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Are physiological individuals evolutionary individuals? The case of the holobiont

Arjun Devanesan

King's College London, Department of Philosophy
arjun.devanesan@kcl.ac.uk

Abstract:

In this paper I present the immunological account of physiological individuality courtesy of Thomas Pradeu (2012) and the evolutionary account of biological individuality from Ellen Clarke (2012, 2013). I argue that in combination, the logic of these two accounts implies that all physiological individuals are capable of undergoing evolution by natural selection. The main objection to this view is the case of holobionts (Godfrey-Smith 2013, Pradeu 2016). Here, I will argue that this objection is unjustified and that holobionts meet basic criteria for evolutionary individuality. As such, this supports the view that physiological individuals are also evolutionary individuals.

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Introduction:

The main aim of this paper is to point out that, according to the combined logic of the immunological account of physiological individuality courtesy of Thomas Pradeu (2012) and the evolutionary account of biological individuality from Ellen Clarke (2012, 2013), all physiological individuals are evolutionary individuals. However, for Godfrey-Smith (2013), Pradeu (2016a) and many others[1], the main objection to this conclusion is the holobiont i.e. an individual comprised of a host and its physiologically integrated symbiotic microorganisms. This is generally taken to be a physiological individual which is not also an evolutionary individual (see Section 1.2, figure 1).

Here, I suggest that this assessment is too quick, the objection is unjustified and that the distinction between physiological and evolutionary individuality is not what many take it to be. It is worth noting, however, that I do not consider all sorts of physiological individuals here[2] or every account of evolutionary individuality. The main aim of the paper is simply to clarify the relationship between physiological and evolutionary individuality to the extent that we take Thomas Pradeu and Ellen Clarke to be our guide in these matters. This conclusion may well not follow from other accounts of physiological and evolutionary individuality.

I begin by examining Clarke's (2012, 2013) account of evolutionary individuality[3] which aims to unify other accounts by proposing two basic mechanisms which determine units of natural selection. She calls them policing and demarcating mechanisms. Policing mechanisms

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[1] The idea that holobionts are rarely, if ever, evolutionary individuals is a popular view expressed by a number of authors (Booth 2016, Queller and Strassmann 2016, Douglas and Werren 2016, DiFrisco 2019, Wilson and Barker 2024) though, it is not universally accepted (Tauber and Sapp 2012, Bosch and Miller 2016).

[2] There is also a popular view in the literature on physiological individuality that physiological individuals are metabolically integrated wholes (Dupre and O'Malley 2009). I do not consider the metabolic account in this paper. This is mainly because, like Pradeu (2016) and Clarke (2020), I do not find the metabolic account particularly convincing. That said, the purpose of this paper is not to prove that every sort of physiological individual is an evolutionary individual but to suggest that immunological individuals are. If one takes Pradeu's immunological account to be definitive of physiological individuality (and it appears that at least he does), then one might be convinced that all physiological individuals are evolutionary individuals.

[3] It is not clear to what extent this account is generally accepted by philosophers and biologists but it has been available in the literature for over a decade, is highly cited and there has been no major dissent as yet. It also has the advantage of presenting a unified account of evolutionary individuality and as such a good starting point for my argument.

reduce intra-individual variations in fitness and demarcating mechanisms increase or maintain inter-individual variation in fitness. In tandem, these mechanisms determine what counts as a unitary bearer of evolutionary fitness and determines the level at which natural selection occurs.

Policing and demarcating mechanisms are multiply realisable by different physiological systems in different kingdoms, phyla and species. One system proposed by Clarke (2013) which is both a policing and demarcating mechanism is the immune system. As such, any entity policed and demarcated by an immune system will be capable of undergoing natural selection. For Pradeu (2012), however, the immune system plays a different role. He argues that it is present in all living things and serves as the *de facto* arbiter of physiological individuality. That is, anything which interacts with the immune system and is not rejected by it counts as part of the physiological individual to which that immune system belongs.

So for Clarke, immune systems pick out evolutionary individuals while for Pradeu they pick out physiological individuals, including holobionts. If holobionts are not evolutionary individuals, as is generally supposed, then either Clarke or Pradeu must be wrong. However, I shall argue that they are both right, on the grounds that holobionts are perfectly respectable evolutionary individuals.

At first pass, it might seem wrong to count holobionts and similar entities as evolutionary individuals (though see Gilbert, Sapp and Tauber 2012 for a dissenting view). Surely the selection pressures operating on the symbionts are different from those operating on their hosts, they reproduce independently and form separate lineages (Godfrey-Smith 2013). However, I will argue that holobionts meet Lewontin's (1970) conditions for undergoing natural selection. Precisely because of the way the immune system polices and demarcates the whole, holobionts vary in their traits in ways that have a bearing on holobiont fitness and this can be transmitted across generations by epigenetic means and the transmission of immune phenotype.

Section 1: Pluralism and biological individuality

A number of different authors (Clarke 2010, Godfrey-Smith 2013, Pradeu 2016a, DiFrisco 2019, Wilson and Barker 2024) have pointed out that the term 'biological individual' can refer to a variety of different sorts of entities depending on which biological theory it is being used for, or the aims of the biologists that use it. One particular distinction which has gained traction in the philosophical literature is the distinction between physiological and evolutionary individuals (Godfrey-Smith 2013, Pradeu 2016a, Wilson and Barker 2024), with the term ‘physiological individual’ usually being used interchangeably with ‘organism’ (Pradeu 2016a, 2016b). In this section, I will start by roughly outlining a prominent account of biological individuality in the context of evolutionary theory courtesy of Ellen Clarke (2012, 2013, 2016a). I will then contrast this with an equally influential account of the physiological individual according to Thomas Pradeu (2012, 2016a, 2016b, 2019). I then present Pradeu’s (2016a, 2016b) argument that not all physiological individuals are evolutionary individuals (and vice versa). In particular, I will focus on the case of holobionts.

