Adaptive Regeneration Across Scales: Replicators and Interactors from Limbs to Forests

S. Andrew Inkpen* and W. Ford Doolittle†

Here we endorse Hull's replicator/interactor framework as providing the overarching understanding sought by MacCord and Maienschein. We suggest that difficulties in seeing the regeneration of limbs by salamanders and of forest ecosystems after fires as similar evolutionary processes can be overcome in this framework. In generalizing Dawkins's "selfish gene" perspective, Hull defined natural selection as "a process in which the differential extinction and proliferation of interactors causes the differential perpetuation of the replicators that produced them". Although genes and bacteria are simultaneously both replicators and interactors, communities and ecosystems are generally only interactors. As reproducers, members of sexual species are intermediate. Within such species, organisms are indeed the interactors whose "differential extinction and proliferation" causes the "differential perpetuation" of replicators (genes). But sexually-reproducing organisms do not individually replicate, persist, or recur as interactors, and in consequence it is only those genes causing an interactor differential that are specifically perpetuated in the long run. Higher-level interactors (multi-species communities and ecosystems) may seldom if ever reproduce, but their recurrence does enable the "differential perpetuation" of replicators specifically responsible for their "differential extinction and proliferation". In offering answers to the question "What are the replicators specifically responsible for the differential extinction and proliferation of such higher-level entities?" we hope to unify adaptive regeneration across scales, from organisms to ecosystems.

Keywords

regeneration • ecology • evolution • replicator-interactor • Hull, David • multi-level selection theory • microbiomics • holobionts

we are interested in the possibility of finding **an overarching understanding or theory** that can explain how regeneration works at all levels, from individual organisms through to microbial communities and ecosystems, and this is likely to require us to think carefully about the **basic units and mechanisms** involved in regeneration.

—MacCord and Maienschein (2019, e46569)

*Department of Philosophy, Mount Allison University, Sackville, New Brunswick, Canada, ainkpen@mta.ca

<https://orcid.org/0000-0003-4824-5632>

†Department of Biochemistry and Molecular Biology, Dalhousie University, Halifax, Nova Scotia, Canada, ford@dal.ca <https://orcid.org/0000-0002-4675-8832>

Received 12 May 2020; Revised 24 August 2020; Accepted 24 August 2020
doi:10.3998/ptpbio.16039257.0013.001

1 Introduction

Diverse living systems possess the capacity for regeneration; that is, they can under some circumstances repair, re-produce, and maintain themselves in the face of disturbance or damage (Birnbaum and Alvarado 2008; MacCord and Maienschein 2019). Think of systems as diverse as forests, microbial biofilms, corals, salamanders, hydra, and human skin cells.¹ This capacity is fundamental to life—without it, many biological systems would be too fragile to cope with stress and would frequently collapse—but because it is multiply realized in wildly different living systems at many scales, finding a common understanding may seem futile, and in fact research has proceeded along independent lines. For example, the sciences of organismal regeneration and ecological regeneration appear to have little more than a nominal relationship (notwithstanding their historical relatedness; see Clements 1916). Progress towards unification can be made, we think, by turning to evolutionary theory, specifically by synthesizing recent discussions of the evolution of individuals versus collectives with older literature about replicators versus interactors. This allows us to provide a partial answer in response to MacCord and Maienschein's call for “basic units and mechanisms” of regeneration, relevant when that process is “adaptive”. We argue that the basics of adaptive regeneration can be understood and generalized through a modification of David Hull's replicator-interactor framework.

To help clarify our goal in this paper, consider three putative examples of regeneration. A paradigmatic case of organismal regeneration is the adult salamander limb (Gilbert 2000). Experimentally amputating the limb at any point along its proximal-distal axis will trigger the formation of a “wound epidermis” as epidermal cells from the stump migrate to cover the wound surface. During the next few days, the cells beneath this surface—cells that were previously bone, cartilage, neural, etc.—undergo dedifferentiation, then proliferation, and eventually redifferentiate to form the new regenerated limb structures. Compare this with a paradigmatic case of ecological regeneration: forest regeneration following a fire. A Canadian boreal forest can naturally regenerate through the establishment of “pioneer” species, especially those that are adapted to such conditions, such as the lodgepole pine. This pine produces cones protected by a waxy coating that require the heat of a fire to release their seeds. Forest communities that possess such species will have a better chance of regenerating following a fire. Finally, and perhaps somewhere between the above, is the human gut microbiome, that is, the community of microorganisms that is harboured in the human intestinal tract. In healthy human adults, the activities of this microbial community are integrated into fundamental physiological processes of the human host, such as the metabolic functions of digestion and vitamin production. Antibiotic treatment can disrupt the functions of this microbial community, which can be detrimental to the health of the human host (Blaser 2006). Following treatment in an otherwise healthy adult human, the microbial community can regenerate something resembling its previous state, and once again provide vital functions.

What do these sorts of cases have in common that might warrant a unifying theory? A *prima facie* obstacle to unification is that regeneration is accomplished through different kinds of processes. Organismal regeneration, such as limb regeneration in salamanders, is driven by developmental processes, whereas forest regeneration is driven by ecological community dynamics and assembly rules. Regeneration of the gut microbiome is thought to be accomplished by a mix of host physiological control and the community ecology of the microbes (Foster et al. 2017).

