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The evosystem: A centerpiece for evolutionary studies

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Abstract

In this paper, we redefine the target of evolutionary explanations by proposing the "evosystem" as an alternative to populations, lineages and species. Evosystems account for changes in the distribution of heritable variation within individual Darwinian populations (evolution by natural selection, drift, or constructive neutral evolution), but also for changes in the networks of interactions within or between Darwinian populations and changes in the abiotic environment (whether these changes are caused by the organic entities or not). The evosystem can thereby become a centerpiece for a redefined evolutionary science, that is, evolutionary studies, that apprehends through a single framework the variety of evolutionary processes that lie at various scales. To illustrate the importance of this broadened perspective on evolution, we use a case of antimicrobial resistance evolution: the spread of the bla_{NDM} gene family and the related resistance to carbapenem antibiotics observed globally, and show how evolutionary studies can contribute to answering contemporary socially relevant challenges.

INTRODUCTION: THE EVOSYSTEM, EXPANDING THE TARGET OF EXPLANATION

In the standard rationale of evolutionary biology, explanations target homogeneous populations,[1–3] also called Darwinian populations[4] (*homogeneous* means that the units forming the population are of the same kind, but not identical, as variation is a necessary condition for evolution by natural selection). Evolution corresponds to changes in the distribution of variation within such populations, explained mostly by natural selection, drift or constructive neutral evolution. These concepts are biased towards the disciplines that were at the core of the establishment of the Modern Synthesis and its legacy, such as population genetics and phylogenetics. Consequently, the environment (both organic and abiotic) is considered external to the target of explanation (it drives the evolution of populations but is external to them). Understanding many evolutionary phenomena (e.g., the case study explored below) requires an alternative conceptualization of the target of explanation: the evosystem.

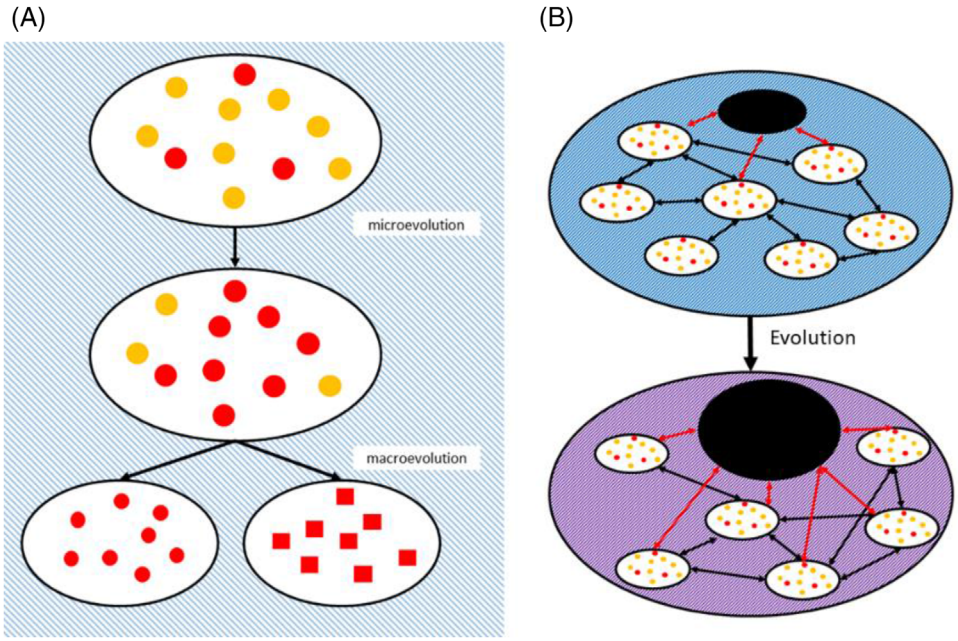

FIGURE 1 Alternative representations of evolutionary phenomena. Figure 1 is meant to compare traditional representations of evolutionary phenomena with evosystem-based ones. In Figure 1A, a more traditional approach is illustrated. Evolution happens within Darwinian populations and leads to the divergence of lineages. In that framework, the selective environment is metaphorically in the background, as represented here literally. In contrast, Figure 1B illustrates changes across time within an evosystem. The selective environment is still represented as the background (for lack of better representational options), but it is included *within* the system under inquiry. Moreover, evosystems are composed of many Darwinian populations interacting with each other, and that form parts of each other's environment. There are no restrictions on the nature of interactions to be represented (trophic, reproductive, etc.). There is also the possibility to focus on some aspects of the selective environment to study their specific impact on evolutionary dynamics. Here, for example, the black ellipse represents greenhouse gases produced by human societies (and other biological entities). As they gain in importance, we can model their impact on specific Darwinian populations or on more local evosystems (nested in larger ones), but also on the topology of all components involved.