1.1: Evolutionary or Darwinian individuals

In her 2010 paper, Ellen Clarke argues that “it is hard to overemphasize the importance of individuals within the Modern Synthesis. They are central to the inner logic of evolution by natural selection, according to which evolution occurs because of the differential survival and reproduction of individuals” (Clarke 2010, p313). She also points out that there are a number of different ways biological individuals are defined and counted for the purposes of evolutionary theory. She lists thirteen different ways in which authors have proposed we might define and count biological individuals and the most common criteria include a reproductive bottleneck, germ/soma differentiation and spatial boundaries/contiguity (*ibid* 2010).

The bottleneck view takes each individual to begin life either as a single cell or a small number of genetically homogenous cells. It also takes the individual to be the entire meiotic or mitotic product of the bottleneck stage in its lifecycle. The bottleneck stage is also important in that it distinguishes parent from offspring and reproduction from growth. When a single cell divides to produce two new cells in an organism, that is usually taken to be growth of the same organism so the number of organisms does not increase. However, if a cell peels off and start dividing such that it produces a new organism then that is considered reproduction and so the number of organisms increases.

The germ/soma view takes it to be an essential property of a biological individual that there is reproductive division of labour such that some parts of the individual (somatic parts e.g. epithelial skin cells) only carry out physiological functions which support the whole organism but are incapable of producing (by reproduction) a new organism by themselves. Germ cells e.g. sperm or ova cells, on the other hand, are those cells whose function it is to produce another organism.

The spatial boundaries/contiguity view takes biological individuals to be physically discrete and spatially localised. Usually this involves the individual being surrounded by a physical barrier such as a skin or membrane which isolates it from the environment and other individuals of the same or another kind.

However, Clarke (2012) argues that the standard ways in which biological individuality is determined in evolutionary theories runs into major difficulties when applied in the case of plants. She starts by pointing to the inadequacy of traditional criteria such as germ/soma differentiation and reproductive bottlenecks in the case of individual plants. In organisms which have germ/soma differentiation the somatic parts (like skin cells in animals) can only increase their inclusive fitness by contributing to the success of the whole. It is in virtue of this feature that they are considered parts of that larger whole. As such, worker bees would be considered parts of a colony and the colony would be considered the evolutionary individual on this view. However, in many plants, while there may be specific germ lines, all parts can reproduce independently. While roses, for example, can reproduce sexually, a cutting of a stem from a rosebush can be used to produce a whole new plant. So all parts have some degree of reproductive independence and so germ/soma differentiation cannot be the grounds for the intuition that stems, for example, are parts of rose bushes.

Similarly, with respect to the reproductive bottleneck, plants which reproduce vegetatively can do so via multicellular propagules like runners or bulbs. While some (Janzen 1977, Harper 1977, Ariew and Lewontin 2004) would take vegetative reproduction to be mere growth, Dawkins (1982) points out that multicellular runners are efficient at transmitting mutations and so vegetative propagation is capable of producing the kind of heritable variation which drives evolutionary processes. Moreover, many plants (ferns being the classic example) have two single cell stages in their lifecycle - a spore which produces a sporophyte and a zygote which produces a gametophyte. Taking a bottleneck to define the boundaries of parents and offspring would imply that sporophytes and gametophytes, rather than being stages in the life cycle of a single individual, would be distinct individuals and this would create problems for the notion of parent-offspring similarity (Godfrey-Smith 2009).

One response might simply be to discount plants as evolutionary individuals but that seems like an extreme and unpalatable response. Instead, Clarke (2012) proposes that the standard accounts all point towards two generic mechanisms which are multiply realised in different taxa i.e. "the classical criteria achieve their success by homing in on mechanisms which constrain the hierarchical level at which selection is able to act" (Clarke 2012, p338). That is to say, these criteria are really pointing towards general principles which succeed "in picking out the optimal unit for evolution tracking purposes in the same way: by identifying a mechanism which successfully manipulates heritable variance in fitness amongst … parts so that evolution by natural selection can only occur at one level" (ibid p342).

She calls these the principles of policing and demarcating and these are multiply realised by different mechanisms in different species. Policing mechanisms are defined by Clarke (2013, p421) as 'any mechanism that inhibits the capacity of an object to undergo within-object selection'. That is to say, policing mechanisms limit intra-individual variation, therefore reducing selection within evolutionary individuals. On the other hand, demarcating mechanisms are 'any mechanism that increases or maintains the capacity of an object to undergo between-object selection' (*ibid* p424). Demarcating mechanisms promote, permit or maintain inter-individual variation therefore generating selection between evolutionary individuals.

Examples of policing mechanisms include single-cell bottlenecks, germ/soma differentiation and the immune system. For example, by having passed through the same bottleneck, the cells comprising an organism will have a high degree of genetic similarity and this limits the amount of evolutionary selection that can occur between them. Another policing mechanism is the immune system. One function of the immune system is to identify and destroy cancerous cells i.e. cells with certain mutations which give rise to novel phenotypes. The immune system employs a number of different methods to identify cells which share the same genetic lineage (e.g. major histocompatibility complexes) and often will eliminate entities which fail to display them. The immune system therefore constrains the phenotypical variation within the organism and therefore the degree of selection between its different parts.

Demarcating mechanisms on the other hand include things like sexual reproduction, physical barriers and also the immune system. These mechanisms favour inter-individual phenotypical variation by either creating it through sexual recombination events or maintaining it by preventing the migration of parts of one evolutionary individual into another. As Clarke argues, “sexual reproduction increases the capacity for populations of pigs to undergo evolution by natural selection, by increasing the extent to which those populations exhibit genetic variance” (Clarke 2012 p340).