1. A similarly broad understanding of regeneration is used in sustainability, such as in discussions of the regenerative capacities of the biosphere (Barrett et al. 2020).

We think there is a way of seeing unity in this diversity by focusing on the evolutionary replicators which in part produce regenerated structures. In what follows, we first review claims about “holobiosis” (section 2) and the evolutionary theory (“It’s the song not the singer[s]” or “TTSNTS”) devised to make sense of this phenomenon (section 3). We suggest that ITSNTS may be inadequate for the task of unifying regeneration, but show that this theory helps motivate an additional way forward. We then employ Hull’s replicator/interactor framework to this end (sections 4–6).

2 Holobiosis

A reasonable suggestion is that regeneration is often an adaptation: an evolved capacity of salamanders, forests, and microbiomes. This suggestion is implausible given the inapplicability of evolution by natural selection (ENS) as traditionally conceived to many collective entities—those composed of independently evolving lineages—and the case of holobiosis will here illustrate the point.

Holobionts comprise animal, plant or protist “hosts” and their associated microbiomes. Some exhibit “vertical inheritance” (hosts passing on symbiotic microbes to their progeny) but others are recurrently assembled by recruitment of environmental microbes (“horizontal inheritance”). Early versions of the hologenome theory of evolution (see Rosenberg and Zilber-Rosenberg 2018 for a review) treated both sorts of holobionts as “units of selection”, directly subject to evolution by natural selection. Many have argued that this was wrong. For example, Doolittle and Inkpen (2018) reasoned that one cannot legitimately regard all holobionts as such units, assigning to them something like specific holobiont-level adaptations and “functions”, if many of them comprise collections of taxa that are “horizontally” acquired—re-recruited every time a new host is born (Doolittle and Booth 2017; Doolittle and Inkpen 2018). Such holobionts do not *reproduce* as units and thus are not members of what Godfrey-Smith (2009) would call “Darwinian populations”, even marginally. Godfrey-Smith (2012) writes:

Evolution by natural selection is change in a population owing to variation, heredity and differential reproductive success. This is usually seen as a micro-evolutionary process acting on organisms, but the criteria required are abstract; genes, cells, social groups and species can all, in principle, enter into change of this kind. For any objects to be *units of selection* in this sense, however, they must be connected by parent–offspring relations; they must have the capacity to reproduce. *Units of selection* in this sense can be called Darwinian individuals. (2161, emphasis ours)

Other critics (for example, Moran and Sloan 2015; Douglas and Werren 2016) have generally also adopted Godfrey-Smith’s strict Darwinian perspective.

Doolittle and Inkpen (2018) saw as equally problematic claims that communities without designated hosts (biofilms, for instance) or ecosystems could be “units of selection”. The *heredity* component in Lewontin’s recipe (Lewontin 1970) is not present when collective reproduction producing unambiguous parent–offspring lineages of such collective entities doesn’t occur (Okasha 2006; Doolittle and Inkpen 2018). In many often-cited studies claiming community ENS, community reproduction has been artificially enforced by the investigator (see for example, Swenson et al. 2000; Goodnight 2000; Rainey and Quickstad 2020).

Defending holobiont theory, Roughgarden et al. (2018, see also Lloyd and Wade 2019) responded to critics by acknowledging that many holobionts (those based on “horizontal inheritance” or recurring environmental recruitment) are indeed not “units of selection” as reproducers or *replicators*. But, they argued, even such holobionts are well-integrated *interactors* and *bearers of adaptation*, subject to ENS. They offer as “holobiont evolution” (see also Roughgarden 2020) what looks to us very like MLS1 (multi-level selection 1; Okasha 2006). With MLS1, group composition affects the reproduction of group constituents, and thus the frequency of constituent types forming the next generation of groups and the composition of those groups does change. But this is not really an MLS2 (multi-level selection 2) solution, if groups themselves do not reproduce *as* groups. Groups do not then acquire adaptations according to the ordinary use of that term, since the characters selected are properties of constituents (e.g., “being an altruist”), not properties of groups (e.g., “proportion of altruists”; Okasha 2006). The public excitement about holobiosis resided and still resides, critics feel, in the inference that holobionts are “units of selection” and bear adaptations in an MLS2 sense.

Roughgarden et al.’s introduction of replicator/interactor language does seem apt, however, and we aim here to extend their work by fleshing out what might be the associated replicators. In a sense, we are proposing a further extension of the “extended replicator” of Sterelny et al. (1996). To bring this all back to regeneration, we argue (in sections 4–6) that *if* there is to be an adequately mechanistic and broad “*overarching understanding or theory*” uniting regeneration at the level of organisms and the recurrence of similar communities or ecosystems (as in “forest regeneration”), this may best or only be accomplished in Hull’s replicator/interactor framework. But first (section 3), as a segue, we explain why a recent theory aiming to make sense of the holobiosis phenomenon may not be the regeneration theory MacCord and Maienschein seek.

