A part-dependent account of biological individuality: why holobionts are individuals *and* ecosystems simultaneously

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ABSTRACT

Given one conception of biological individuality (evolutionary, physiological, etc.), can a holobiont – that is the host + its symbiotic (mutualistic, commensalist and parasitic) microbiome – be simultaneously a biological individual *and* an ecological community? Herein, we support this possibility by arguing that the notion of biological individuality is part-dependent. In our account, the individuality of a biological ensemble should not only be determined by the conception of biological individuality in use, but also by the biological characteristics of the *part* of the ensemble under investigation. In the specific case of holobionts, evaluations of their individuality should be made either host-relative or microbe-relative. We support the claim that biological individuality is part-dependent by drawing upon recent empirical evidence regarding the physiology of hosts and microbes, and the recent characterization of the 'demibiont'. Our account shows that contemporary disagreements about the individuality of the holobiont derive from an incorrect understanding of the ontology of biological individuality. We show that collaboration between philosophers and biologists can be very fruitful in attempts to solve some contemporary biological debates.

Key words: holobiont, hologenome, microbiota, demibiont, biological individuality, physiological individuality, organism, levels of selection, units of selection

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I. INTRODUCTION

Holobionts are multispecies assemblages formed by the aggregation of a host plus its symbiotic microbiome, where 'symbiosis' is understood in de Bary's (1879) sense as encompassing any long-term relationship between organisms of different species, no matter whether they are mutualists, commensalists or parasitic (Zilber-Rosenberg & Rosenberg, 2008; Theis *et al.*, 2016; Roughgarden *et al.*, 2017; Suárez, 2018). As such, holobionts necessarily include a macrobe host (animal or plant) plus the set of symbiotic microbes (bacteria, fungi, viruses, etc.) that constitute its microbiome (Mindell, 1992; Dupré & O'Malley, 2009; Bordenstein & Theis, 2015). For example, humans and their gut microbiome, ruminants and the microbiome of their rumen, or aphids and their symbionts have been hypothesized to constitute cases of holobiosis. In recent years, this type of multispecies assemblage has caught the attention of numerous biologists and philosophers, who have carried out their research with the aim of understanding the effects of the microbiome on the macrobe host that bears it (e.g. Ley *et al.*, 2008; Turnbaugh *et al.*, 2008; Brucker & Bordenstein, 2012, 2013*a*; McFall-Ngai *et al.*, 2013; Osmanovic *et al.*, 2017; Mendoza *et al.*, 2018; Rudman *et al.*, 2019).

Despite increasing interest in holobiont and microbiome research, and the importance of fully understanding their significance for contemporary biology, recent literature reflects a substantial disagreement about the ontological status of holobionts. This leads to the existence of two conflicting positions: on the one hand, some researchers argue that holobionts are biological individuals (henceforth 'individuality thesis') (Zilber-Rosenberg & Rosenberg, 2008; Dupré & O'Malley, 2009; Gilbert, Sapp, & Tauber, 2012; Rosenberg & Zilber-Rosenberg, 2013; Díaz, 2015; Theis *et al.*, 2016; Gilbert, Rosenberg, & Zilber-Rosenberg, 2017; Richardson, 2017; Roughgarden *et al.*, 2017; Lloyd, 2017*a*; Suárez & Triviño, 2019, 2020; Suárez, 2020); on the other, some researchers argue that holobionts are ecological communities of independent individuals (henceforth 'ecological-community thesis') (Moran & Sloan, 2015; Douglas & Werren, 2016; Skillings, 2016; Stencel, 2016; Hurst, 2017; Stencel & Wloch-Salamon, 2018). These interpretations are at odds with each other, as they assume a radically different *ontology* for holobionts.

Herein, we use 'ontology' to refer to the set of assumptions about the basic structure of the notion of biological individuality that a group of researchers share (*Encyclopaedia Britannica*, https://www.britannica.com/topic/ontology-metaphysics, 10th April 2020). These assumptions include the rules that must be followed to apply properly the notion to a group of entities, as well as essential properties of the concept such as reflexivity, symmetry or transitivity, but not the criteria or properties (immunology, physiology, evolution, etc.) that may be used to single out biological individuals – to which we will refer as the *conception* or *concept* of biological individuality. Given this context, the existence of two groups of researchers that rely on radically different views on the

ontology of holobionts raises a question: is there a way to solve the tension between these interpretations such that it is possible to find a resolution to the debate about their nature? In other words, is it possible to argue that the ontological nature of the notion of biological individuality is such that it admits the existence of apparently incompatible interpretations of the individuality of holobionts?

One possible way to reply to these questions is to adopt a pluralistic stance by distinguishing different conceptions of biological individuality. For instance, it could be argued that the notion of biological individuality is not univocal, and there are different non-identical criteria or conceptions (metabolic, immunological, etc.) to decide whether an entity is or is not a biological individual (Pepper & Herron, 2008; Clarke, 2010, 2013; Dupré, 2010, 2012; Kovaka, 2015; Pradeu, 2016*a*, 2016*b*; DiFrisco, 2017). Therefore, holobionts are biological individuals according to some conceptions, but not according to others.

While the latter is a legitimate option, herein we go one step further to argue that the difficulty still appears even if one is committed to using a specific conception of individuality. By building on Lloyd & Wade's (2019) recent distinction between the concepts of 'holobiont', 'euholobiont' and 'demibiont', and grounding it on the sharp ontological difference between macrobes and microbes, we argue that the problem with the former solution is that it still assumes a view of the notion of biological individuality that emphasizes the perspective of the whole. We call this view of biological individuality 'whole-dependent'. According to it, a whole is a biological individual if and only if *all the elements that constitute the whole* satisfy a specific criterion of individuality (physiological, immunological, evolutionary, etc.). If some of the parts of the whole do not satisfy the criterion, then the whole is not a biological individual. As every conception of biological individuality relies on 'whole-dependency', we claim, the option of dividing the individuality thesis into several theses does not solve the dispute about the nature of the holobiont.

Herein, we defend that, contrary to what the recent literature has assumed, the notion of biological individuality is not whole-dependent, but *part-dependent*. The part-dependent account of biological individuality emphasises the role played by *each of the elements* that compose the whole. Thus, according to it, a whole is a biological individual only if all the elements that are included in the whole fulfil a certain criterion *in relation to a given element of the whole that one is prioritizing*. In that vein, our approach introduces a new layer of pluralism in the debate of biological individuality. The individuality of a group of objects does not depend exclusively on the conception that one chooses to use, but also on the element of the whole that one prioritizes.

We motivate our argument for the part-dependent account of biological individuality by relying on the different verdicts about the individuality of holobionts that follow from contemporary biological practice. We show that the dependency relations that are created between the parts that compose a holobiont (host *versus* microbes of the microbiome) are not always symmetric, and while the host depends

physiologically on its microbes, the opposite is usually not the case. Building on that observation we argue that holobionts fulfil the conditions for being physiological individuals when they are approached from the perspective of the host. However, when they are approached from the microbe perspective, holobionts fail to qualify as biological individuals, and they rather qualify as ecological communities. The apparent tension between the two perspectives is solved by arguing that the notion of biological individuality is part-dependent. That is to say, biological individuality does not require symmetry of the relations of dependency between the parts that make up a biological ensemble and, thus, holobionts are biological individuals from the perspective of the host *and* ecological communities from the perspective of the microbes.

In Section II, we examine the contemporary debate about the nature of the holobiont. In Section III, we introduce the debate on biological individuality, with emphasis on the physiological conception of individuality. In Sections IV and V, we argue that even adopting exclusively the physiological conception of individuality, there is still a legitimate disagreement about the individuality of the holobiont depending on the perspective that one adopts (host perspective/symbiont perspective). In Section VI, we diagnose the reason for this disagreement and argue that defenders and detractors of the individuality thesis have failed to appreciate that the notion of biological individuality is part-dependent. Finally, we extrapolate our arguments to other conceptions of individuality (Section VII) and present our conclusions (Section VIII).

II. THE NATURE OF THE HOLOBIONT: BIOLOGICAL INDIVIDUALS OR ECOLOGICAL COMMUNITIES?

Contemporary biological and philosophical literature has provided two different and contradictory approaches to the ontological nature of the holobiont: the individuality and the ecological-community theses.