Similarly, “boundaries or barriers around a collection of parts can help to keep within-boundary variance lower than across boundary variance” (ibid 2012 p340). Many of these barriers are also regulated by the immune system. Mucous membranes and interfaces with the environment are usually particularly rich in immune cells (Murphy et al 2022). These immune populations interact with the environment and will accept or reject entities which they come into contact with, depending on whether they are considered harmful or benign (Matzinger 1994). So the immune system is also has an important role in maintaining inter-individual differences in fitness.

According to Clarke, biological individuals are units which under go natural selection i.e. evolutionary individuals, to the extent that they possess both policing and demarcating mechanisms. While, in principle, the more policing and demarcating mechanisms one possesses, the more of an evolutionary individual one is, only one of each will suffice to allow an individual to undergo natural selection. Clarke (2013, p425) clearly recognises that the immune system is both a policing and demarcating mechanism, pointing out that ‘immunity can function as a policing mechanism, such as when the vertebrate "adaptive" immune system polices the organism by eliminating mutant cells. In addition to this, there are clear cases in which immunity plays a demarcating role’, but she seems not to note its significance. Given that an immune system can serve as both a policing and demarcating mechanism, any entity individuated by an immune system is capable of undergoing natural selection according to Clarke’s account. That means that according to Clarke (2012, 2013), immunological individuals are, at least minimally, evolutionary individuals.

Now it is worth emphasising that Clarke (2013) takes the individuality to be a property that objects might possess to a greater or lesser degree i.e. it is a continuous rather than discrete variable. This leads her to a pragmatic thesis that ‘a population-biological model that omits objects with a weak capacity for participating in a selection process will make smaller errors than a model that omits objects with a stronger capacity’ (*ibid* p429). It is then left open how one might quantify the capacity of objects with both policing and demarcating mechanisms to undergo natural selection. So, in Section 2 I will argue that the immune system is a sufficient policer and demarcater such that holobionts do seem to have the capacity to undergo natural selection and are plausible candidates for evolutionary individuals. However, I make no specific claim about the degree of evolutionary individuality they possess.

1.2: Physiological or immunological individuals

It is now widely supposed that not all biological individuals are evolutionary individuals in Clarke’s sense (Godfrey-Smith 2013, DiFrisco 2019, Wilson and Barker 2024). Pradeu (2016a) argues that there is at least one other kind of biological individual, the physiological individual or organism, and that physiological individuals are not always evolutionary individuals because some of them are holobionts. Godfrey-Smith (2013) in particular cites the case of the Hawaiian bobtail squid and its symbiotic vibrio bacteria as a case of a holobiont which is not an evolutionary individual.

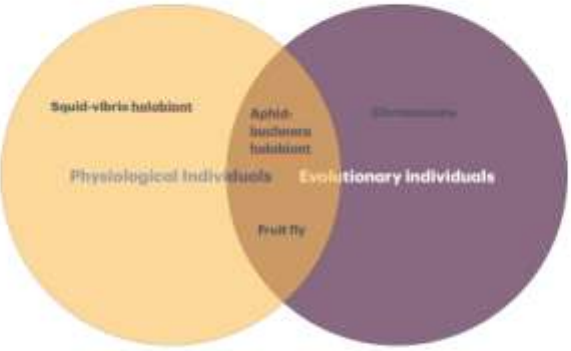

Figure 1 (based on a diagram from Godfrey-Smith 2013 p30): physiological individuals and evolutionary individuals form overlapping sets where some individuals are both physiological individuals and evolutionary individuals like fruit flies and aphids with their *Buchnera* symbionts (aphids holobionts), while some individuals are evolutionary individuals but not physiological individuals like chromosomes, and some individuals are physiological individuals like squid with their symbiotic *Vibrio* species (squid holobionts) but not evolutionary individuals.

However, it is a longstanding objection amongst philosophers of biology that physiological accounts of biological individuality are too vague to settle substantial disputes (Hull 1992). In response, Thomas Pradeu (2012, 2016b, 2019) argues that the immune system can provide a precise and substantive account of biological individuality because it is the immune system which determines the constitution of an organism[4] i.e. what is and is not a part of it. Pradeu’s argument is that “immunology strives to offer a criterion of immunogenicity, which is itself a criterion of individuality. As [he]… point[s] out, the immune system, with its surveillance activity, determines what is accepted or rejected by the organism. A criterion of immunogenicity thus constitutes a criterion of inclusion: the distinction between entities that are interconnected and form a whole as constituents of the organism and those that are rejected is carried out by the immune system” (Pradeu 2012, p240).

Part of the appeal of the immunological account of biological individuality is that it relies on a very simple and widely accepted premise - everything that interacts with an immune system and is not rejected by it is part of the organism to which that immune system belongs. Together with a theory of immunology i.e. an account of how the immune system interacts with entities and determines what is tolerated and what is rejected, Pradeu constructs a precise and substantive physiological theory of biological individuality. He also argues that “all living things have an immune system, including prokaryotes, plants, invertebrates and vertebrates, so an immunity-based account of biological individuality applies to the whole living world” (Pradeu 2016b p804).