3 ITSNTS pointing the way

“It’s the song, not the singer” (ITSNTS) theory (Doolittle and Inkpen 2018) may not be the “*overarching understanding*” called for by MacCord and Maienschein, although it points the way to one, as we will now explain. ITSNTS theory calls for a gestalt switch in our understanding of evolution: it proposes that it is the process or pattern of interaction (“the song”) of a recurring multi-species community or ecosystem that is the relevant “unit of selection”—not the organisms or species (“the singers”) implementing it. Processes or patterns of interaction make up populations in which ENS favors differential persistence, and traits promoting persistence thus carry out the “functions” of such entities. In this context, the fraught term “ecosystem function” refers to functions belonging to systems, not to the communities or taxa that implement them. An ITSNTS theory of regeneration would treat regenerated systems—interaction patterns characteristic of forest communities, for example—as evolved processes, and regeneration as an evolved response to system disturbance. But ITSNTS theory may not supply the “*basic units and mechanisms*” for regeneration that MacCord and Maienschein believe are required.

This is principally because *processes* (“songs”) do not operate *directly* among things (“singers”) by recruiting taxa to perform their operations. Such recruitment is perhaps more often directly caused by end-products (metabolic or developmental) of other singers, so the necessary explanations at the level of mechanisms might already be provided by the well-established theory of “niche construction” (Odling-Smee et al. 2003). Processes might be taken as emergent from or supervenient on the interactions between things, and it is useful to see them as evolving by differential persistence—as evolutionarily stable states, for instance (Borelli et al. 2015)—and in section 5, we do consider the possibility that they are “replicators”. But processes may not directly *cause* things to behave in one way or another and thus cannot answer MacCord and

Maienschein's call for mechanisms. We see this as a problem for process ontology (Nicholson and Dupré 2018) in general, and hint at some possible solutions below.

ITSNTS's insistence that differential persistence, re-production, or recurrence should be seen as legitimate outcomes of ENS is in any case important to our argument here, and ITSNTS does provide background for the theory sought. Moreover, the problem that ITSNTS promised to solve (assigning of functions associated with collectives that do not reproduce collectively) is relevant to the problem we address here: How can we explain the adaptive regeneration of individuals and communities in common evolutionary terms?²

4 Replicators and interactors

Hull's (1980) replicator/interactor terminology is a refinement and generalization of Dawkins's (1976) gene/vehicle distinction, defining those terms and ENS as follows:

replicator: an entity that passes on its structure directly in replication; **interactor:** an entity that directly interacts as a cohesive whole with its environment in such a way that replication is differential ...; **selection:** a process in which the differential extinction and proliferation of interactors cause the differential perpetuation of the replicators that produced them. (318, emphasis ours; see also footnote 3)

In this section, we will use these definitions and consider how they cash out as we proceed up an organizational hierarchy from genes to ecosystems. The fact that this framework applies across scales is central to its usefulness for making sense of adaptive regeneration. Note that Hull here refers to the "proliferation" of interactors, which includes but is not limited to their reproduction, and we see the differential perpetuation (persistence) of replicators producing such successfully proliferating interactors as an outcome of selection.³

Admittedly, the replicator/interactor framework should be seen as a less-than-fully-general model of ENS, because formulations of ENS incorporating "Lewontin's Recipe" don't seem to need it. That recipe has it that any entities showing heritable variation in fitness (the last usually cashed out as differential reproduction) will inevitably experience ENS. As Godfrey-Smith (2009) puts it:

all that we need is that reproduction lead to parent-offspring similarity at the level at which evolution is to occur. It does not matter what particular mechanism underlies this pattern of similarity, so long as the pattern is present. (34)

Interactors that reproduce like organisms in sexual species like ours indeed do show such parent-offspring similarity, both parents generally being recognizable in children, even though each contributes only half a genome. Here we employ the replicator/interactor framework knowing that it is an idealized model of evolution, but one we find useful within the context of illuminating adaptive regenerative processes across scales. Godfrey-Smith indeed admits the utility of seeing as interactors the joint constructions of several independent replicators, writing in 2014 that:

2. It is unity of explanation and a framework for understanding that are our goals here: we do not intend to make ontological claims.

3. "Proliferation" includes "re-production" and "recurrence" as well as "reproduction": all can be means of more-making. "Perpetuation" means (for us and possibly for Hull) "persistence", which is normally accomplished by differential replication, but might be accomplished otherwise (Doolittle 2013; Doolittle and Inkpen 2018).

the other part of the framework, the idea of an interactor as an evolved object, might be useful in dealing with symbioses and the like. There are objects that recur in evolution without reproducing as units. Their parts reproduce, and the parts come together to make more of these recurring objects. Looser symbioses are easy to see in this way Perhaps human beings are interactors in this same sense. (79)

In elaborating this notion, we envision a spectrum at one extreme of which interactors are the very same entities as replicators and at the other extreme of which they are quite clearly separable. As detailed below, Dawkins's gene/vehicle distinction and Hull's replicator/interactor framework may be most obviously applied in explanations focused at the "middle" of the spectrum, where we consider organisms within a sexually-reproducing species to be. But they also permit the unification of concepts of regeneration at all scales, providing a common language.

4.1 *Selfish DNA*

Within genomes, there is selection for differential representation of alleles without (necessarily) consequences for organismal phenotype, and "selfish DNAs" (meiotic drivers and transposable elements) are its products. It is the *interaction* of the DNA structure or sequence with organismal or cellular machinery for gamete formation or DNA replication that ensures differential reproduction/perpetuation, not phenotypic expression (which might even be deleterious to organisms; Doolittle and Sapienza 1980; Hickey 1982). For selfish DNAs, the replicator and the interactor are the same entity.