Evosystems are systems encompassing various levels of organization, composed of heterogeneous interactions (e.g., selective, neutral, reproductive, reproductive, genealogical, functional interactions) that change across time. (The word "evosystem" has been used before, in the ecosystem services literature[5] but our use of the word is unrelated.) Evosystems form a whole in the sense that their parts, which can be evosystems themselves, are to some degree integrated, in interaction with each other. The larger evosystem therefore constitute the changing environment in which its parts evolve. Relevant change in evosystems may involve changes in the distribution of heritable variation within the whole (or within individual Darwinian populations that compose the whole), but it may also involve changes in the networks of interactions within or between Darwinian populations and changes in the abiotic environment (whether these changes are caused by organic entities or not). For instance, this may imply changes in the distribution, topology or nature of interactions. This redefined target of explanation is more comprehensive than the traditional one as it describes the whole system that evolves, not only the parts studied by historically important disciplines (see Figure 1). It should be noted that the target of explanation must not be confused with another important concept in evolutionary biology, the units of selection, that is, the targets of selection that form Darwinian populations (see Box 1).

For instance, the largest evosystem relevant to the study of life on Earth is the Earth System itself. Understanding diversification and spread of eukaryotes, for example, can undeniably be helped by phylogenetic analysis (which served to posit the underlying endosymbiosis), but a more comprehensive explanation must emphasize a major shift in the environment, that is, the second stage of oxidation of the atmosphere and oceans. The stark increase that led to modern O_2 levels played an important role in the diversification and increase in size and numbers of eukaryotes.[6] The system that evolves *includes* the atmosphere: without its oxidation, evolutionary history would have played out differently.

The evosystem is a pragmatic concept. It is tied neither to specific objects nor to a given level of organization. *Local* evosystems can and should also be studied. For instance, research on eco-evolutionary dynamics[7–10] can be reinterpreted as the study of local evosystems, which integrate population genetics with ecological principles. Nevertheless, we go beyond eco-evolutionary dynamics by insisting that local evosystem evolution is just the embodiment of processes that can be observed at global scales also, and by stressing that doing so requires a broad explanatory target. The interplay between more local and more global study of evosystems could also yield important insights in health-related issues, as our case study perfectly illustrates.

Box 1 – Units of selection and evosystems

Besides the explanatory target of disciplines such as population genetics, the units of selection concept is another type of entities central to evolutionary theories. Historically, units of selection have attracted more attention than populations or even lineages.[62] Units of selection, in the traditional perspective, are the components of Darwinian populations, that is, they are fitness bearers, entities that reproduce, are re-produced and persist differentially from one another such that the population they form changes across time.[3,4,15,20] Genes and organisms have traditionally been conceived as paradigmatic units of selection. More recently, other candidates have been proposed, with a focus on multispecies communities. Doolittle and colleagues[19,20] even suggested networks of interactions could be conceived as units of selection, even though they are often being reproduced rather than reproducing by themselves. This effectively bridges the gap between the nascent evosystemic perspective (evosystems are networks of interactions) and the units of selection literature (albeit in a way that stretches the traditional Lewontinian perspective on the matter).

The evosystem perspective reshapes the relationship between units of selection and the target of explanation. Indeed, in the classical view of evolution, units of selection are the *only* components of populations (or lineages, or species) whose evolution we are trying to explain. Or, in other words, the target of explanation is nothing but a grouping of units of selection. Conversely, evosystems encompass a plurality of heterogeneous components, where only a subset aligns with the unit of selection concept. Functional interactions as well as abiotic components exemplify this: despite various interpretations of the unit of selection concept, none of them is comprehensive enough to include all these evosystem components.[63]

However, it should be noted that a given biological system can be both a unit of selection and an evosystem. Indeed, an evosystem can function as a fitness bearer and, consequently, as a unit of selection within a broader evolutionary process: evolution can happen both within and without a given entity, such that some changes at the evosystem level will explain changes at lower levels, and vice-versa.[64] For instance, a macrobial organism could be conceived as a complex evosystem (composed of a macrobe and a great variety of microbial communities, as well as mobile genetic elements, abiotic elements [e.g., chemical elements, nutrients, bones, etc.] and the interactions between these elements). Simultaneously, it can also be conceived as a unit of selection, subject to selective pressures and a building block within higher-level Darwinian populations or evosystems. This rationale is already present in evolutionary biology, for example, to tackle important issues such as cancer,[7] albeit using different terms than those employed here.

The fact that biological entities may correspond to two distinct ontological categories showcases the power of the evosystem concept: by modeling biological entities central to evolutionary processes as complex networks of interactions, they become comparable in terms of network sciences regardless of their scale (e.g., networks of microbial interactions or Earth System level networks of interactions). Just like how the study of DNA leveled differences between organisms as different as plants, animals and bacteria in order to study them side-by-side,[65] the evosystem can bridge the divide between scales of evolutionary processes. The evosystem can thereby serve as a centerpiece for a redefined evolutionary science, namely evolutionary studies, that apprehends through a single framework the variety of evolutionary processes occurring across various scales.