One significant upshot of Pradeu’s theory is that if anything which interacts with the immune system and is not rejected by it counts as part of the physiological individual, and the immune

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[4] Pradeu (2016b) uses the terms immunological individual, physiological individual and organism interchangeably and I will follow suit here. However, Clarke (2013) also uses biological individual and organism interchangeably and I take this to be a substantial claim given that pluralism is now the standard view, and there are clearly evolutionary individuals like RNA fragments which are not organisms. As such, I distinguish evolutionary individuals and physiological individuals, with organism referring only to the later, and the dispute being raised here is whether all organisms are evolutionary individuals.

system interacts with and accepts the various symbiotic bacteria in the gut, skin, respiratory and urogenital tract, then those bacteria count as part of the physiological individual. This is a feature of immune interactions in physiological individuals that Pradeu (2012, 2016a, 2016b) is keen to point out. The immune systems of most, if not all, physiological individuals interact with a host of other living things like archaea, protists, bacteria and fungi, but accept rather than reject them. Some of these regularly interact with the rich and active immune system in the lining of the gut and are accepted there, while others are rejected.

If we then accept the premise that anything which interacts with the immune system but is not rejected by it is part of the physiological individual (or organism) to which the immune system belongs, we should accept that these bacteria are part of the physiological individual and therefore this individual is composed of a much more genetically diverse set of constituent parts than previously thought. As Pradeu (2016b, p784) argues, "the physiological individual, immunologically, is the unit made of the association of a host and many microbes ... If this view is correct, then all the criteria of the supposedly paradigmatic "unitary organisms" … are problematic."

1.3: Holobionts as physiological and evolutionary individuals

Lynn Margulis (1991) is usually credited with introducing the term 'holobiont'. Originally this referred to a host and a single inherited symbiont (usually a microorganism). Now, the term has been extended to refer to a host and a community of microorganisms which interact with the host in either mutualistic or parasitic symbiosis. Holobionts are typically thought of as physiological individuals (Pradeu 2016a, 2016b) because they are tightly physiologically integrated. However, as DiFrisco (2019) points out, "the component symbionts tend to have correlated mortality rates, but they are not transmitted vertically from the same source and they reproduce independently. That makes it difficult to meaningfully assign parent–offspring lineages between successive 'generations 'of whole holobionts, putting the heritability of holobiont-level properties into question." So, holobionts are thought not to be evolutionary individuals. In what follows, I will clarify the role of heritability and lineage-formation in the classical logic of evolution by natural selection to show that this view is unjustified.

Pradeu (2016b), picking up on Godfrey-Smith (2009, 2013), takes evolutionary individuals to necessarily be reproducing units. Furthermore, he points out that "a major result of recent biological research is precisely that very often a physiological individual is not as such a reproducing entity, but rather a local nexus of different lineages of reproducing entities. Indeed, work on symbiosis has shown that virtually all physiological individuals are multispecies units" (Pradeu 2016b p809). If, as Pradeu argues here, holobionts do not collectively reproduce but are groups of independently reproducing individuals, it is hard to see how they might be units of natural selection.

In some cases, as DiFrisco (2019) and Pradeu (2016b) point out, the symbiotes which colonise a parent are not vertically or directly transmitted to their offspring. Offspring may acquire the same kinds of symbiotic microbes from the environment during the course of its development, but "in the case of horizontal transmission, physiological individuals understood as host-microbe associations do not constitute lineages as associations. Rather, those associations are local concentrations of different lineages. For example, a physiologically- defined human being is the locus of one genetically "human" lineage, and many microbial lineages" (Pradeu 2016b p810).

But this raises an important issue. According to Pradeu's immune account of physiological individuality, holobionts are physiological individuals because the immune system of a host tolerates all its symbionts. Furthermore, as argued above, according to Clarke's (2012, 2013) account of evolutionary individuality, the immune system serves as a policing and demarcating mechanism. If so, holobionts meet Pradeu's (2012, 2016b) criteria for physiological individuality and meet Clarke's (2013, p427) definition of a biological (evolutionary) individual: all and only those objects which possess both kinds of individuating mechanisms i.e. policing and demarcating mechanisms.

So as far as Pradeu's (2012, 2016b) account of physiological individuality and Clarke's (2012, 2013) account of evolutionary individuality are concerned, given that physiological individuals are definitively constituted according to the behaviour of the immune system, and the immune system is a policing and demarcating mechanism, this suggest that any such physiological individual is also an evolutionary individual, including holobionts. This is simply what follows from the logic of these two accounts. If holobionts are not evolutionary individuals as Pradeu himself and others seem to suggest, then something has gone wrong with these accounts.

What this shows is that Pradeu's account of physiological individuality and Clarke's account of evolutionary individuality, taken together, are in tension with the view that holobionts are not evolutionary individuals. In order to resolve this tension, in the next section I will argue that holobionts are plausible candidates for evolutionary individuals. Furthermore, given that holobionts are the main counterexample to the view that all physiological individuals are evolutionary individuals (Godfrey-Smith 2013, Pradeu 2016a, Wilson and Barker 2024), a convincing argument that holobionts are evolutionary individuals should make us reconsider the distinction between physiological and evolutionary individuals.

Section 2: Holobionts and evolutionary individuality revisited

Humans are multicellular organisms which seem to be paradigm evolutionary individuals (Godfrey-Smith 2009). However, as Wilson and Sober argued (Wilson and Sober 1989), if groups of cells can be units of natural selection in the case of multicellular organisms like humans, what is to stop other sorts of groups behaving as units undergoing evolution by natural selection as well? As Richard Lewontin (1970) also pointed out it is at least logically possible for evolution by natural selection to occur at any hierarchical level so he proposed a set of necessary and sufficient conditions for evolution by natural selection which have now become orthodox.