4.2 *Bacteria*

For asexual organisms (which is what we once thought bacteria to be) replicators and interactors are separable but causally-coupled entities. The central dogma of molecular biology encourages us to believe that information from the former (a bacterium's genome) is used to make the latter (its cell). But there's a one-to-one mapping of interactors to replicators, so we could just as reasonably say that a genome is a cell's way of making another cell as *vice versa*. The environment interacts with cells but their differential reproduction entails the differential replication of all and only those cell's "own" genomes. The replicator and the interactor are no longer the same entities but both reproduce and form parent-offspring lineages, so either might be considered a "unit of selection" à la Godfrey-Smith.

4.3 *Sexual species*

Once there is sex, the mapping gets more complicated, and interactors don't "reproduce" in the sense of replicating: we often say of individual organisms within a sexual species that they "reproduce their own kind". Nevertheless, interactors (such organisms) are usually not problematic to define, and interactors' interactions with environments do result in differential perpetuation of the replicators that "make" them. It's just that, because of sex and recombination, it's not the whole genome, but only the genes specifically responsible for an interactor's differential reproduction, that are "perpetuated" in the long run. (In most organisms and in population genetic modeling, this perpetuation plays out as differential gene or allele replication, but we might also see replicator persistence as a consequence of selection). Dawkins's *The Selfish Gene* (1976) makes sense in both contexts, and he does there describe genes as "immortal coils".

Some would argue that Dawkins's book should have been titled *The Selfish Allele*, because for eukaryotes it's mostly within the population of alleles at a locus that competition occurs (through expression in phenotype). This was indeed Dawkins's principal concern, but prokaryotes often differ strain-to-strain in gene content (Mira et al. 2010) as well. So we might see all DNA sequences encoding homologs and analogs (iso-functional products) regardless of chromosomal location as the population in which competition occurs (for example, Javor 2003).⁴

In any case, it is the fact that sexual eukaryotic interactors harbor a mix of the genomes from two parents and pass on only individual alleles to remote descendants that made Dawkins's "genes-eye" view widely appealing if not, indeed, necessary. Although genes reproduce and are connected by "parent-offspring relationships", already there is some dilution of the coupling between such relationships and those involving the reproductive lineages of interactors. Indeed it is inevitable that some generations back we (as members of a typical sexual species) have reproductive ancestors from whom we have inherited no DNA. Godfrey-Smith (2012) allows for this; the passage quoted on page 3 continues:

An evolutionarily relevant case of reproduction can take many forms. There need not be replication, the faithful production of copies. Replicators are Darwinian individuals with high-fidelity, asexual reproduction, and it is possible to have evolution by natural selection on units where reproduction is sexual and heredity is weak. (2161)

But further:

there must be some parent-offspring similarity, and the clarity of a 'parent-offspring' relation of the relevant kind is inversely related to the number of parents—if there are too many parents, there are no parents at all. (2164)

4.4 Communities and ecosystems

Multi-species communities and ecosystems might also be taken as interactors, variously integrated and having community or system-level properties that are targeted by selection at some high level (Roughgarden et al. 2018; see Sterelny 2011 for why this framework is similarly valuable for symbiotic alliances). But for most of these there are many more "parents" than two—too many parents in Godfrey-Smith's sense—and most exhibit the functional redundancy that initially motivated ITSNTS thinking (Doolittle and Booth 2017). We've gone way beyond Godfrey-Smith's conception of "weak", when it comes to any claim about "heredity" or interactors reproducing or forming parent-offspring lineages. That is, there are "too many parents"—too many lineages of too many species that can (and often do) fill a particular role in a community's or system's collective activities. It's these activities and the differential success of communities exhibiting them that needs explaining.

Concomitantly, communities and ecosystems *recur* rather than reproduce: in other words they are *re-produced* by the taxa that make them up. If the frequency of such re-productions increases, we could see that as "proliferation" favoring the replicators that promote such frequency increase. If there are community-level properties that are relevant to the differential success (recurrence *or* persistence) of communities, they should be seen as different from those properties that, at a lower organizational level, support the existence of such taxa. Similar thinking is part-and-parcel of multi-level selection theory and its representation in "major transitions theory" (Szathmary and Maynard Smith 1995).

4. Many prokaryotic species boast "pan-genomes", comprising hundreds or thousands of whole and presumably expressed genes that are found in only one or a few strains, and which often confer strain-specific ecologically relevant activities (Mira et al. 2010).

To restate this: although all traits at whatever level might be said to supervene on DNA sequence, selection sees the effects of differences at different levels differently.⁵ A passage from Rabosky and McCune (2009) expresses this notion succinctly, in the case of species selection.

Selection at the individual level contributes to trait variation between species by transforming intraspecific variation into species differences that might result in species selection. However, the mechanism by which a trait becomes fixed within a species, whether through selection or drift, need not be the same as the mechanism by which the trait influences diversification. (70)

The existence of sexual reproduction, for instance—to the extent it is maintained among species because its loss leads to extinction—is not to be explained in the same way as the existence of all the organismal genes necessary to ensure participation in it. These are present because in a species that reproduces only sexually, individuals are selected for and maintain genes promoting this activity, even if incurring a two-fold cost (having to mix genes with mates) by doing so.