The individuality thesis emphasises that holobionts should be regarded as biological individuals. Proponents of this view often argue that most of the biological processes that characterize the biology of macrobes (metabolism, immunology, evolution, etc.) cannot be explained by exclusively relying on the internal development of a pre-established genetic programme in the animal or plant's genome. On the contrary, these processes are only realized as a consequence of a complex network of interactions between the host and the symbiotic microorganisms that compose their microbiome, to the point that some authors have even claimed that "we have never been individuals", but individual symbiotic collectives (Gilbert *et al.*, 2012; Gilbert *et al.*, 2017; see also O'Malley & Dupré, 2007; Dupré & O'Malley, 2009; Lloyd, 2017*a*; Richardson, 2017).

This thesis was clearly formulated for the first time in the work of Zilber-Rosenberg & Rosenberg (2008); see also Rosenberg &

Zilber-Rosenberg, 2013), who developed the notion that holobionts are evolutionary individuals under the framework of the hologenome concept of evolution. After their work, different researchers have developed different conceptions of the holobiont and the hologenome, with distinct accounts of the specific boundaries of holobionts. While Zilber-Rosenberg and Rosenberg, on the one hand, and Bordenstein and his collaborators, on the other, believed that the holobiont, when considered as a *structural concept*, should encompass every microorganism that interacts symbiotically with the host (Rosenberg & Zilber-Rosenberg, 2013, 2018; Bordenstein & Theis, 2015; Shropshire & Bordenstein, 2016; Theis *et al.*, 2016), the latter were more precise in defining the hologenome as an evolutionary individual. This is because Bordenstein and his collaborators soon argued that the hologenome, as an evolutionary unit, only encompasses a species-specific fraction of the host microbiome, namely, the fraction that stands in a relation of phylosymbiosis with the host (Brucker & Bordenstein, 2012, 2013*a*, 2013*b*; Bordenstein & Theis, 2015; van Opstal & Bordenstein, 2015; Brooks *et al.*, 2016; Shropshire & Bordenstein, 2016). Zilber-Rosenberg and Rosenberg, on the contrary, considered every microorganism in the host microbiome as a member of the hologenome. Even more radically, some researchers have recently suggested that the fraction of the microbiome that should be considered as part of the individuality of the hologenome must be restricted to the set of functional elements of the microbiome, rather than to its species-specific composition (Taxis *et al.*, 2015; Doolittle & Booth, 2017; Lemanceau *et al.*, 2017; Suárez & Triviño, 2019, 2020; Suárez, 2020).

Irrespective of the subtle discrepancies about the definition of the holobiont/hologenome among defenders of the individuality thesis, their view of the nature of the holobiont relies on the belief that biological individuality does not need to be 'harmonic', that is that holobionts encompass the whole set of microorganisms that symbiotically interact with a macrobe host, irrespective of whether their interactions are mutualistic, commensalist or parasitic. In this sense, these views align closely with the view of biological individuality derived from de Bary's (1879) seminal work on symbiosis, and its further development by Schneider (1897), and contrasts with the view of individuality assumed by holobiont detractors [see Suárez, 2018 for a review].

Contrary to the former position, defenders of the ecological-community thesis argue that none of the evidence presented by those who defend the individuality thesis is persuasive enough to claim that holobionts are biological individuals (Moran & Sloan, 2015; Douglas & Werren, 2016; Skillings, 2016; Stencel, 2016; Hurst, 2017; Stencel & Wloch-Salamon, 2018). Furthermore, they claim that taking the individuality thesis for granted may obfuscate our understanding of the complexity of the interactions between the host and its microbiome. In their view, defending that holobionts are biological individuals entails assuming that host–microbiome associations constitute 'harmonic', that is purely mutualistic, wholes. In other words, according to holobiont detractors, the individuality thesis presupposes that the host and the lineages that compose its microbiome interact cohesively to guarantee the common benefit. Insofar as our

contemporary evidence suggests that the holobiont includes not only mutualistic, but also commensalist and parasitic host–microbe interactions, these authors deny the validity of the individuality thesis and argue that holobionts must be considered as 'ecological communities' of independent individuals.

Holobiont detractors assume a view of biological individuality that requires 'harmony' among the parts that compose an individual. Their view aligns closely with some of the arguments developed by Pound (1893), who argued against de Bary's view of symbiosis and individuality by emphasising the lack of common interest that normally ties symbiotic partners together [see Suárez, 2018, for a review]. Insofar as holobiont detractors presuppose a view of individuality that conflicts sharply with the view presupposed by most holobiont defenders, they reach opposing conclusions about the individuality of holobionts, which leaves very little room for a productive conversation between the two groups.

With the aim of showing that holobiont defenders and holobiont detractors rely on different concepts of individuality, Lloyd & Wade (2019) have recently coined the concepts of 'euholobiont' and 'demibiont' to mediate between these two groups of scholars. They observe that those discussing the individuality of holobionts have failed to notice that the process of adaptation between the host and its symbionts is, in many cases, a one-way process. That is, one of the species adapts to the other, but there is little or almost no reciprocity. Since this is so, Lloyd & Wade (2019) believe that it is crucial to distinguish the holobiont, which they define as a host–microbiome symbiotic association, where symbiosis is understood in de Bary's sense, from the two related but not equivalent categories of euholobiont and demibiont. In their account, euholobiont refers to "genuine[ly] genetically integrated, co-adapted communities of obligately mutualistic organisms" (Lloyd & Wade, 2019, p. 152), and demibiont refers to the symbiotic communities that result from the one-way process of evolution in which one species adapts to another without the latter necessarily adapting to the former. The concept of demibiont "emphasizes the long-term adaptation by species one to species two and includes cases in which both species receive benefits from one another yet evolution affects (primarily) one of the two interacting species" (Lloyd & Wade, 2019, p. 152).

Lloyd and Wade's concepts – strongly supported by genetic models – suppose an important conceptual progress in the way we should understand the nature of the holobiont, as they disambiguate the different outcomes that may result from a process of host–symbiont coadaptation/evolution. Their concept of demibiont emphasises that host–symbiont relationships may give rise to an asymmetric regime of dependency, and thus holobionts should never be directly conceived as 'euholobionts', as this may mask the real evolution of many host–symbiont associations. Nonetheless, it is important to note, although in passing, that Lloyd and Wade's account still raises the same type of questions that have motivated our paper, and that ground contemporary disagreements about the ontological status of holobionts: in cases where the dependencies between the partners are asymmetric (i.e. demibionts), should we consider the host–symbiont association a biological individual or an ecological community? The case of the demibiont seems, thus, problematic, and while introducing the concept supposes a clear progress in the holobiont debate, it does not solve our initial question. Defenders of the ecological-community thesis would still claim that the asymmetry of dependency grounds their view, whereas defenders of the individuality thesis would argue otherwise.

Thus, to solve the problem over the individuality of the holobiont we believe it is better to return to the basic concepts, and to rethink the main features that define the notion of biological individuality in light of the problems triggered by holobiont research, and clearly diagnosed by Lloyd and Wade. We do so in Sections IV–VI. But before doing so, we need to introduce the debate about biological individuality to understand correctly the context in which the holobiont debate has been held in recent years.

III. THE PROBLEM OF BIOLOGICAL INDIVIDUALITY

(1) What counts as a biological individual?

Discerning what counts as a biological individual constitutes a central problem in the agenda of biologists (Pepper & Herron, 2008; Gilbert *et al.*, 2012; Rees, Bosch, & Douglas, 2018), and philosophers (Godfrey-Smith, 2013; Clarke, 2013; Kovaka, 2015; Smith, 2017; Stencel & Proszewska, 2018; Suárez, 2018; Wilson & Barker, 2019; *cf.* Section II in Smith-Ferguson & Beekman, 2019). Following Pradeu (2016b, p. 762), we also believe that "[i]n general, asking what a biological individual is means asking what constitutes a countable, relatively well-delineated, and cohesive unit in the living world". However, it is sometimes very hard to decide whether a given entity is cohesive enough to be considered an individual on its own or, instead, a group of distinguishable individuals interacting with each other. A classic example of this debate is found in eusocial organisms, such as ant colonies or honeybees, whose status as biological individuals or as groups of interdependent individuals still induces confusion among biologists (Helanterä, 2016; Canciani, Arnellos, & Moreno, 2019). More recently, most discussions about biological individuality have concentrated on the study of holobionts. Part of the reason for these disagreements derives from the fact that biologists rely on a plurality of non-co-extensional conceptions of biological individuality (physiological, evolutionary, developmental, etc.) (Dupré & O'Malley, 2009; Godfrey-Smith, 2013; Pradeu, 2016a, 2016b; DiFrisco, 2017; Molter, 2019).