Those who advocate for natural selection occurring at multiple hierarchical levels generally try to stipulate conditions which must be met for evolution by natural selection to occur or define the properties any sort of group must possess in order for it to undergo such a process. The most famous formulation of conditions for evolution by natural selection was proposed by Lewontin (1970). These are that there must be a population with phenotypic variation[5] i.e. individuals in the population have morphological differences, these differences give rise to variation in fitness i.e. different individuals produce more or fewer offspring in virtue of their phenotype, and finally, this phenotypical variation is heritable such that parents pass their phenotypical features on to their offspring.

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[5] The phenotype of an organism is its observable characteristics such as its anatomy, physiology, external appearance, behaviour and development. In the case of a holobiont, this includes both the composition of the holobiont in terms of the host and associated symbionts, their physiological interactions e.g. mutualistic symbiosis, and their developmental trajectory.

A number of refinements have been proposed (see Godfrey-Smith 2007), but for the purposes of this paper, what is important is that they all propose some principle of variance, differential fitness and inheritance. More importantly, in order for these criteria to be met, we must first be able to divide up a population into individual units, each with a specific phenotype and evolutionary fitness and we must be able to distinguish growth from reproduction. In that way, Clarke's and Lewontin's accounts are complementary. In order to know whether Lewontin's conditions obtain we must first have a principled means by which we divide up a population into units. Clarke (2012, 2013) provides a method for doing that.

However, once we have divided up the population by attending to policing and demarcating mechanisms, it is still a substantial question whether they meet Lewontin's conditions for evolution by natural selection. For example, even if we divide up a population into units based on the behaviour of immune systems, anatomical boundaries, germ/soma differentiation and such, it does not follow that these individuals will have differences in phenotype relevant to their fitness or that these differences in phenotype between individuals will be inherited by their offspring in the way required by Lewontin's conditions. That is to say, phenotypical variation and heritability of differential fitness does not logically follow from Clarke's (2012, 2013) account. This is especially important when we think about holobionts because, as previously argued, they appear to meet Clarke's criteria for counting as evolutionary individuals but the main reason they are generally supposed not be is that they are thought not to form appropriate parent-offspring relationships.

It is reasonably straightforward to show that holobionts meet Lewontin's first two conditions i.e. phenotypical variation and differential fitness. In the case of humans, associations with certain microbial species over evolutionary time have led to mechanisms which actively facilitate colonisation with some microbes in the gut but not others e.g many *Bacteroides* species are tolerated by the immune system of the gut but *Listeria* are not. It is also worth emphasising that this phenotypical variation occurs at multiple levels including at the level of the holobiont.

That means that, for example, monozygotic i.e. 'identical' twins can (and probably will) form nonidentical holobionts because the composition of their microbial communities will differ. Holobionts will only be phenotypically identical if the hosts are identical and are colonised with exactly the same proportions of exactly the same microbial species and physiologically interact with their symbionts in the same way. This is highly unlikely to occur so phenotypical variation is practically guaranteed. Whether these phenotypical differences given rise to differences in fitness is, however, a substantial and important question and I will argue that it does.

The immune system, being the main way in which human hosts regulate their interaction with microbes, is thought to have developed its receptor morphologies partly in response to evolutionary and selection pressures (Mushegian and Medzhitov 2001, Nyholm and Graf 2012, Devanesan 2024). The ability of the immune system to delicately regulate the colonisation of the host with symbiotic microbes is an active and evolved process whereby "the immune system can discriminate between pathogens and the microbiota through recognition of symbiotic bacterial molecules in a process that engenders commensal colonization" (Round et al. 2010 p974).

These microbes also facilitate a number of other critical physiological processes in the human gut including the production of essential vitamins. In this way, it is thought that associations with certain microbes may have relaxed selective pressures on the host to obtain foods with these vitamins and facilitated dietary transitions, and this enabled colonisation of new environments (Moeller and Sanders 2020). So it is clear that holobionts can show variations in phenotype depending at least in part on the kinds of bacterial symbionts that comprise them, and these difference have an impact on fitness.

However, unless these variations in phenotype are also heritable, we will not have satisfied the conditions for evolution by natural selection. The most uncontroversial cases occur in species in which there is vertical transmission of obligate symbionts. In the case of aphids, *Buchnera aphidicola* are maternally inherited obligate symbionts. The aphids are nutritionally dependent on their *Buchnera* for providing essential amino acids. The bacterial symbionts are transmitted from mother to offspring by specialised cells called bacteriocytes which ensures the continuation of a specific relationship between the descendants of a particular aphid and descendants of its symbionts (Koga et al 2012).

So, it is now generally accepted that such obligate symbiotic relationships are heritable and shape the evolution of the holobiont complex as a whole. As Bennett and Moran (2015) point out, “acquiring a heritable symbiont is effectively a mutation of major effect, increasing host fitness at the population and clade level. In many, although not all, identified cases, these acquisitions have resulted in a proliferation of descendant lineages, usually comprised of species restricted to a particular dietary niche. Thus, long-term, heritable symbiosis underlies many dominant insect lifestyles and has shaped macroevolutionary and ecological patterns.” While this is well documented in insects, and aphids in particular, what about the case with facultative (non-obligate) symbiosis and symbiosis in mammals?

One mechanism which facilitates transmission of holobiont phenotype involving both obligate and facultative symbiosis, particularly in mammals, is our beloved immune system. Until very recently, the standard view of immunology divided the immune system into the innate and adaptive systems. The innate system is characterised by genetically encoded receptors which trigger specific immune responses without the need for prior exposure and without an augmented response given repeated exposure. The acquired system, on the other hand is characterised by requiring exposure to an antigen to develop and repeated exposure augments the response[6].