Genes with community-level functions may often be genes shared by horizontal gene transfer (HGT), at least in microbial systems. Indeed, if HGT itself is taken to be a community-level function (promoting community persistence), then genes promoting conjugation or transduction may be not only selfish in themselves and through promoting the infectivity of the agents they comprise but also in having this community-level selected effect. Indeed, Novick and Doolittle (2019) suggest that genes might exhibit a sort of “selfishness” based on the ability to be readily horizontally transferred between species, and there might be a sense in which genes “belong” to the community-level processes they implement as much as to the taxa in which they currently reside. Rainey and Quistad (2020) have very recently pointed out that in many real microbial communities it is the diversity of taxa that facilitates HGT and thus the persistence of microbial communities with some ecologically relevant and integrated function. They write that:

There exists the intriguing possibility that the genetic information moved between entities defines a community-level interaction network that achieves a dynamic and functional effect that vastly exceeds the sum of the component HGT events. (5)

Whatever their origin (HGT or “vertical descent”) and current taxonomic affiliation, it is those genes whose activities are realized at a community level that matter—in Sober’s language are *selected for* at the level of the collective. The rest of a redundant organism’s genes (and other activities of the same genes) might be seen as dragged along—there is only *selection of* them, in Sober’s sense (Sober 1984). In this same sense, if a bacterium is selected to be antibiotic resistant, it’s the gene for resistance that is selected for and the rest are just dragged along, and, if there *were* recombination, even those wouldn’t be dragged along for long.

5 If communities are interactors, what are their replicators?

If holobionts, multi-species communities and ecosystems are to be seen as interactors (as per Roughgarden et al. 2018) whose differential “proliferation” (re-production if not reproduction) causes the “differential perpetuation of the replicators that produced them”, then what might be the cognate replicators? At “lower” levels in the hierarchy above, the replicators are obvious, but for communities we need to say a little more. We can imagine three answers to this

5. See especially Okasha (2006, chapter 3), for how selection at different levels can be variously conceptually and mathematically separated out into components representing how characters at different levels causally influence the fitness of replicators (“particles,” in Okasha’s terminology).

question, each providing an explanatory context and each with its own domain or generality of applicability.

5.1 Genes

In this perspective, genes play the same role as Dawkins imagined for them in *The Selfish Gene*. More specifically, it is the genes that are responsible for community-level functions that are the relevant replicators. All other genes play a “background” role comparable to organismal genes not under positive selection in a single-species recombining population or genes supporting sexual reproduction, as argued above. So the relevant replicators do not comprise the collection of *all* the genomes of *all* the involved taxa (as in the hologenome concept of Rosenberg and Zilber-Rosenberg 2018), but rather those genes that have been selected for and are maintained by selection for community-level functions, such as cross-feeding of metabolites or exchange of genes (Rainey and Quistad 2020; Doulcier et al. 2020).⁶

Identifying such genes is the daunting task of what is now called “community genetics” (Whitham et al. 2008; Wimp et al. 2019). The objection that the genes determining different functions in any one community or ecosystem don’t reside in any one genome seems to us no more compelling than that the competing alleles determining different but collaborating functions in the sexual-species case don’t reside at any one locus or in any one organism, and are constantly being reshuffled among conspecifics, by recombination. They “want” to co-operate like rowers in the same boat (to use Dawkins’s 1976 analogy) and are selected not only to do their own thing better than iso-functional homologs and analogs, but also to get along with each other by the formation of successful communities or ecosystems. There, success is scored as differential representation (“proliferation”) of the ecosystem type on this planet—and *thus differential reproduction or persistence of the genes responsible*. This is selfishness in Dawkins’s sense, but at an organizational level higher than he considered, and addressing only a subset of genes. It embraces “group selection” in the MLS1 sense modeled by Roughgarden (2020) but is not a rebuttal of holobiosis’s critics. There need be no MLS2.

5.2 Genomes or lineages

For microbial communities (and bacteria, to the extent they are asexual) any such selfishness might be ascribed to whole genomes, not just to those genes whose expression in phenotype confers an advantage at the community level. Because of the “reciprocal causation” (Laland et al. 2011) inherent in the reproduction of asexuals (Section 4.2), we also might as well say that it is the lineages harboring the genes with community-level selectable effects (rather than their genomes) that are relevant replicators. Doing this would satisfy Godfrey-Smith’s concern that it is only reproduction and parent-offspring similarity that ENS requires, not some specific mechanism causing the similarity.

A problem with this is that often such lineages exhibit “functional redundancy”. That is, microbial communities (including those involved in “holobionts”) may comprise different strains or different species over time or between hosts, and yet collectively carry out pretty much the same metabolic activities. We, as such hosts, would not be so generally “healthy” otherwise. So we might instead see “guilds” of bacteria, taxonomically heterogeneous lineages united in their

6. There is another possibly pertinent precedent here, too. Some of us (for instance Brunet and Doolittle 2015) treat the >50% of our (human) DNA that comprises transposable elements or their derivatives as initially the products of genome-level selection, irrelevant to selection at the level of organisms. So, extrapolating this reasoning up the organizational hierarchy, relevant replicators for communities could exclude most taxon-specific genes involved in the biology of those taxa but incidental to community-level function.

ability to carry out some particular metabolic reaction (sometimes because they share genes via HGT) as the relevant replicators whose perpetuation is caused by our success as interactors. Not all member species in a guild benefit in any one case, but this too has a lower-level precedent. We would regard mutants of a selfish gene differing amongst themselves only in function-irrelevant synonymous nucleotide substitutions as “the same replicators”, as would Dawkins. Inevitably (by the coalescent process) one such mutant lineage will come to replace all others, but not because it confers greater fitness on its vehicles.