Specifically, we believe our approach is compatible with the One Health and Global Health perspectives.[11]

IMPLICATIONS OF THE EVOSYSTEM–BASED CONCEPTUAL SHIFT

We want to emphasize three consequences related to metascientific aspects of evolutionary studies that the evosystem-based perspective entails.

First, the boundaries of the discipline concerned with evolution would gain to be redrawn. An important part of the work done by the "architects" of the Modern Synthesis was to establish such boundaries, to set a line between what is part of the scientific core meant to tackle evolution, and what is not. Historians and sociologists refer to this aspect of scientists' work as "boundary work," a crucial aspect of any scientific endeavor.[12,13] In the case of the Modern Synthesis, this meant centering evolutionary biology on a few disciplines: population genetics (hence genetics and the relevant mathematics), paleontology, taxonomy, plant and animal biology; phylogenetics was integrated shortly thereafter.[12] We believe that if the field studying evolution is tied to the expression "evolutionary biology," it will preferentially address the problem agenda of these core disciplines, with added weight for that of population genetics and phylogenetics. By contrast, recentering the field on the expression "evolutionary studies," which was in vogue before the crystallization of "evolutionary biology," opens the door to contributions from a wider variety of disciplines (see the case study for examples), contributions that are necessary to tackle evosystems. Boundary work, after all, is an ongoing process.

The second consequence of adopting the evosystem concept is that it entails redefining the phenomenon of interest, namely evolution itself. As Futuyma[2] and many others construe it,[3,4,15,16] evolution consists of changes in the distribution of heritable variation within Darwinian populations. Even accounts of evolution that challenge the

Modern Synthesis and its legacy tend to be centered on organisms, their features and on the Darwinian populations that they form.[17] In contrast, we argue that evolution refers to the set of changes that characterize an evosystem, with only a subset of these changes being related to the distribution of variation within populations, and a (potentially) bigger subset referring to changes regarding the interactions between and within populations as well as other elements of the evosystem (including those that have traditionally been considered part of "the environment"). Simply stated, change occurs in complex systems that often involve *many* Darwinian populations *as well as* abiotic elements and their interactions. Evosystems are meant to reflect this complexity.

A third consequence, entailed by the second, is a drastic change of perspective on what is often thought of as the "environment." Although evolutionary biologists seldom offer a precise definition, it is commonly used to denote "the state or quality of being the causal context for something else".[18] In evolutionary biology, relevant causality related to the environment refers mostly to selective pressures. This means that the environment is the *context* in which something (a population or lineage) evolves. However, with an evosystem-based approach, the evolutionary context itself becomes the primary focus of investigation. Organisms and the populations within evosystems are then seen as constitutive parts, often interchangeable and functionally redundant,[19,20] that acquire biological significance solely through their embedment in it.[21] The evosystem is more than the context in which something else evolves. The evosystem *is* the thing that evolves.

A CASE STUDY TO ILLUSTRATE INSIGHTS OF AN EVOSYSTEMIC APPROACH TO EVOLUTION: THE GLOBAL SPREAD OF *bla*$_{NDM}$

Genes encoding carbapenemases – enzymes conferring resistance to carbapenem antibiotics – are concerning from a public health standpoint,[22] since carbapenems, beta-lactam large spectrum antibiotics, serve as a last resort to treat infections resistant to many other widely used antibiotics.[23] Explaining the global spread of an antimicrobial resistance (AMR) gene family, namely *bla*$_{NDM}$, exemplifies the relevance of the evosystem concept.

This gene family originated and spread globally because of what seems to be fitness-increasing capacities. Despite its recent emergence, *bla*$_{NDM}$ ranks as the most prevalent carbapenemase gene worldwide.[24,25] Such widespread and rapid dispersal (the earliest known NDM-positive isolate, found in Israel, dates back to 2004;[26] 10 years later, by 2014, the gene was already globally observable and the most prevalent carbapenemase[24]) reflects the high transmissibility of the mobile genetic elements (MGEs, e.g., plasmids, transposons) harbouring *bla*$_{NDM}$.[27,28] Indeed, *bla*$_{NDM}$ is thought to have emerged in the *Acinetobacter* genus.[27,29] Despite this, most carbapenem-resistant species in that genus rely on genes from the *bla*$_{OXA}$ family rather than *bla*$_{NDM}$.[30,31] Furthermore, a wide variety of bacteria ranging across various genera, such as *Pseudomonas* or members of the *Enterobacteriaceae* family, harbor different *bla*$_{NDM}$ variants.[24,30,32]