In philosophy, it is it is common to distinguish between the *intension* of a concept, and its *extension*. The intension of a concept refers to its defining features (e.g. what you find in a dictionary), whereas the extension refers to the range of objects to which the concept applies. For instance, the intension of

'chordate' is 'creature with notochord', and its extension encompasses all the animals of the phylum Chordata, including fish, amphibians, mammals, etc. (*Encyclopaedia Britannica*, https://www.britannica.com/topic/intension, 10th April 2020). We believe that this distinction is crucial, for it may serve to disambiguate some of the disagreement among biologists. When we say that biologists rely on a plurality of 'non-co-extensional' definitions of biological individuality we mean that they appeal to definitory properties of individuals (physiology, evolution, etc.) that do not capture exactly the same range of objects and, thus, what some would count as an individual will be excluded by others, and *vice versa*(-Clarke, 2010, 2013; Godfrey-Smith, 2013). The existence of non-co-extensional conceptions of biological individuality is one source of important disagreements among philosophers and biologists.

For example, if a group of biologists is studying the evolution of some traits in a lineage, they will single out individuals according to their evolutionary properties, including their reproductive fitness and/or their capacity to participate in the process of natural selection. In that vein, there is a popular interpretation of biological individuality according to which to be a biological individual is to be a unit of selection (Hull, 1980; Okasha, 2006; Lloyd, 2017*b*). If one follows this approach, then biological individuality needs to be linked to reproduction of some sort. Following that conception, one must try to identify the *interactors* (entities that do not directly form lineages, but interact cohesively with the environment in a way that leads to the differential reproduction of the lineages that compose them) and/or the *reproducers* or *Darwinian individuals* (entities with the capacity of forming parent–offspring lineages) (Janzen, 1977; Godfrey-Smith, 2009, 2013; Clarke, 2010, 2013, 2016; Skillings, 2016). Thus, if an entity either fails to form parent–offspring lineages, or fails to interact as a cohesive whole that leads to the differential reproduction of the lineages that compose them, then the entity should be considered a conglomerate of independent individuals, rather than as a single individual.

On the other hand, alternative conceptions of biological individuality have for instance relied on physiological assumptions, rather than on ability of the entity to form parent–offspring lineages (Dupré & O'Malley, 2009; Gilbert *et al.*, 2012; Godfrey-Smith, 2013; Pradeu, 2016*a*; Gilbert *et al.*, 2017; Smith, 2017). According to the physiological conception of individuality, if a group of entities engage in a significant amount of physiological (especially metabolic) interactions with each other, then the group of entities will be considered a physiological individual. Importantly, a group of entities can engage in a significant amount of physiological interactions despite not forming parent–offspring lineages, or *vice versa*, as has been shown in contemporary literature (Clarke, 2010, 2013; DiFrisco, 2017; Wilson & Barker, 2019). This situation illustrates a legitimate concern about the individuality thesis: it might be the case that holobionts are biological individuals according to some conceptions of individuality (e.g. physiological individuals,

developmental individuals), but not according to other conceptions (e.g. evolutionarily).

Some authors have recently appealed to the existence of different conceptions of biological individuality to solve the debate about the individuality of the holobiont. For example, Godfrey-Smith (2013, 2015) and Smith (2017) believe that holobionts are physiological individuals (*organisms*, in their words), but not evolutionary individuals. Different versions of that solution have also been defended by Griesemer (2016) and Chiu & Eberl (2016), who recently suggested that holobionts can be conceived as hybrids. According to the former, holobionts would be developmental individuals, whereas according to the latter, holobionts would be eco-immunological individuals. In any case, both agree that holobionts do not fulfil all the conceptions of biological individuality, and thus the individuality thesis would only be true for some specific conceptions of biological individuality.

While we agree that this solution is legitimate, we believe it is not completely satisfactory. Rather than solving the problem, as their proponents believe, it raises additional issues that exacerbate it. In fact, we believe that dissociating the individuality thesis in different theses, depending on the conception of individuality that is relevant, is still problematic in the case of holobionts for the ontological implications of their symbiotic nature (Section V). In this sense, this solution, without a previous reflection on the ontological nature of the notion of biological individuality, fails to provide a satisfactory answer to the question about their individuality, thus not solving the sharp disagreements among biologists and philosophers that motivated proposing the solution in the first place. For reasons of space, herein we will illustrate the problem by relying mainly on the physiological conception of individuality – although we will say a few words about how we believe that our view of the ontology of the notion of biological individuality would affect other conceptions of individuality (Section VII). We will illustrate how even those who are committed to using the physiological conception may still disagree about the individuality thesis, and we will argue that this is so because they assume a questionable view about the ontological nature of the notion of biological individuality.

(2) The physiological conception of individuality

The notion of physiological individuality has been studied from different perspectives. One view that has recently gained popularity is the 'immunological perspective' of individuality. This perspective encompasses the family of theories according to which the physiological individuality of a biological ensemble is determined by the interactions that happen in the immunological system. According to the immunological view, a group of biological elements constitutes an individual only if there is an immunological system that can actively determine which elements belong to the group, and which elements are excluded from it (Tauber, 1994, 2016; Pradeu, 2010, 2012, 2016*b*; Pradeu & Vivier, 2016). Traditionally, the immunological conception

of individuality assumed that the immunological system acted as a 'barrier' that determined the boundaries between the self and the non-self, eliminating any possible intruders, and tolerating those elements that were parts of the self. However, more recently, the immunological view of individuality not only emphasizes the active role of the immune system in excluding intruders, and tolerating elements of the individual, but also in reinforcing the bonds between the components of the biological individual (Pradeu, 2019, 2020). According to the new view, the boundaries of the individual are less fixed, and are constantly being redefined by the action of the immunological system.

A second approach to physiological individuality has been recently proposed by Smith (2017), who conceives physiology and development as two faces of the same coin (and, thus, development plays a key role in her account of physiological individuality). Grounded on that view, and building on Godfrey-Smith's (2013, 2015) work, Smith (2017) defines organisms (physiological individuals) as "essentially *persisters*" whose persistence is manifested ontogenetically, in their capacity to respond as a whole and integrated system to the contingencies of their environments. Smith defends that an essential characteristic of organisms as essential persisters is their capacity for systemic phenotypic accommodation (integration and cohesiveness), which is grounded on the high level of developmental, physiological and ecological dependencies that exist among the parts that compose them. In her own words, organisms are biological systems with "the capacity (…) to respond *as a whole* to environmental contingencies which threaten or promote their persistence. (…) [This] is made possible by the fact that organisms function as integrated, cohesive wholes" (Smith, 2017, p. 7, original emphasis retained).

Another popular approach to physiological individuality rests on metabolic assumptions (e.g. Dupré & O'Malley, 2009; Gilbert *et al.*, 2012; Godfrey-Smith, 2013; Gilbert *et al.*, 2017; Roughgarden *et al.*, 2017). According to this view, a physiological individual is a cohesive whole of elements that work together to sustain the functionality of the whole, i.e. to keep it alive. As presented by Godfrey-Smith (2013, p.12): "This is [the] metabolic view: organisms [physiological individuals] are systems comprised of diverse parts which work together to maintain the system's structure, despite turnover of material, by making use of sources of energy and other resources from their environment". In a similar way, Gilbert *et al.* (2012, p. 329) state that "the physiological view of animal individuality regards the organism as comprised of parts that cooperate for the good of the whole". In this vein, the essence of the metabolic view of physiological individuality states that a biological individual is a 'system' that can maintain its structure and functionality over time as a consequence of the causal interactions between the elements that compose it. The paradigmatic case of physiological individuality is multicellular organisms, which are made of cells of different types that perform different functions, and that allow the system to maintain its structure and functionality. However, the idea is also applicable to microorganisms, which maintain their functionality through the action of their molecular components (O'Malley, 2014; Moreno & Mossio, 2015).

The view that holobionts are physiological individuals in a metabolic sense has recently gained some popularity among philosophers and biologists (Dupré & O'Malley, 2009; Gilbert *et al.*, 2012; Godfrey-Smith, 2013; Catania *et al.*, 2017; Gilbert *et al.*, 2017; Roughgarden *et al.*, 2017; Smith, 2017). However, it has also been recently questioned, and disregarded as host-centric. The most paradigmatic case of the latter is Skillings (2016, p. 881), who writes: "I take physiological individuality to be host-centric, subordinating microbe individuality to functional, immunological, and developmental considerations regarding the host". Those who questioned the application of the physiological conception of individuality to holobionts have embraced the ecological-community thesis, according to which holobionts are not biological individuals, but ecological communities (Moran & Sloan, 2015; Douglas & Werren, 2016; Hester *et al.*, 2016; Skillings, 2016).

