figure 5).

Such events are doubtless rare in evolution, but hundreds of millions of years of coevolution and tens if not hundreds of two-by-two interactions have increased the probability. What is more, when functions are lost in the host or microbe, the mutations that would restore these functions (reverse mutations) are unlikely. This drift toward dependence is therefore unlikely to be reversed and secondarily strengthens the interaction. The dependence works and increases symmetrically for the microbes, as shown, for example, by genome reduction in the endosymbiotic bacteria of insects referred to above, and by mitochondria and plastids. Loss of dependence in the holobiont is an authentic product of coevolution.

This is a harsh lesson for those who wanted to postpone the teaching of ecology until after learning about physiology, development, reproduction, and so on, the biology of organisms in effect. The interactions between microbes, or between microbes and their host, shape part of the biology of organisms into a complex ecology. Because, in the end, the holobiont is a stage for ecological interactions. Ecology is no longer subordinated to the biology of organisms: like the chicken and the egg, these disciplines mutually underpin each other.

The limits of the holobiont: toward networks of interactions

Now we come to the limits of the holobiontic vision. A modern concept in vogue, I feel it already has a whiff of the outdated about it. Interactions, particularly microbial, deny the

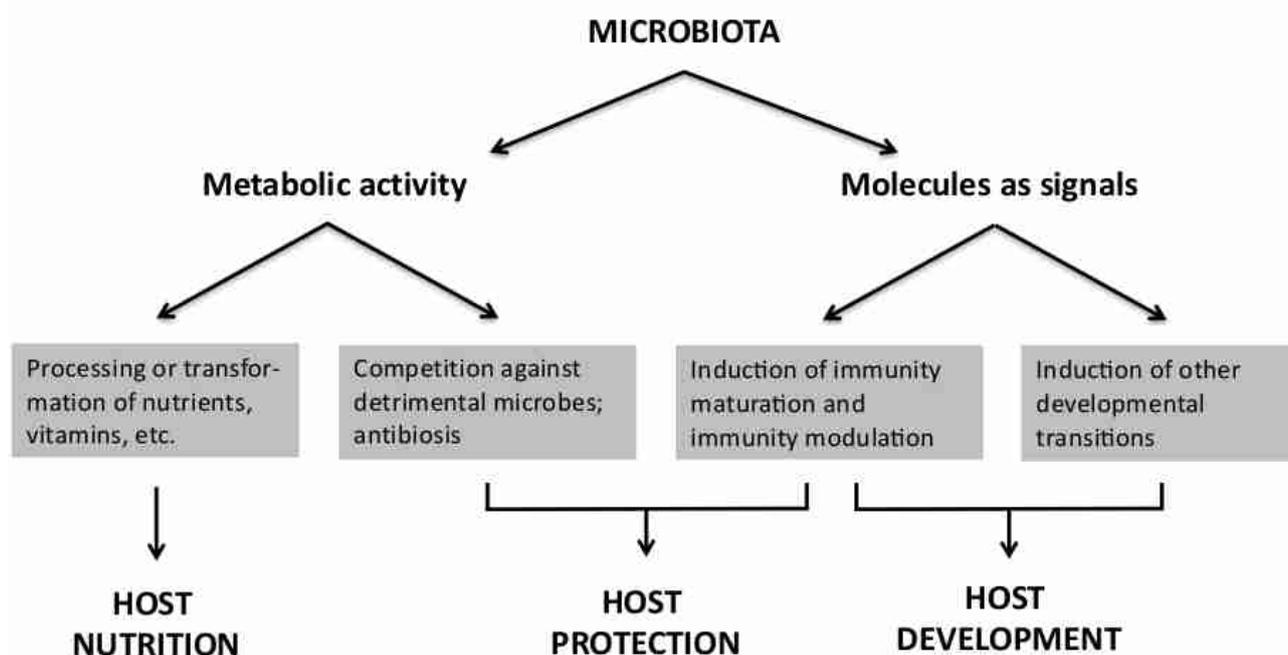


Figure 5. Microbial symbionts provide both their metabolic activity and their molecules as signals to hosts (Selosse et al., 2014).

relevance of an independent vision of the organism: this is appreciable for endosymbiotic microbes, for example, but germ-free mice and other animals show that the isolated organism is unable to function correctly in an independent fashion. The holobiont enables the survival of the organism as an enlarged unit, but in a world of interactions, are there still really discernible "units?" Consider for a moment an interaction that is life-sustaining for 90 % of plants: the abovementioned mycorrhizal association, which is studied by my own research team.