5.3 *Traits or processes.*

It seems then but a short step to say that it is the activities, interactions, or processes that iso-functional genes or guilds of redundant species implement that are actually perpetuated by the “differential extinction and proliferation” of interactors (communities or ecosystems). To say this is to gloss over the problems inherent in processes directly causing material change discussed in section 3, and so we suggest it here only as one answer; albeit an answer requiring considerably more philosophical elaboration. Such a development might assert that “its processes all the way down” and deny the ontological primacy of “things” (Nicholson and Dupré 2018), insist on the legitimacy of the subtle connection that Dawkins made in *The Selfish Gene* between potentially immortal, informational genes and their material tokens in DNA (Haig 2014), or see processes as emergent properties of things (implementing taxa) and invoke a kind of supervenient replication.

6 What does this have to do with regeneration?

An analogy between organismal regeneration and community/ecosystem recurrence and the “*basic units and mechanisms involved*” for either *can* then be formulated in this way. Surely, regeneration is, at least some of the time, an adaptation, rather than just a consequence of more-or-less accidental redeployment of evolved developmental programs. It is for such adaptive instances that the replicator/interactor framework advocated here seems appropriate, and we can draw further lower-level analogies, for instance to redundancy of genes. Surely, at least some of the time, “the same” structure or process is regenerated with the aid of different genes (Redden et al. 2005).⁷ Wagner’s (2007) defining as homologous different instances of “the same” gene-regulatory network, even if underwritten by different genes, is a useful bridge to a lower-level phenomenon here, with the gene regulatory network being the interactor and the environment with which it interacts being the rest of the cell or organism. So the regenerated limb *is* like a regenerated forest in important ways. To the extent that there is selection for genes or gene complexes or even guilds promoting either, we have the “*basic units and mechanism*” called for by MacCord and Maienschein. Genes, gene complexes or guilds promote regeneration at either level because it’s in their interests to do so.

And, at the highest level, thinking this way relieves us of the burden of thinking of the biosphere as either a replicator *or* as a persistor, as one is tempted to do in “Darwinizing Gaia” (Doolittle 2017). Gaia is actually the interactor, and all the genes contributing to her “functioning” are the replicators, broadly distributed among many taxa. Most genes of course don’t contribute, but then much of our own genome is made up of entities with their own private

7. Such non-homologous regeneration also occurs with the aid of cells of various developmental origins (Wagner 2014). For example, experimentally removing a salamander’s eye lens triggers tissue formation and induction resulting in a fully regenerated lens derived from the cells of the iris at the rim of the eye cup. This importantly differs from the initial development of the lens, which derives from the undifferentiated embryonic epidermis.

agendas. Genes selected for lower level (organismal) purposes might thus equally be discounted at the level of community function.

Dawkins's rower analogy, and his gene-centric way of thinking, may thus provide the best (and only?) entrée into an “*overarching understanding*”, though there are also likely many idle passengers riding in the community rowing shell, some even detrimental to its progress.⁸ But we must reduce the notion of replicator down to the gene level, not considering the taxa making up any holobiont or community, and certainly not those holobionts or communities themselves, as anything more than recurring interactors.

Evolutionary thinking, and in particular a modified version of Hull's framework, allows us to see unity in the diversity of living systems possessing the capacity for regeneration. We hope that this explanatory unification will inspire productive communication between disciplines studying this phenomenon at different biological scales.

Acknowledgments

The authors thank Kate MacCord, Jane Maienschein, Fritz Davis, Kat Maxson-Jones, Jim Collins, Lucie Laplane, and two anonymous referees for their very helpful thoughts about the manuscript.

Literature cited

- Barrett, Scott, Aisha Dasgupta, Partha Dasgupta, W. Neil Adger, John Anderies, Jeroen Van Den Bergh, Caroline Bledsoe, et al. 2020. “Social Dimensions of Fertility Behavior and Consumption Patterns in the Anthropocene.” *Proceedings of the National Academy of Sciences* 117 (12): 6300–6307.
- Birnbaum, Kenneth D., and Alejandro Sánchez Alvarado. 2008. “Slicing Across Kingdoms: Regeneration in Plants and Animals.” *Cell* 132 (4): 697–710.
- Blaser, Martin J. 2006. “Who Are We? Indigenous Microbes and the Ecology of Human Diseases.” *EMBO Reports* 7 (10): 956–960. <https://doi.org/10.1038/sj.embor.7400812>.
- Borrelli, Jonathan J., Stefano Allesina, Priyanga Amarasekare, Roger Arditi, Ivan Chase, John Damuth, Robert D. Holt, et al. 2015. “Selection on Stability Across Ecological Scales.” *Trends in Ecology and Evolution* 30 (7): 417–425. <https://doi.org/10.1016/j.tree.2015.05.001>.
- Brunet, Tyler D.P., and W. Ford Doolittle. 2015. “Multilevel Selection Theory and the Evolutionary Functions of Transposable Elements.” *Genome Biology and Evolution* 7 (8): 2445–2457. <https://doi.org/10.1093/gbe/evv152>.
- Clements, Frederic E. 1916. *Plant Succession: An Analysis of the Development of Vegetation*. Washington, DC: Carnegie Institution of Washington.
- Dawkins, Richard. 1976. *The Selfish Gene*. New York: Oxford University Press.
- Doolittle, W. Ford. 2014. “Natural Selection Through Survival Alone, and the Possibility of Gaia.” *Biology and Philosophy* 29 (3): 415–423. <https://doi.org/10.1007/s10539-013-9384-0>.
- Doolittle, W. Ford. 2017. “Darwinizing Gaia.” *Journal of Theoretical Biology* 434:11–19.