Interestingly, we believe that all these authors have missed that the disagreement between holobiont defenders and holobiont detractors arises even when the individuality of the holobiont is analysed exclusively in physiological terms. In the next sections, we will present two cases that, in close connection with what is at stake in the debate about the individuality of holobionts (Section II), suggest that: (*i*) the physiological conception of individuality can be applied both to the macrobe host and to the microbes that compose its microbiome; (*ii*) in both cases, one reaches opposing conclusions about the individuality thesis: while holobionts are physiological individuals from the host perspective, they are ecological communities from the microbe perspective.

IV. THE MACROBE/HOST PERSPECTIVE – HOLOBIONTS AS INDIVIDUALS

To prove our case that the ontological status of holobionts will differ depending on the perspective adopted, even while one adopts *a specific conception of individuality*, we will study how the criterion of physiological individuality would apply first to a host, and second to one of the microorganisms that inhabit its microbiome, and that plays an essential function in the physiology of the host. Note that 'perspective' is not used anthropomorphically, but simply to refer to the group of entities whose individuality is being studied, i.e. either the host or the microbe.

As a first case, let us consider the influence of the gut microbiome in the physiology and development of mice. We will particularly focus on research that has recently studied the normal maturation of the gastrointestinal tract. In mice (as is also the case in humans), the gastrointestinal tract presents a very high content of bacterial species from different phyla (mainly Bacteroides and Firmicutes) (Nguyen *et al.*, 2015; Rinninella *et al.*, 2019), which are innocuous in

that environment, but might become virulent if they cross the intestinal barrier (a mucus layer) and travel to other tissues in the body (a process called 'bacterial infiltration') (Murphy *et al.*, 2011). Interestingly, several comparative studies between germ-free mice and conventionally raised mice have shown that the microbiome plays a fundamental role in the maturation and maintenance of the intestinal layer, convincingly suggesting that germ-free mice cannot survive in their usual environment. Germ-free mice, in contrast with conventionally raised mice, show a reduction in the thickness of their mucus layer, which is accompanied by a denaturalization (an alteration of its normal properties) (Fiebiger, Bereswill, & Heimesaat, 2016; Kennedy, King, & Baldridge, 2018). It has been demonstrated that these alterations in the intestinal barrier are a consequence of the role that the intestinal microbiome plays in inducing the differentiation of RORγt+NKp46+ natural killer (NK)-like cells, a very specific type of lymphocyte, which aids the construction of the normal gastrointestinal tract (Zheng *et al.*, 2008; Sanos *et al.*, 2009; Jakobsson *et al.*, 2015).

These discoveries support the hypothesis that the bacteria that induce these processes are at least partially integrated into the gut of mice. Indeed, it is not enough that these microorganisms are *present* in the gut during this process. For gut maturation to occur normally these microorganisms have to interact with mice in molecularly sophisticated ways (by producing certain biomolecular components) to trigger the differentiation of the lymphocytes that would further induce the construction of the gastrointestinal tract. Furthermore, in the case of gut maturation, the interaction is temporally restricted and is required to happen during the developmental stage, otherwise maturation is not possible, even if the microorganisms that induce these processes are provided after the maturation should have taken place (Olszak *et al.*, 2012). This example shows how important it is that the host–microbiome interaction occurs at the appropriate developmental stage of the host and is triggered by adequate signals (biomolecular components), creating a particular form of interaction. In this vein, normal maturation requires a series of consecutive host–microbiome co-responses which alter the nature of the mouse and its microbiome, to make both entities "partners through development" (Gilbert, 2017).

In addition to the normal maturation of the intestinal barrier, the gut microbiome of mice has also been shown to play an essential role in determining intestinal homeostasis. It has been shown to balance the fragile equilibrium between different pro- and anti-inflammatory T cells (another particular type of lymphocyte), which actively maintains the intestinal barrier (Neish, 2009; Pradeu & Vivier, 2016; Alam & Neish, 2018). For instance, it has been shown experimentally that the level of iNKT pro-inflammatory cells is higher in gnotobiotic mice than in conventionally raised mice (Zeissig & Blumberg, 2013). This higher incidence correlates with a higher incidence of colitis (Smith & Garrett, 2011). Furthermore, it has been shown that restoration of the equilibrium in iNKT pro-inflammatory cells is only possible if the

colonization occurs at birth. If mice are colonized in their adult stages, they never restore their normal homeostatic levels (Olszak *et al.*, 2012). This last observation suggests that the phenomenon of gut maturation, and the maintenance of its equilibrium (i.e. homeorhesis and homeostasis) are intimately connected in the system formed by the mouse and its microbiome.

Further experiments carried out under specific conditions have allowed identification of the particular bacterial strains, and the biomolecular markers, that are responsible for the particular pro- and anti-inflammatory cell responses in mice. Round *et al.* (2011) have shown that *Bacteroides fragilis* is in control of some of these processes by activating the toll-like receptor pathways that suppress the inflammatory response. The specific suppression is mediated by the suppression of T helper 17 responses, and induction of the differentiation of $CD4^+$ T cells into regulatory T cells (see also Mazmanian, Round, & Kasper, 2008). This process is mediated by polysaccharide A of the bacterial wall of *B. fragilis* (Round & Mazmanian, 2009).

We believe that this last point is especially remarkable if one aims to understand the physiological features of the mouse holobiont, particularly the type of interactions that occur between the host and the microbiome. As we said before, the microbiome will trigger the adequate response only if it interacts in an adequate way with the host. In the case of mice, this interaction must be mediated by polysaccharide A, and needs to occur at the correct stage of mouse development to be conducive to the result. Furthermore, the type of mediation that exists between *B. fragilis* and the host seems strikingly different from the mediation that would occur if the inorganic compounds that mediate this type of interaction were inoculated independently of the microorganisms that carry them (Round & Mazmanian, 2009). This is because the microorganisms of the microbiome are also active throughout the process of mediation, and they might trigger different types of responses, giving rise to different physiological states and, in some circumstances, damaging or even killing the host. In the most striking examples, the microorganisms of the microbiome can even replace a whole organ of the host, playing a role that is essential for the host's survival and, at the same time, can be identified with one of its physiological functions. It is in this sense that we believe that the microbiome cannot be ignored to understand the development, maturation and physiological functioning of their hosts, insofar as the latter can only realize their physiological functions if they interact in the appropriate way with their microbiome *and* their microbiome also interacts in the appropriate way with them [see Stencel & Proszewska, 2018, and Triviño & Suárez, in press for similar arguments].

A further element must be emphasized at this point to justify why we believe that this evidence suggests that the holobiont is the physiological individual. One might agree with our observations about the role that microbes play in host physiology, and wonder why we want to restrict our claim

to the microbiome, instead of extending it to every element that plays a substantial role at some point during the developmental cycle of the host, as those defending developmental systems theory do (Griffiths & Gray, 1994, 1997; Oyama, Griffiths, & Gray, 2001). Indeed, fairly recently, Bourrat & Griffiths (2018) criticized the individuality thesis on the basis that its defenders do not offer any criterion to distinguish the interactions between the elements that compose a holobiont and any other interaction between the host and its environment (they specifically mention the gravitational field). Although we agree that this is an important criticism to the individuality thesis, we think it does not rule out the existence of a substantial difference between the microbes of the host's microbiome, and all the inorganic external elements that play a role during host development. Firstly, in contrast with inorganic elements, the microbes that compose the host microbiome play an active role in these physiological processes, and the processes they engage in with the host have physiological consequences for their own individuality (Gilbert, 2017). This is not the case for inorganic elements, which do not need to maintain their own individuality actively through interaction with the host, or with any of the microbes of the microbiome. Secondly, the interactions between the host and its microbes are normally mediated by host traits and the traits of the microbes that compose the host microbiome. The fact that host and microbiome traits mediate these physiological interactions has important biological consequences that make these interactions different from host–inorganic environment interactions, as some researchers have recently emphasized (Sandoval-Motta, Aldana, & Frank, 2017; Bapteste & Huneman, 2018; Huitzil *et al.*, 2018; Lloyd & Wade, 2019; Suárez & Triviño, 2019, 2020; Suárez, 2020). We consider that this evidence is solid enough to illustrate that the holobiont is a physiological individual from the perspective of the host.