It is generally accepted that the receptor profile of the innate immune system is inherited and so the dispositions of the innate immune system of a parent will determine (to a significant extent) the dispositions of the innate immune system of offspring (Boraschi 2024). For example, while immune receptors in general demonstrate remarkable plasticity, Natural Killer cell receptors in humans are the result of convergent evolution and are thought to have co-evolved with MHC-I receptors in mammals because certain combinations will lead to problems with mammalian pregnancy (Parham and Moffett 2013). Similarly, innate immune cells play a crucial role in regulating the colonisation of the gut with microbes, and the immune system of the gut in turn does not properly develop and mature without microbial colonisation (Khan et al 2021).

However, even if the disposition of the innate immune system is inherited and the innate immune system influences composition and therefore phenotype of the holobiont, that does not yet entail that the phenotype of the holobiont is inherited. First, it is important to

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[6] Current thinking increasingly disputes this dichotomy and views innate and acquired immunity as a continuum (Netea 2020).

distinguish reproduction at the level of the host and reproduction at the level of the holobiont. In human holobionts, host reproduction is of the familiar sort - sexual reproduction which produces a fertilised zygote, a unicellular bottleneck, which is gestated for nine months or so and then born. Once born, the new human host is colonised by an array of microbes, primarily acquired from its mother’s genital tract, skin and gut but also from the environment. This then forms a new holobiont.

In order to show that this new holobiont is the offspring of some parent holobiont, we must show that the parent holobiont significantly (but not necessarily entirely) determines the existence and phenotype of the offspring. And in order to satisfy Lewontin’s criteria, the phenotype of the offspring must be similar to the parent to a degree higher than would be expected due to random chance. So far I have shown that the immune phenotype of a parent host influences the phenotype of the holobiont which it is a part of (the parent holobiont) and this immune phenotype is transmitted to its offspring through the usual mechanism of sexual or asexual reproduction. In such offspring, the inherited immune phenotype will influence the constitution and phenotype of the holobiont that it will be a part of later in its development (the offspring holobiont).

However, there is one element left to demonstrate. Why should we think that the immune phenotype of the parent host, when transmitted to its offspring, should result in an offspring holobiont phenotype which is similar to the parent holobiont phenotype? As I will show below, this is because the interaction between the immune system and microbial communities results in covariation in parent and offspring holobiont phenotype.

Recent research, for example, has shown that what was classically thought of as innate immune systems have the ability to modulate their response to an antigen given repeat exposure in what is now being called ‘trained immunity’ (Prigot-Maurice et al 2022). This is most clearly demonstrated in the gut where it is now well known that the gut immune system only properly develops in conjunction with certain bacteria (Khan et al 2021, Boraschi et al 2024). Also, the composition of the gut flora required for proper maturation of the gut immune system is host-specific (Chung et al 2012). That is to say, certain host species require colonisation by certain microbial species in specific proportions in order to properly develop. So, the immune system determines the composition of gut microbial flora which in turn influences the dispositions of the immune system in a mutually reinforcing feedback loop.

This ‘trained immunity’ is thought to be the result of epigenetic reprogramming of immune cells in a way that can be inherited, possibly by gametic DNA methylation and chromatin remodelling (de Candida and Materese 2021). While this has been primarily studied in the context of immune responses to infections (Katzmarski et al 2021), there is also emerging evidence that inheritance of immune traits also has a bearing on immune tolerance of symbionts (Prigot-Maurice et al 2022). So both the innate and acquired immune phenotype is influenced, over time, by exposure to the antigens carried on symbiotic bacteria and fungi. And this can be passed on to offspring such that they then enter into symbiotic relationships with similar species of microbes in similar proportions.

The inheritance of immune traits ensures that the next generation enters into the same or similar symbiotic partnerships as their parents even in the case where the symbionts are not directly transmitted from parent to offspring like the case of aphids and *Buchnera*, but are acquired from the environment. Even in such cases of horizontal transmission of symbionts, the mechanisms by which the host immune system tolerates such symbionts are inherited (Nyholm and Graf 2012) and this facilitates reproduction of holobiont phenotype. What this demonstrates is that there is a mechanism, the transmission of immune phenotype through reproduction at the host level, which ensures that reproduction occurs at the level of the holobiont. This requires a broader view of reproduction than the one Godfrey-Smith and others appear to standardly endorse, but there is an increasing body of literature which puts pressure on this notion (Laland et al 2015, Griesemer 2016, Veigl 2022).

If holobiont phenotype of one generation is partly determined by the holobiont phenotype of the previous generation, and these phenotypes show differences in fitness, this is sufficient to meet Lewontin’s criterion of heritability of differential fitness. As Godfrey-Smith (2007 p494) points out, “It is sufficient for [Evolution by Natural Selection] (given other conditions) that parent and offspring be more similar than randomly chosen individuals of different generations”. This is a reasonably weak condition which appears to be adequately satisfied in the case of holobionts because of the transmission of immune phenotype. As such, given that holobionts show heritable variation in phenotype and fitness, we should be willing to grant that they are evolutionary individuals at least in a minimal but significant sense.

Objections:

One objection one might raise at this point is that, appearances notwithstanding, unless holobionts can collectively reproduce they cannot be evolutionary individuals. This point was raised by Peter Godfrey-Smith (2013) and is one of the main reasons that Pradeu (2016b) rejects the possibility that holobionts are evolutionary individuals, the other one being that holobionts do not form appropriate parent-offspring lineages. Godfrey-Smith (2013) points to the case of the Hawaiian bobtail squid and the symbiotic vibrio bacteria which provide the squid with bioluminescence. The bobtail squid has specialised crypts which accommodate a specific bioluminescent vibrio bacteria (*Vibrio fischeri*). Its immune system prevents other bacteria colonising these crypts but tolerates *Vibrio* species. Every night, the bacteria light up and are thought to help camouflage the squid. At dawn, most of the bacteria are expelled into the surrounding water and are allowed to regrow from a small retained population during the day.