8. Dawkins (1976, 47) said, of the excess DNA making up more than half our genome, “The simplest way to explain the surplus DNA is to suppose that it is a parasite, or at best a harmless passenger, hitching a ride in the survival machines created by the other DNA”.

- Doolittle, W. Ford, and Austin Booth. 2017. "It's the Song, Not the Singer: An Exploration of Holobiosis and Evolutionary Theory." *Biology and Philosophy* 32 (1): 5–24. <https://doi.org/10.1007/s10539-016-9542-2>.
- Doolittle, W. Ford, and S. Andrew Inkpen. 2018. "Processes and Patterns of Interaction as Units of Selection: An Introduction to ITSNTS Thinking." *Proceedings of the National Academy of Sciences* 115 (16): 4006–4014. <https://doi.org/10.1073/pnas.1722232115>.
- Doolittle, W. Ford, and Carmen Sapienza. 1980. "Selfish Genes, the Phenotype Paradigm and Genome Evolution." *Nature* 284 (5757): 601–603. <https://doi.org/10.1038/284601a0>.
- Douglas, Angela E., and John H. Werren. 2016. "Holes in the Hologenome: Why Host-Microbe Symbioses Are Not Holobionts." *mBio* 7 (2). <https://doi.org/10.1128/mbio.02099-15>.
- Doulcier, Guilhem, Amaury Lambert, Silvia De Monte, and Paul B. Rainey. 2020. "Eco-Evolutionary Dynamics of Nested Darwinian Populations and the Emergence of Community-Level Heredity." *eLife* 9:e53433.
- Foster, Kevin R., Jonas Schluter, Katharine Z. Coyte, and Seth Rakoff-Nahoum. 2017. "The Evolution of the Host Microbiome as an Ecosystem on a Leash." *Nature* 548 (7665): 43–51. <https://doi.org/10.1038/nature23292>.
- Gilbert, Scott F. 2000. *Developmental Biology*. 6th ed. Sunderland, MA: Sinauer Associates.
- Godfrey-Smith, Peter. 2009. *Darwinian Populations and Natural Selection*. Oxford: Oxford University Press.
- Godfrey-Smith, Peter. 2012. "Darwinism and Cultural Change." *Philosophical Transactions of the Royal Society B. Biological Sciences* 367 (1599): 2160–2170. <https://doi.org/10.1098/rstb.2012.0118>.
- Godfrey-Smith, Peter. 2016. *Philosophy of Biology*. Princeton, NJ: Princeton University Press.
- Goodnight, Charles J. 2000. "Heritability at the Ecosystem Level." *Proceedings of the National Academy of Sciences* 97 (17): 9365–9366. <https://doi.org/10.1073/pnas.97.17.9365>.
- Haig, David. 2014. "Fighting the Good Cause: Meaning, Purpose, Difference, and Choice." *Biology and Philosophy* 29 (5): 675–697. <https://doi.org/10.1007/s10539-014-9432-4>.
- Hickey, Donal A. 1982. "Selfish DNA: A Sexually-Transmitted Nuclear Parasite." *Genetics* 101 (3–4): 519–531. <https://doi.org/10.1038/311417d0>.
- Hull, David L. 1980. "Individuality and Selection." *Annual Review of Ecology and Systematics* 11:311–332. <https://doi.org/10.1146/annurev.es.11.110180.001523>.
- Laland, Kevin N., Kim Sterelny, John Odling-Smee, William Hoppitt, and Tobias Uller. 2011. "Cause and Effect in Biology Revisited: Is Mayr's Proximate-Ultimate Dichotomy Still Useful?" *Science* 334 (6062): 1512–1516. <https://doi.org/10.1007/s10539-012-9335-1>.
- Lewontin, Richard. 1970. "The Units of Selection." *Annual Review of Ecology and Systematics* 1:1–18. <https://doi.org/10.1146/annurev.es.01.110170.000245>.
- Lloyd, Elisabeth A., and Michael J. Wade. 2019. "Criteria for Holobionts from Community Genetics." *Biological Theory* 14 (3): 151–170. <https://doi.org/10.1007/s13752-019-00322-w>.
- MacCord, Kate, and Jane Maienschein. 2019. "Understanding Regeneration at Different Scales." *eLife* 8:e46569. <https://doi.org/10.7554/elife.46569>.
- Mira, Alex, Ana B. Martín-Cuadrado Ana B.-Cuadrado, Giuseppe D'Auria, and Francisco Rodríguez-Valera. 2010. "The Bacterial Pan-Genome: A New Paradigm in Microbiology." *Int Microbiol* 13 (2): 45–57. <https://doi.org/10.1038/npre.2009.3489.1>.