From these points follows an important biological consequence. Macrobes will not be expected to interact constantly with the same species of microorganisms in order to maintain their physiological individuality. On the contrary, as host–microbiome relationships are mediated by the traits that the microbiome bears, and some of these can be shared by different species, macrobes are expected to require interaction with any of the microorganisms that cover their physiological necessities. Since these necessities could change at different stages of development (Gilbert & Chiu, 2015; Gilbert, 2017), and the acquisition of these microorganisms could be entirely opportunistic (Taxis *et al.*, 2015; Hester *et al.*, 2016; Doolittle & Booth, 2017; Lemanceau *et al.*, 2017), the taxa that compose the microbiome of a host might be very broad, and might differ in different members of the host population. Nonetheless, this does not affect our point: since the physiological individuality of the host is always determined by its interactions with the microbiome (no host is naturally germ-free), the holobiont is a physiological individual from the host perspective [see Chiu & Eberl, 2016 for a similar argument with a different conclusion].

V. THE MICROBE/SYMBIONT PERSPECTIVE – HOLOBIONTS AS ECOLOGICAL COMMUNITIES

So far, we have addressed the physiological individuality of holobionts when they are considered from the macrobe perspective. Now we adopt the microbe perspective to argue that, physiologically, holobionts are not individuals from their perspective, but ecological communities. In this sense, from the combination of Sections IV and V, it follows that the division of the individuality thesis into different theses that depend on the conception of individuality adopted does not solve the paradox that holobionts pose for the notion of biological individuality. But first let us show why the physiological individuality of the microbe entails that the holobiont is an ecological community, rather than a biological individual.

As described in Section IV, *B. fragilis* is a bacterial strain that is present in the gut of mice and it is in control of triggering a subset of inflammatory responses which are essential for mice homeorhesis and homeostasis (Round & Mazmanian, 2009; Round *et al.*, 2011). Therefore, we argued, it is justified to consider *B. fragilis* as a part of the physiological individuality of mice, since it plays an active role in maintaining their functionality. Now, let us ask the same question from the perspective of the bacterium. Is it the case that the mouse, and its microbiome, are part of the physiological individuality of *B. fragilis*, so that the holobiont is an individual from the microbe's perspective? The answer to this question is negative, since the normal functionality of *B. fragilis* does not depend on its interaction with mice, nor on its interactions with the microbiome.

Our answer is supported ontologically, by the differences in scale between a mouse and the bacteria that reside within its microbiome, and the consequences that derive from them. The first difference concerns body size, and refers to differences in physical scale that exist between *B. fragilis*, and the body of the mouse in which the bacteria reside. On the one hand, mice are very complex, multicellular units. As a consequence of their large multicellular bodies, they have many different specialized organs and tissues, through which they can permanently interact with a massive number of microbes. Indeed, due to their multicellular and specialized structure, macrobes incorporate many different microbial taxa in their different body parts. Their different organs and tissues offer different environmental opportunities for the microbes, for which they serve as ecological niches to colonize, grow, and reproduce. On the other hand, *B. fragilis* does not have the possibility of engaging in the same degree of ecologically diverse relationships as mice do. *B. fragilis* is not a multicellular organism, which makes it lack the set of tissues and complex structures that are required to interact with the abundant and diverse set of microorganisms that mice interact with. For this reason, *B. fragilis* does not interact with the entire physiological microbiome of the host, but only with a small fraction that resides in the same niche as *B. fragilis*. And the same applies to the specialized cell types of mice: *B. fragilis* only interacts with the cell types of the

specific body site where it resides, but not with other cell types that constitute different body sites of mice. Therefore, as a question of size, the number of microbes that are essential for the proper physiological functionality of *B. fragilis* is necessarily much smaller than the number of microbes that are required for the normal functioning of the mouse that harbours the bacteria.

An important second difference in scale concerns differences in the duration of the life cycle. *B. fragilis* is a bacterium, and bacteria are known for reproducing by binary division and doing so very quickly, giving rise to several generations of the strain in a single day. Mice, on the contrary, are multicellular organisms, and even if their cells specialize and reproduce constantly, at a temporal scale which is similar to the temporal scale of bacteria, this does not entail that mice reproduce at the same scale. On the contrary, it usually takes a few months, or even years, for mice to reproduce. By the time mice reproduce, the bacteria growing in their microbiome would have reproduced billions of times. This does not only accelerate the evolutionary rate of bacteria with respect to the evolutionary rate of the macrobe (Osmanovic *et al.*, 2017), but also supports the belief that there must be striking differences in the biological features of both entities in many other dimensions, including their physiological properties.

The difference in scale between mice and *B. fragilis* has substantial consequences for the individuality of the latter. Since the individuality of *B. fragilis* needs to be addressed at a different scale than the individuality of mice, it follows that the physiological necessities of the former are radically different from the physiological necessities of the later (de Freitas *et al.*, 2016). While *B. fragilis* belongs to the bacterial domain, mice belong to the domain of eukaryotes. Due to this, the inner biochemical processes that keep them alive, in what are usually far from equilibrium conditions (Moreno & Mossio, 2015), are radically different. For example, *B. fragilis* is an obligate anaerobe, which means that it does not require access to oxygen for its biochemical machinery (indeed, oxygen is toxic to *B. fragilis*), whereas mice are aerobic. Furthermore, they do not rely on the same kind of nutrients, nor need to have access to the same biochemical basic compounds for their survival. Therefore, because of these biochemical differences, *B. fragilis* does not need to interact with the same microbes as mice to keep its individuality working, but only with a fraction of the microbes that mice interact with. This suggests that the majority of microbes that live within the holobiont are not necessary to support the physiological processes that keep *B. fragilis* in far from equilibrium conditions.

Our argument is reinforced by appreciating the diversity of ecological niches where this taxon can live. *B. fragilis* is found not only in mice but also in abundance in humans (Mazmanian *et al.*, 2008), bears (Sommer *et al.*, 2016), camels (Paul & Dey, 2015), pigs (Tajima & Aminov, 2015), etc. Of course, the physiological microbiomes of such different macrobe species are not the same: they reside in different niches, they differ in their physiological properties and, more importantly, each of these host species interacts with different microbial taxa (Ley *et al.*, 2008). The fact that *B. fragilis* can be found within such different holobionts suggests that the majority of the functions that the microbes of its surroundings perform are not necessary to maintain its basic physiological properties. In other words, *B. fragilis* can maintain its own structure and functionality over time without any contact with any species-specific type of microbiome. Therefore, it follows that the different microbial species of its surroundings are not necessary for maintaining its basic physiological properties, suggesting that the microbiome where *B. fragilis* happens to reside is not a necessary element for defining its physiological individuality. An inverse situation, however, occurs in the case of some obligate symbionts, like *Buchnera aphidicola*, which can only live in association with a concrete host and its microbiome. These cases do not undermine our point in this paragraph, because even if in some cases the microbiome is necessary for defining the individuality of a bacterial species, this is far from being a general case.

The last two paragraphs illustrate that *B. fragilis* is not metabolically required to interact with the same microorganisms as mice, and the reason why this is so is ontological. In short, mice and *B. fragilis* survive and reproduce at different temporal and physical scales and, therefore, it is unrealistic to think that their physiological individuality could be studied at the same scale [see Vázquez & Saborido, 2018, for a general argument along these lines]. In fact, the physiological properties of the bacterium are so radically different from the physiological properties of mice that we believe that there is no point in arguing that their physiological individuality is coextensional. Indeed, we claim, from the perspective of *B. fragilis*, that the holobiont is not a biological individual, but an ecological community, and thus the ecological-community thesis is true in this case.

One might still raise a final concern and argue that we are wrong, and that it makes sense to argue that the physiological individuality of the macrobe is co-extensional with that of the bacterium because some of the microbes that are necessary for the maintenance of the physiology of the macrobe do indirectly influence the physiology of *B. fragilis*. For instance, a change in the composition of the mouse's skin microbiome might allow the gut to be colonized by some pathogens that will eventually displace *B. fragilis*. This might be true. However, we do not think this should suggest that the physiological individuality of the bacterium and the mouse are coextensional, and thus that the holobiont is also a biological individual from the microbe's perspective. Recall that, according to the definition of physiological individuality that we offered in Section III.2, an entity is a physiological individual only if some of its parts work together to maintain its functionality and structure over time. In the case of mice, the microbiome is a structural element of its physiological individuality, insofar as its physiology is maintained exclusively through interactions between the host cells and the microbe cells. However, the same cannot be said about some microbes: as a consequence of their scale, microbial cells are only involved in a substantially smaller number of

interactions with each other, which suggests that their physiological individuality cannot rest on interactions with the same number of cells does as the individuality of the host. Rather than being involved in a metabolic network with the host and the other microbes of the microbiome, microbes are engaged in an ecological network, thus influencing some aspects of each other's physiology in a non-constitutive manner.