On the question of whether the squid-vibrio holobiont is an evolutionary individual, Godfrey-Smith objects that “if we accept that the [squid-vibrio] combination is an organism, then we find that the combination does not reproduce in the sense that is relevant to being a Darwinian individual. The combinations do not form parent-offspring lineages” (Godfrey-Smith 2013 p29). The reason he claims that they do not reproduce in the sense relevant to being a Darwinian individual i.e. evolutionary individual, is because the bacteria are not passed directly from parent to offspring but are acquired from the environment. He argues further that “if you are a squid, there is no mechanism ensuring that the bacteria in you are the offspring of bacteria in your parents, or any other specific individuals. The bacteria in you might come from many sources, and some might have not been inside squid for many generations. Squid-Vibrio combinations "make more of themselves" in *one* sense, but not in the sense that gives rise to parent-offspring lineages” (*ibid* p29).

So Godfrey-Smith (2013) accepts that squid-vibrio holobionts ‘make more of themselves’ because one generation of holobionts ‘make’ a successive generation in the sense of being causally responsible for its existence and phenotype[7]. However, he rejects the idea that this

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[7] Here, ‘causally responsible’ is not taken to mean that the cause exactly and sufficiently determines the effect. Instead, it is a weaker notion where covariation in parent and offspring phenotypes is grounded by some causal mechanism or set of mechanisms.

counts as ‘reproduction’ because ‘the parent-offspring lines connect only the parts – they connect bacteria with bacteria and squid with squid’. That is to say, the squid-vibrio holobiont does not seem to reproduce as a whole. Its parts reproduce independently and separately only to come together to form a new holobiont at some later time[8]. More importantly, the squid-vibrio holobiont does not seem to form parent-offspring lineages in the way that Godfrey-Smith thinks is required of Darwinian individuals because “some of the bacteria that initiate a colony may have an ancestry that can be traced back to other colonies just a few bacterial generations back. Others may have not have ancestors inside squid-Vibrio complexes for a great many generations – perhaps ever. This is not a case where each squid-Vibrio collective has a definite and reasonably small number of parent collectives, even though each squid has exactly two parent squid and each colony-initiating bacterium has one parent bacterium” (*ibid*, p30).

However, there is nothing in Lewontin’s criteria for evolution by natural selection which requires that offspring derive all their parts from their parents, that offspring have any specific number of parents or that all of an offspring’s parts from their parents arrive at the same time[9]. Bacteria are well-known to exchange genetic material with other members of the same generation and yet I cannot imagine anyone would deny that bacteria are evolutionary individuals. If bacteria can acquire parts from the environment or other bacteria and remain evolutionary individuals, then why not squid?

Strictly speaking, as far as Lewontin’s criteria are concerned, all that is required of ‘reproduction’ is that parents are causally responsible for the existence and phenotype of their offspring[10]. And in the case of squid-vibrio holobionts, Godfrey-Smith admits that they do in fact ‘make more of themselves’ in this sense. Perhaps this ‘making more of’ could be more precisely articulated as a case of scaffolded reproduction in the sense proposed by Griesemer (2016) and others. There is no space to fully articulate this idea here but, insofar as we accept

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[8] Interestingly this is similar to the case of the Portuguese Man ‘O’ War jellyfish in which parts appear to reproduce independently and offspring jellyfish are assembled from independently reproduced parts. As such, it is a subject of current discussion as to whether this and other jellyfish are single organisms or colonies. Godfrey-Smith (2017) argues that Portuguese Man ‘O ’War jellyfish are organisms, though he is not clear on whether he thinks they are also evolutionary individuals

[9] My thanks to an anonymous reviewer for this last point

[10] The same is true of analyses which favour the Price equation

that there are successive generations of holobionts *at all* we ought to grant that squid-vibrio and other holobionts which ‘make more of themselves’ do so in a way that allows for evolution by natural selection.

It is also clear that holobionts stretch our understanding of lineages. Derek Skillings illustrates the point with a hypothetical case of a doctor who delivers a baby, the baby acquires a bacterium from the doctor and is quickly colonised by it. Here, Skillings argues that “we can now pick out a new parent-offspring relation between the doctor holobiont and the baby holobiont. From a lineage-neutral perspective at the holobiont level, this is no stranger than saying that the parent-offspring relation is between the mother holobiont and the baby holobiont” (Skillings 2016 p 883).

It may sound strange that the baby holobiont has, as its parents, the father holobiont, the mother holobiont and the doctor holobiont but I see no reason why this strangeness should undermine the view that the baby holobiont is an evolutionary individual. While Lewontin’s criteria requires that evolutionary individuals form lineages, there is no stipulation or restriction on the number or complexity of the parent-offspring lineages any particular individual is allowed to be part of. All that is required is that any individual has *some* parent or parents, and is a part of *some* lineage and in the case of holobionts, both of these are true.

Derek Skillings (2016) makes the further point that “high partner fidelity is a prerequisite for evolutionary individuality because the holobiont can only evolve as a unit if the host and its symbionts co-occur across multiple host generations” (Skillings 2016 p884). He argues that partner fidelity is important because it aligns the fitness of the host and its associated symbionts and without this, there is an “expectation of increased conflict between the members of the holobiont as they ‘‘pursue their own goals’’; namely, selection for increased replication of one’s own lineage at the expense of the success of the multi-lineage holobiont. As conflicts of interests among partners increase (e.g., due to weak partner fidelity), then the holobiont is undermined as a higher- level unit of selection” (*ibid* 2016 p884).