- Moran, Nancy A., and Daniel B. Sloan. 2015. "The Hologenome Concept: Helpful or Hollow?" *PLoS Biology* 13 (12): e1002311. <https://doi.org/10.1371/journal.pbio.1002311>.
- Nicholson, Daniel J., and John Dupré, eds. 2018. *Everything Flows: Towards a Processual Philosophy of Biology*. Oxford University Press. <http://fdslive.oup.com/www.oup.com/academic/pdf/openaccess/9780198779636.pdf>.
- Novick, Aaron, and W. Ford Doolittle. 2020. "Horizontal Persistence and the Complexity Hypothesis." *Biology and Philosophy* 35 (1): 2. <https://doi.org/10.1007/s10539-019-9727-6>.
- Odling-Smee, John, Kevin Laland, and Marc Feldman. 2003. *Niche Construction: The Neglected Process in Evolution*. Princeton, N.J.: Princeton University Press.
- Rainey, Paul B., and Steven D. Quistad. 2020. "Toward a Dynamical Understanding of Microbial Communities." *Philosophical Transactions of the Royal Society B* 375 (1798): 20190248. <https://doi.org/10.1098/rstb.2019.0248>.
- Reddien, Peter W., Adam L. Bermange, Kenneth J. Murfitt, Joya R. Jennings, and Alejandro Sánchez Alvarado. 2005. "Identification of Genes Needed for Regeneration, Stem Cell Function, and Tissue Homeostasis by Systematic Gene Perturbation in Planaria." *Developmental Cell* 8 (5): 635–649. <https://doi.org/10.1016/j.devcel.2005.02.014>.
- Rosenberg, Eugene, and Ilana Zilber-Rosenberg. 2018. "The Hologenome Concept of Evolution after 10 Years." *Microbiome* 6 (1): 1–14. <https://doi.org/10.1186/s40168-018-0457-9>.
- Roughgarden, Joan. 2020. "Holobiont Evolution: Mathematical Model With Vertical vs. Horizontal Microbiome Transmission." *Philosophy, Theory, and Practice in Biology* 12 (2). <https://doi.org/10.3998/ptpbio.16039257.0012.002>.
- Roughgarden, Joan, Scott F. Gilbert, Eugene Rosenberg, Ilana Zilber-Rosenberg, and Elisabeth A. Lloyd. 2018. "Holobionts as Units of Selection and a Model of Their Population Dynamics and Evolution." *Biological Theory* 13 (1): 44–65. <https://doi.org/10.1007/s13752-017-0287-1>.
- Sober, Elliott. 1984. *The Nature of Selection: Evolutionary Theory in Philosophical Focus*. Chicago: University of Chicago Press.
- Sterelny, Kim. 2011. "Evolvability Reconsidered." In *The Major Transitions in Evolution Revisited*, edited by Brett Calcott and Kim Sterelny. Cambridge, MA: MIT Press.
- Sterelny, Kim, Kelly C. Smith, and Michael Dickison. 1996. "The Extended Replicator." *Biology and Philosophy* 11 (3): 377–403. <https://doi.org/10.1007/BF00128788>.
- Swenson, William, David Sloan Wilson, and Roberta Elias. 2000. "Artificial Ecosystem Selection." *Proceedings of the National Academy of Sciences* 97 (16): 9110–9114. <https://doi.org/10.1046/j.1462-2920.2000.00140.x>.
- Szathmáry, Eörs, and John Maynard Smith. 1995. "The Major Evolutionary Transitions." *Nature* 374 (6519): 227–232. <https://doi.org/10.1093/oso/9780198502944.001.0001>.
- Wagner, Günter P. 2007. "The Developmental Genetics of Homology." *Nature Reviews Genetics* 8 (6): 473–479. <https://doi.org/10.1038/nrg2099>.
- Wagner, Günter P. 2018. *Homology, Genes, and Evolutionary Innovation*. Princeton, NJ: Princeton University Press.
- Whitham, Thomas G., Stephen P. Difazio, Jennifer A. Schweitzer, Stephen M. Shuster, Gery J. Allan, Joseph K. Bailey, and Scott A. Woolbright. 2008. "Extending Genomics to Natural Communities and Ecosystems." *Science* 320 (5875): 492–495. <https://doi.org/10.1126/science.1153918>.

- Wimp, Gina M., Jewel Tomasula, and Matthew B. Hamilton. 2019. "Putting the Genes into Community Genetics." *Molecular Ecology* 28 (19): 4351–4353. <https://doi.org/10.1111/mec.15209>.
- Zhang, Haitao, and G.T. Javor. 2003. "Regulation of the Isofunctional Genes *ubiD* and *ubiX* of the Ubiquinone Biosynthetic Pathway of *Escherichia coli*." *FEMS Microbiology Letters* 223 (1): 67–72. [https://doi.org/10.1016/s0378-1097\(03\)00343-4](https://doi.org/10.1016/s0378-1097(03)00343-4).

© 2021 Author(s)

This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International license, which permits anyone to download, copy, distribute, display, or adapt the text without asking for permission, provided that the creator(s) are given full credit.

ISSN 2475-3025