VI. A PART-DEPENDENT ACCOUNT OF BIOLOGICAL INDIVIDUALITY – HOLOBIONTS AS INDIVIDUALS AND ECOLOGICAL COMMUNITIES

The cases we have presented illustrate the existence of two non-co-extensional responses to the question about the individuality of holobionts, even when the problem is approached applying the same conception of individuality. Even relying exclusively on the physiological conception of individuality, holobionts can be considered biological individuals *and* ecological communities, depending on the perspective adopted (host perspective or symbiont perspective). This suggests that the strategy of dividing the individuality thesis into several theses depending on the conception of individuality that is adopted is not valid to resolve the problems of individuation raised by holobionts, contrary to what some authors have argued (Godfrey-Smith, 2013, 2015; Chiu & Eberl, 2016; Griesemer, 2016, 2017; Smith, 2017). Indeed, contemporary literature about the individuality of the holobiont is a clear proof of why the last solution is not valid, with two groups of researchers who deeply disagree (Morris, 2018; Suárez, 2018). Our analysis raises two substantial philosophical issues. First, it is necessary to discern where this incompatibility comes from, i.e. which are the ontological assumptions about the notion of 'biological individuality' that generate opposing judgments about the individuality of holobionts. Second, we must find a way out of the incompatibility. That is to say, we must find a way of discerning an appropriate ontological characterization of the notion of biological individuality that shows why holobionts can be simultaneously biological individuals *and* ecological communities without contradiction.

To answer the first concern, we must return to the discussion of the notion of biological individuality that we introduced in Section III. It seems to us that, regardless of the conception of biological individuality that one uses, the process of delineating biological individuals relies on an ontological assumption according to which the dependency relations among the total amount of elements that compose the whole whose individuality is evaluated are interpreted symmetrically. In other words, the whole qualifies as an individual if and only if all the parts that compose it *mutually* depend on each other. This idea applies equally to accounts of individuality that do not admit 'degrees' of individuality (e.g. Santelices, 1999; Moreno & Mossio, 2015), and to

accounts that admit them (e.g. Godfrey-Smith, 2009, 2013). In both cases, these accounts depart from the assumption that the entities that form the whole need to stand in symmetric relations, and derive the degree of individuality of the ensemble by relying on one of the standard criteria of the field (evolutionary, physiological, immunological, etc.).

For instance, a biologist studying the physiology of a coral might wonder whether the coral–microbiome system should be considered a physiological individual. To answer this question, they would certainly need to consider whether all the parts (coral + its microbiome) qualify as an individual according to the standard physiological criterion provided. It will be in virtue of this sort of judgment that they would decide whether the coral holobiont is (or is not) a physiological individual. In this sense, the whole would be a biological individual if and only if *all its elements* satisfy the criterion that the physiological conception of individuality requires. If some of the parts of the ensemble (e.g. some elements of the microbiome) do not fulfil the criterion, or satisfy it to a very low extent, then the whole is not a biological individual. We suggest calling this approach 'whole-dependent'.

What we call the whole-dependent approach is the standard approach in the literature on biological individuality [see Elwick, 2017, for an analysis], and it has been used to elaborate the different conceptions of biological individuality. For example, the concept of physiological individuality is frequently interpreted under the premise of the whole-dependent approach. In that vein, it is argued that a group of elements constitutes a biological individual only if all the elements in the group are functionally dependent on each other, and commonly integrated. Thus, if some of the elements are proven to be functionally independent or disintegrated, then the whole is not a physiological individual. In other words, one can consider elements a and b as part of an ensemble O when a depends on b, a is functionality integrated with b, and *vice versa*. If that happens, then O is a biological individual, and O's boundaries would be delineated based on the co-dependence between a and b.

But, what would happen if a is functionally dependent on b, but b is not dependent on a? Would O still be a biological individual? Insofar as the physiological conception of individuality has been traditionally interpreted whole-dependently, then the answer would be negative. That reasoning is particularly evident in the statement by Godfrey-Smith (2013, p. 26) that "if the parts of a system have a significant amount of metabolic autonomy, and can keep themselves going somewhat independently, this reduces the degree to which the larger system counts as an organism". And the same is true of Smith's recent account of the organism as an essential persister, an account that stresses that "[o]rganisms (…) must have well-*differentiated* and well-*integrated* phenotypes that enable them to respond to the contingencies that they encounter. The integration of differentiated parts, which allows for *phenotypic accommodation*, provides the basis for the idea that organisms are in some sense *whole* systems" (Smith, 2017, p. 2, original emphasis retained). However, we find two problems with their answer: (*i*) it presupposes that

functional dependency and functional integration are necessarily symmetric relations among all the parts of the ensemble; and (*ii*) it assumes that the criteria for finding "cohesive, well-delineated units" is exclusively whole-dependent. But neither (*i*), nor (*ii*) are true, as evidenced in Sections IV and V.

First, assumption (*i*) is not true because the elements that interact in nature to form biological ensembles can be biologically highly heterogeneous, with a very different structure, and very different biological requirements. A consequence of this is that the relations of functional dependency between different parts of such groups are *non-symmetric*. Note that non-symmetric is not the same as asymmetric. We do not neglect that some of the elements in a holobiont might interact symmetrically with the host, as for example in Lloyd & Wade's (2019) euholobionts (e.g. *B. aphidicola* in the case of aphids). Our point is rather that this is not true for all the elements of the microbiome, many of which will establish asymmetric relations of functional dependency with the host. Thus, non-symmetry.

As we argued in Sections IV and V, given a concrete biological ensemble (mouse holobiont), and given a concrete element of that ensemble (mouse), it is possible that there is a second element of the ensemble (*B. fragilis*) such that: (*i*) the second element is physiologically necessary for the first element of the ensemble, while (*ii*) the second element of the ensemble is physiologically independent of the first element of the ensemble. Therefore, there is a substantial dependency relationship between the two elements of the ensemble (in virtue of the dependency of the first element on the second element), but this dependency is not symmetric, as the two elements do not depend on each other to an equal magnitude. This situation is exemplified by holobionts and, possibly, by any other biological ensemble that is heterogeneous enough that the dependency relationships between their parts is non-symmetric.

Notice that the lack of symmetry that we point out here parallels the host–symbiont asymmetry perceived by Lloyd & Wade (2019). Their perception moved them to propose the concept of 'demibiont' as a middle ground between the concept of euholobiont and the selectively neutral concept of the holobiont. The idea of demibiont, however, rests primarily on evolutionary assumptions, and is agnostic with respect to the ontology of biological individuals. As we argued in Section II, both defenders of the individuality thesis and defenders of the ecological-community thesis may agree that it is important to recognize the reality of the demibiont [which Lloyd & Wade, 2019 clearly exemplify with their study of squid–*Vibrio* interactions], while disagreeing on their verdicts about its individuality. So, a key question is to determine whether the existence of asymmetric situations jeopardizes the application of the notion of biological individuality to the demibiont and, by extension, to the holobiont.

The existence of this situation, we claim, is not problematic for the notion of biological individuality. We illustrated this in Sections IV and V, showing that it was possible to ascribe individuality either to the microbe or to the holobiont, depending on the perspective adopted. Importantly, we have proved that the role that the microbiome plays in mouse development and functioning suggests that considering the holobiont as a physiological individual from the host's perspective is ontologically justified. Building on this observation, our hypothesis is that, instead of rejecting that holobionts are biological individuals (or that they are ecological communities), we should accept that any biological ensemble can be a biological individual from the perspective of some of its parts, *and* an ecological community of independent individuals from the perspective of the others (Fig. 1).

Second, if assumption (*i*) is not true, then it follows that the ontological assumption according to which the notion of biological individuality is whole-dependent is false. We claim that rejecting whole-dependency, and thus dispelling the 'symmetry condition' that is bound with it, is a precondition for explaining the empirical fact that holobionts are biological individuals *and* ecological communities simultaneously. Importantly, therefore, our claim is that the ontological nature of the notion of biological individuality is not whole-dependent, and thus the relationships that exist between the parts that compose any biological ensemble do not need to be symmetric in order to consider the whole as a biological individual. Notice that this claim clearly contrasts with the position of Pradeu (2012), Godfrey-Smith (2013), Smith (2017), and others, who assume that symmetry is an essential component of individuality ('whole-dependency').