While this sounds reasonable, and some symbiont exchange is probably fairly commonplace, it is not obvious that this undermines holobiont evolutionary individuality in any particular case. While the whole point of demarcating mechanisms is to minimise the extent to which different individuals exchange parts, it is not necessary for these mechanisms to prohibit any exchange whatsoever. Ultimately, what matters is whether that mechanism keeps inter-individual variation in fitness higher than intra-individual variation in fitness.

So, while Skillings' point is well taken, partner fidelity and material exchange depends on the strength and specificity of demarcating mechanisms and the immune system is a particularly strong and specific example of one. As Clarke (2016) argues in the case of herds, "the giraffe herds qualify as individuals, on this view, only if there are mechanisms enforcing the between-group variance and the within-group homogeneity". Whether the effect of these mechanisms is enough in case the case of any particular holobiont is a substantial question but I see no reason why Skillings' objection should undermine the view that, given sufficient policing and demarcation by the immune system, holobionts will undergo natural selection.

However, one might respond with the objection that in the case of holobionts, the immune system does not appear to be functioning as a demarcating mechanism at all. After all, by allowing microbes to colonise the host, the immune system of the host is increasing intra-organismal variation relative to inter-organismal variation[11]. However, this objection is due to a misunderstanding about the different levels of immune systems in an organism or holobiont. There is no space here to fully describe the architecture of holobiont immune systems but some basic distinctions are in order. In the same way that the human brain has a distinct immune system which is part of the immune system of a human organism, a human organism (minus its symbiotic microbes) has an immune system which is part of the immune system of a human holobiont.

That is to say, the holobiont immune system is larger than the host immune system (see Schneider 2021 for a suggestion in this direction). For example, in the human gut, while the composition of microbial species changes with diet and diseases, it also shows remarkable stability over time. This is thought to be due to a number of mechanisms including interaction with the host immune system. This includes the host immune system actively tolerating or destroying certain species as mentioned above, or the immune system being induced by one bacteria to destroy another. For example, *Bacteroides* species induce intestinal Paneth cells to produce angiogenin which suppresses the growth of *Listeria* species (Cash 2006).

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[11] my thanks to an anonymous reviewer for pointing this out

In addition, microbes show both competitive and commensal behaviours. Some species actively devour others or produce waste products which are toxic to competitors. Some species also actively foster other species by producing waste which other species feed on or by maintaining a certain pH which is conducive to some species of microbes but not others. This system results in a balanced microbial ecosystem characteristic of a healthy gut (Coyte and Rakoff-Nahoum 2019). So, the holobiont immune system extends beyond the immune system of the host to include the competitive and commensal behaviours of those microbes which constitute the holobiont as a whole. It is this immune system which maintains the composition of the holobiont and acts as a demarcating mechanism.

Finally, it is also worth emphasising that both Clarke (2013) and Godfrey-Smith (2009) view evolutionary individuality as a property of entities which comes in degrees. So an entity such as a human holobiont might be less of an evolutionary individual than a human organism without its commensal microbes, but still be an evolutionary individual nonetheless. In this paper I make no comparison of relative individuality in the case of holobionts. I only argue that they are individuals which are policed and demarcated by the immune system to a sufficient degree to allow them to undergo evolution by natural selection. Moreover, since the argument takes the immune system to generically ground evolutionary individuality, it would follow that all immunological individuals are capable of undergoing natural selection.

Conclusion:

In this paper I started by examining Clarke's (2012, 2013) account of evolutionary individuality and argued that the immune system is both a policing and demarcating mechanism. If so, then any entity individuated by an immune system must be an evolutionary individual. However, Pradeu (2012) argues that the immune system determines the constituent parts of a physiological individual i.e. an organism. If we take the both of these accounts seriously, this should lead us to believe that all immunological individuals *qua* physiological individuals are evolutionary individuals.

While this does not definitively prove that all physiological individuals i.e. organisms are evolutionary individuals, it shows that on at least two important accounts of immunological and evolutionary individuality, this appears to be the case. I have not specifically entertained the notion of a metabolic individual and am open to the possibility that they may be physiological individuals which turn out not to be evolutionary individuals. At present, however, I know of no such cases. At a minimum, what I hope to have shown here is that the way we currently distinguish evolutionary and physiological individuality requires closer evaluation.

What this does not imply is that the concept of physiological individuality is obsolete. After all, I have not shown that all evolutionary individuals are physiological individuals and indeed, at least at face value they do not appear to be. Chromosomes and RNA can undergo natural selection but they are not considered to be physiological individuals. So the concept of a physiological individual would still be important in picking out those evolutionary individuals individuated by physiological systems and those that are not. Physiological individuality can also serve as a different descriptive mode for certain evolutionary individuals where the question of interest e.g. how reproduction occurs in a species, might be better answered by appealing to physiology rather than evolutionary mechanics.

Hopefully, this paper clarifies the nature of the relationship between these two categories of biological individuality. It also forms part of a growing body of literature which challenges traditional ideas about of evolutionary individuality and invites us to critically evaluate our notions of inheritance and reproduction along the lines of an extended evolutionary synthesis (EES) (Laland et al 2015, Griesemer 2016). I have not specifically mentioned the EES here because I think that would be needlessly distracting and require exposition which is beyond the scope of the paper. Instead, I claim that holobionts could be considered evolutionary individuals even according to the logic of the Modern Synthesis.

I argued that holobionts meet Lewontin's conditions for evolution by natural selection. I showed that holobionts show variations in phenotype which affects reproductive success of the holobiont as whole. I also argued that there are a number of ways this variation can be inherited and therefore have important evolutionary consequences. As such, we should be willing to grant that holobionts are evolutionary individuals at least to a minimal but significant degree. This lends further support to the view that physiological individuals are also evolutionary individuals.

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