Mycorrhizal fungi in the soil colonize the roots of various plants, sometimes of different species. Likewise, each plant associates with dozens of species of fungi. Mycorrhizal symbiosis therefore creates a network of plants connected by fungi, and vice versa (Selosse et al., 2006). Now, certain plants feed on this network: they capture from their fungi sugars that the fungi have acquired from neighboring plants. Species of the orchid and heather families have sometimes lost chlorophyll and are entirely fed by the network (Merckx, 2013) (figure 6).

Other plants are still green and are sustained by both photosynthesis and the network (Selosse and Roy, 2009). Most of these plants live in undergrowth where the network provides supplementary carbon in low-light conditions that limit photosynthesis. What is more, the mycorrhizal network can send signals between plants: when a plant is attacked by a parasite, plants connected to the same mycorrhizal network react to this attack by, for example, triggering the synthesis of defense compounds (Gilbert et al., 2013). This is so, for instance, in tomatoes connected by a shared mycorrhizal fungus (Song et al., 2015): when one tomato plant is attacked by *Alternaria*, its neighbors elicit defense responses if, and only if, there is a connection to the same mycorrhizal fungus. Although experiments in "natural" conditions, far from the greenhouse models used hitherto, remain desirable, it seems clear that the plant functions within a mycorrhizal network (Roy and Selosse, 2015).

In this example, how do we delimit the independent units? Where does the holobiont

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Figure 6. The bird-nest orchid (*Neottia nidus-avis*) exploits carbon from fungi shared with surrounding trees, and therefore uses mycorrhizal networks.

end? The plant is linked to fungi, but what these fungi supply to the plant—signals or nutrients—come from other plants, which themselves owe their functioning to other fungi, and so on. By focusing on the microbial symbionts by way of their host organism, the holobiont does not exclude the possibility of a network, but simply put the emphasize far from this fact. Other interaction networks exist: pollinating insects interact with several plants each of which interacts with several insects. Our pathogens also form networks, each of which interact with several hosts, which themselves are linked to several microbes. The network is, of course, materialized in the case of plants, less so for animals.

But the example mentioned above of how the sexual behavior of fruit flies can be manipulated by a clone of bacteria that the flies share, or not, reveals that the sharing of clones between animals can alter their interactions, even their evolution. Another group of examples of manipulation of a host species by a clone is that of *Wolbachia*, which manipulate the sexuality of their host to maximize their own transmission by females (Werren *et al.*, 2008) and can cause

sterility in uninfected males. In *Nasonia*, a genus of wasps, interspecific hybrids survive poorly, except after antibiotic therapy (Trucker and Bordenstein, 2013): the microbial communities inherited from the parents oppose crosses such that, albeit invisible, the network transcends the limits of the organism.

The holobiont made, on the one hand, a first step to actualize the idea of organism and rethink individuality. Yet, on the second hand, it masks the importance of the interactions themselves and delays the shift to another vision of life, that of a network of interactions, which has already been modeled by ecologists (Bascompte and Jordano, 2014). Modern science has transposed a Western philosophy based on the individual into a biology based on the organism. A genuine rupture would be—will be, I believe—to place interactions center stage (Selosse, 2017). A cobweb is not a collection of points where threads cross, but rather the links between these points! Similarly, life comprises organisms and above all the links between them. The notion of organism, in two centuries of research, has yielded a great deal in understanding and knowledge. Increasingly though, this notion seems to be an artefact of the macroscopic world, where the plant or animal is seen as an observable whole, concealing its microbes. Somewhat belatedly, but insistently, our understanding of organisms is now revealing their multiple functional contributions (McFall-Ngai *et al.*, 2013).

Today, interactions are in the spotlight. Tomorrow, the interdependences and interrelations with the microbes we harbor will open new horizons for environmental management, food production, healthcare, and nutrition. Discovering the links of living process to microbial life is one of the way we can re-found our links to nature, and offers powerful tools and concepts for future actions.

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