The perception of the falsity of assumptions (*i*) and (*ii*) moves us to propose what we call the 'part-dependent' account of biological individuality. In contrast with the whole-dependent account, the part-dependent account assumes that a group of elements might be a cohesive, well-delineated and countable unit from the perspective of some elements, but not from the perspective of others. It derives from the observation that dependency relations are non-symmetric, and thus any notion (or conception) of biological individuality that relies on symmetric relations of dependency will provide contradictory verdicts about the individuality of some biological ensembles (concretely, of the biological ensembles made of heterogeneous entities such that there are asymmetric dependency relationships among some of them). These contradictory verdicts will be at odds with biological practice, as the case of holobionts we have developed herein, especially when holobionts adopt the structure of demibionts. Therefore, assuming that the dependency relations that make up a biological individual need to be symmetric is simply a wrong start, as it fails to provide the right ontology for the notion of biological individuality, and thus the whole-dependent account must be rejected as the wrong ontology for biological individuality.

Notice furthermore that the part-dependent account also explains why the whole-dependent account gives the right type of verdict about the individuality of *some* biological ensembles. In those ensembles that are made of homogeneous entities, such that the dependency relations among them are symmetric, the whole-dependent and the
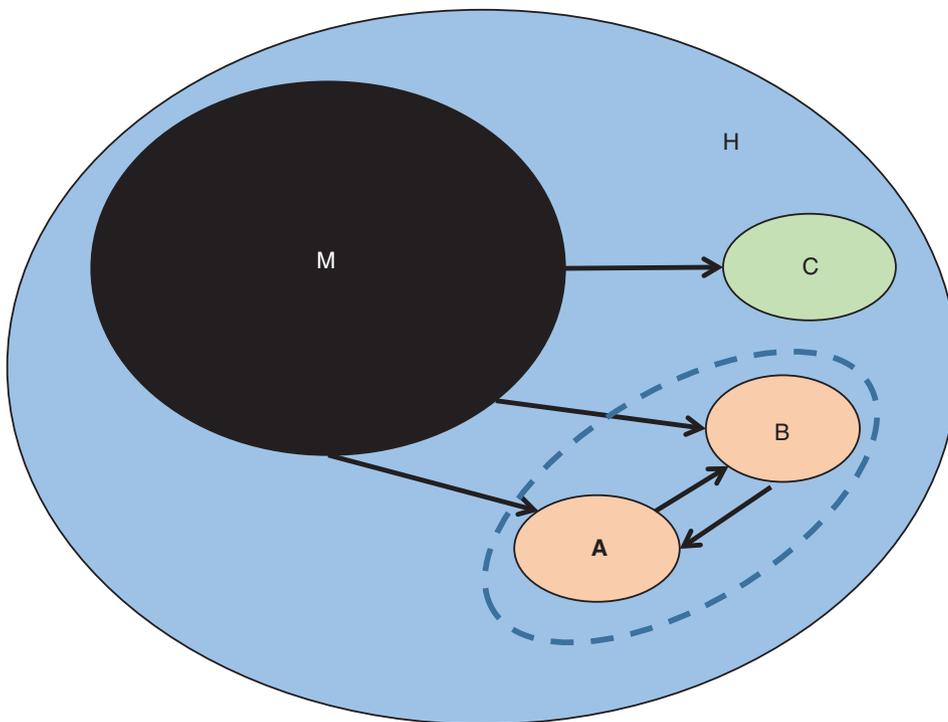
Fig 1 Illustration of different conceptions of individuality. M represents the macrobe host; A, B and C represent its entire microbiome; and H represents the holobiont. The arrows represent functional relations of dependence. In this model, M functionally depends on A, B and C, which suggests that H is the physiological individual. At the same time, the functionality of A is dependent on B and vice versa, so one might say they constitute a biofilm (discontinuous ellipse). Finally, the functionality of C does not depend on any other member of the microbiota, so it can be considered an independent physiological individual.

part-dependent account agree that the ensembles must be considered biological individuals. The problem, we argue, derives from the cases where dependency only works one-way, as in holobionts.

Applied to the holobiont, the part-dependent account entails that the status of a holobiont either as a biological individual or as an ecological community is part-dependent, and that the different conceptions of biological individuality (physiological, developmental, etc.) must be interpreted by prioritizing the elements of the ensemble whose individuality is being studied. In other words, we argue that the question: "Are holobionts biological individuals?" is incomplete and cannot be answered properly due to the important ontological differences among the elements that compose the holobiont. For the question to be complete, some of the entities must be prioritized, so that the right question would rather be: "Are holobionts biological individuals *from the perspective of X*?", where *X* might be the host, or some of the microbes of the host's microbiome.

The part-dependent account of biological individuality explains away current disagreements about the individuality of holobionts that appear in the literature (Morris, 2018; Suárez, 2018). Both defenders and detractors of the individuality thesis are interpreting biological individuality whole-dependently. Since they do so, they fail to appreciate insights from one another, and thus the debate has reached a stage that seems to be a deadlock. The part-dependent account

provides a way of overcoming this impasse: defenders of the individuality thesis are adopting the host perspective, whereas detractors are adopting the microbe perspective. In so doing, they are reaching what *seem to be* contradictory verdicts. However, if the idea of biological individuality is analysed with caution, and its ontological structure is revealed, as we have done herein, one can see why the debate about the individuality of the holobiont has reached its current state. The problem at the basis of the dispute derives from assuming a mistaken ontological nature of the notion of biological individuality, and, therefore, the problem disappears as soon as one realizes that biological individuality is part-dependent.

VII. THE PART-DEPENDENT ACCOUNT BEYOND PHYSIOLOGICAL INDIVIDUALITY

Our review has two important ontological consequences for the notion of biological individuality. First, it entails that the notion of biological individuality is part-dependent, and thus the individuality of biological ensembles needs to be determined by prioritizing some of the elements of the ensemble over others. Second, it entails that the different conceptions of biological individuality (physiological, evolutionary, etc.) need to be re-interpreted part-dependently

too. A consequence of these two points is that our account adds a new layer of pluralism to the debate about the nature of biological individuality. Let us explore these two consequences a little deeper.

First, we have used the case of holobionts to prove that the notion of biological individuality is ontologically part-dependent, rather than whole-dependent, as most of the philosophical and biological literature has assumed. Holobionts, we have argued, constitute a canonical example in which the lack of symmetry between the elements that compose the ensemble shows why the same ensemble can be a biological individual *and* an ecological community simultaneously. Since our claim is not solely about the nature of the holobiont, but about the ontological nature of the notion of biological individuality, we argue that it follows from our account that the individuality of every biological ensemble must be assessed part-dependently, regardless of the level of heterogeneity or homogeneity among its parts. In some cases, the whole-dependent and the part-dependent account will reach the same conclusion about the individuality of a concrete ensemble. In others, though, the whole-dependent account would provide the wrong verdict and, therefore, should be rejected as the wrong type of account of the nature of biological individuals.

Second, since the notion of biological individuality has a part-dependent structure, and this claim is *ontological*, then every conception of biological individuality (physiological, evolutionary, etc.) will be part-dependent too. Therefore, ascriptions of physiological, evolutionary, or developmental individuality must always be made part-dependently. From this position it follows that every ascription of individuality to highly heterogeneous ensembles will give rise to opposing conclusions for different parts of the ensemble, due to the intrinsic lack of symmetry among them. As this lack of symmetry is ontological, rather than biological, the part-dependent account is expected to apply generally, irrespectively of the biological criteria that are used to attribute biological individuality. This is the sense in which our account adds a new layer of pluralism to the current literature on biological individuality (Fig. 2).

Although we cannot elaborate exhaustively how the part-dependent account of biological individuality will apply to every other conception of individuality, we can nonetheless offer a few suggestions of how we believe it can apply to the concept of evolutionary individuality. As the main consequence of our account is that attributions of individuality depend on the perspective adopted, this entails that a conglomerate may be an evolutionary individual from the perspective of some of its elements, but not from the perspective of others. This is because evolutionary dependencies may evolve one-way, thus affecting only one of the partners but not the other (Lloyd & Wade, 2019; Rudman *et al.*, 2019; Suárez, 2020; Suárez & Triviño, 2020).

These empirical observations could be perfectly framed in the context of well-elaborated concepts of evolutionary individuality, in a similar vein to that done here with the concept of physiological individuality. For instance, the interactor

concept can be interpreted part-dependently by arguing that, due to its structural heterogeneity, some holobionts are interactors from the host perspective but not from the perspective of the microbes that compose their microbiome. In that vein, some holobionts are interactors that contain interactors within them. Lloyd & Wade (2019) analysed the symbiosis between the Hawaiian bobtail squid *Euprymna scolopes* and *Vibrio fischeri* by casting it as asymmetric evolution, in which the squid adapts to *V. fischeri* without a reciprocal co-adaptation by *V. fischeri* to the squid. They called these types of one-way evolutionary associations demibionts. We believe that the demibiont is better reconceived as a part-dependent interactor, i.e. the squid is only an interactor in virtue of being a holobiont (as a squid–*Vibrio* symbiosis), whereas the *Vibrio* is an independent interactor. Following Lloyd & Wade's (2019) suggestion that demibionts may be common in nature, we hypothesize that symbiosis usually generates part-dependent interactors [see also Díaz (2015, pp. 16–17)]. Whenever this is the case, community genetic models are required, as they are the appropriate tool to study these forms of evolution (Wade, 2016).

The same argument could be made about the reproducer or Darwinian individual (Godfrey-Smith, 2009). Lloyd & Wade (2019, p. 158) believe that the holobiont would be a reproducer if there is at least some degree of vertical transmission of the microbiome. Although there are strong reasons to think that this may be true in most cases, a part-dependent conception of the reproducer may recast the holobiont as a reproducer even when microbiome transmission is only horizontal. If in some host, the 'birth' of the host is the 'birth' of the holobiont (Gilbert & Chiu, 2015) – i.e. the host only reproduces if it acquires a microbiome – then we can think of the reproducer as a part-dependent individual. In that account, the host is a reproducer only in virtue of being a holobiont, whereas the microbes of the microbiome are reproducers independently of the holobiont. That view of the reproducer seems to be a good way of interpreting the *stability of traits/trait-recurrence* account of the holobiont (Suárez & Triviño, 2019, 2020; Suárez, 2020). According to this account, hologenomic adaptations are traits of the microbiome that are not *necessarily* bound to any bacterial taxon (they move freely between different bacterial taxa through horizontal gene transfer) and are evolving as a part of an 'extended' host genome. Horizontal acquisition does not jeopardize the stability of traits model and, in fact, is to be expected (Suárez, 2020, p. 20). We also believe that Roughgarden's (2020) model of holobiont evolution is part-dependent, as it includes the evolutionary effects of horizontal acquisition that, we believe, will mostly affect the host, which is the entity that evolves as a holobiont. Finally, we believe that Lamm's (2017) idea of the holobiont as a 'structure of evolution' could be interpreted as recasting the holobiont as a part-dependent reproducer.

In conclusion, the two points raised above are connected to one of the main features of our part-dependent approach to holobiont individuality. Our approach is not strictly speaking a novel conception of biological individuality. Rather, it is

Conception   **Perspective**
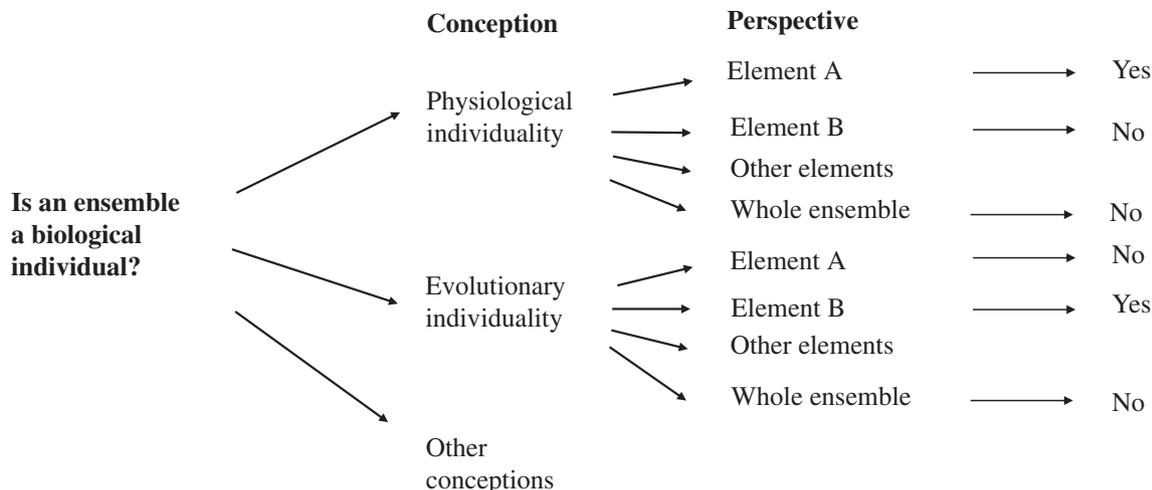
Fig 2 The part-dependent approach to biological individuality is an extension of a pluralistic ontology. According to it, when one has to decide whether a heterogeneous biological ensemble is a biological individual, one should (*i*) choose a conception of biological individuality, and (*ii*) decide the element of the ensemble whose individuality will be studied. If what is picked is the whole ensemble, then the approach adopted would be whole-dependent.

a way of approaching the problem of biological individuality from a different angle which is ontologically more fundamental. In that vein, our approach makes coherent the fact that holobiont thinking is indispensable for understanding many features about the individuality of the host, with the observation that the holobiont/hologenome approach seems totally misguided to understand many of the biological properties of the taxa that compose its microbiome. Insofar as biological individuality is part-dependent, and holobionts are highly heterogeneous biological ensembles, they are simultaneously biological individuals *and* ecological communities.

VIII. CONCLUSIONS

(1) Discussion about the ontological status of holobionts has been very intense in recent years. The debate concerns whether holobionts should be considered as biological individuals or rather as ecological communities. On the one hand, proponents of the holobiont individuality thesis argue that the biological properties of hosts (animals, plants) can only properly be understood if the holobiont is considered a biological individual. Their claim is based on the substantial role that the microbiome plays in host physiology and development. On the other hand, those who deny the utility of the holobiont framework and adopt the ecological approach argue that the host is only one of several suitable niches where microbes can reside. Thus, they claim, overemphasizing the importance of the holobiont would mischaracterize most of the biological properties of the microbiome.

(2) Herein, we review the debate on the concept of biological individuality and its relation to the debate about the individuality of holobionts. By relying on the physiological conception of individuality, we have presented arguments

that are used to support the idea that holobionts are biological individuals, as well as arguments used to support the idea that holobionts are ecological systems. We conclude that both perspectives are justified, because both parties in the dispute use arguments to rationalize their position that seem hard to reject.

(3) To mediate between these two positions, we propose what we call a 'part-dependent' account of biological individuality. In our view, proponents and detractors of the holobiont have not paid enough attention to the differences in their perspectives: while holobiont defenders emphasize the role of the microbes in host development, physiology and evolution, holobiont detractors emphasize that, from the perspective of the microbes, any niche could play exactly the same role as the host. We argue that these two perspectives are based on the existence of an asymmetry between hosts and microbes. Host and microbes differ so much that what constitutes a part of a biological individual from the perspective of the host, can perfectly be an independent biological individual from the perspective of the microbes. We ground that asymmetry in the different durations of the life cycles of microbes and hosts, differences in size, and their different physiological properties.

(4) Drawing upon that asymmetry, we argue that biological individuality should be thought of part-dependently; that is to say, the question "is X a biological individual?" is incomplete. The right question to ask would be: "is X a biological individual *from the perspective of part Y*?". Applied to holobionts, the question that must be asked is not: "is a holobiont a biological individual?", but "is a holobiont a biological individual *from the perspective of the host/from the perspective of the microbes*?"

(5) Our paper shows that contemporary disagreements about the individuality of the holobiont are not a result of the different ways of conceiving how a collective may be a biological individual (physiology, evolution, immunology,

etc.), but a consequence of the lack of a proper understanding of the ontology of the notion of biological individuality. In this sense, we prove that the disagreement is not merely a matter of biology, i.e. a dispute that can be easily solved by appealing to different biological theories or concepts. Rather, it is grounded on philosophical principles, and thus its resolution partially depends on a fruitful interaction between philosophers and biologists.

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