Hence, the phylogenetic history of *bla*$_{NDM}$ is more readily associated with MGEs than with specific lineages of organisms.[33] And yet, even at that finer-grained level of analysis, there are no perfect correlations. Phylogenetic analyses revealed that *bla*$_{NDM}$ is itself a chimera initially associated with the Tn*125* transposon.[27] However, no single plasmid or transposon is tied to the presence of *bla*$_{NDM}$ worldwide (Acman et al.'s Figure 5[28] represents the great diversity of MGEs on which *bla*$_{NDM}$ can be found). This diversity matters as it greatly impacts how the gene family spreads. Plasmids influence transmission within local areas, whereas transposons drive transmission between areas.[23,28] Furthermore, as with many other antibiotic-resistance genes,[34–36] *bla*$_{NDM}$ is believed to have environmental origins.[27] This means that important variation within the gene and organism lineages results from diverse evolutionary trajectories coming together rather than from point mutations. The resulting phylogenetic picture has been compared to a set of nested Russian dolls where mobility is potentiated by the independence of the various levels of organization involved.[37]

The phylogenetic complexity of this case study is mirrored by its functional complexity, transcending the boundaries of Darwinian populations and traditional evolutionary biology to align with evosystems and evolutionary studies. First, consider the molecular level. For *bla*$_{NDM}$ to confer a fitness advantage to its bearers, it must code for an enzyme (a beta-lactamase) capable of defusing (by hydrolysis) beta-lactam antibiotics. This requires the presence of zinc ions that attach themselves to the NDM enzyme and become the linkage point between this protein and the beta-lactams.[38,39] The problem is that in cases where beta-lactams tend to be present in a bacterium's environment, that is, in cases of infection, there tends to be low zinc presence as the result of immune responses of the infected entity.[40] The selective environment in which *bla*$_{NDM}$ might confer an advantage is one in which the chemical prerequisites for its potential role are scarce. This situation makes the high correlation of the presence of the genes *ble*$_{MBL}$ and *bla*$_{NDM}$ (more than 97% of co-occurrence rate[28]) an extremely interesting fact, given they form a constitutively expressed operon.[41]

ble$_{MBL}$ codes for an enzyme that confers resistance to bleomycin, a family of enzymes primarily used to fight certain cancers[41–43] and which also carries antibiotic properties. Some forms of bleomycin also require zinc ions to sustain their antimicrobial effects.[44] Therefore, one might think that bleomycins, present in nosocomial contexts, compete with NDM enzymes for scarce zinc ions. In select circumstances, *ble*$_{MBL}$, through its antibleomycin action, enhances the likelihood that NDM enzymes can access zinc ions necessary for beta-lactam hydrolysis. Furthermore, *ble*$_{MBL}$ has a stabilizing effect on its genetic neighborhood.[41] This whole picture illustrates the irreducible context-dependence of the evolutionary successes of *bla*$_{NDM}$: it relies on its genetic neighborhood (*ble*$_{MBL}$, but also, for example, the IS*Aba*125 insertion sequence[28,32]), on the presence of infectable macroorganisms (that react and that warrant use of antibiotic substances) and on the nosocomial context where bleomycin is occasionally present (such that the *bla*$_{NDM}$-*ble*$_{MBL}$ tandem's fitness increasing capacities become relevant).

There is further complexity to account for. While *bla*$_{NDM}$ is phylogenetically independent of the bacterial lineages that carry it, it is functionally dependent on the biochemical context of Gram-negative cells in many ways. For instance, the NDM protein acts in the periplasm characteristic of these bacteria[38] where zinc ion incorporation into the NDM enzyme is influenced by intra- and extracellular acidity levels.[38,45] This information is important, given that the diversity observed within the *bla*$_{NDM}$ gene family is related to the capacity of the NDM enzyme to realize hydrolysis in the context of zinc scarcity.[46] These conditions (the zinc availability and pH levels) are obviously not determined by *bla*$_{NDM}$; they result from interaction networks featuring intracellular as well as extracellular components and in which genes act as *some* causal elements among many. Even the gene's mobility (and that of the concerned transposons and plasmids) in certain cases relies on bacterial morphological elements such as outer membrane vesicles.[30]

The importance of the environment extends even beyond the biochemical and cellular settings within which *bla*$_{NDM}$ is expressed. It is impossible to account for the spread of a gene such as *bla*$_{NDM}$ without considering the heavy use of antimicrobial substances by human beings. Indeed, the global use of antibiotics has been shown to be a cause for the fixation or spread of AMR genes in microbial populations.[47,48] The fact that such genes emerged in the environment (outside of nosocomial or clinical settings)[49,50] reminds us that the context allowing for them to spread is broader than even the nosocomial setting often associated with antibiotics.[51] Human pressures transform local ecosystems in many ways, and there is a growing recognition that ecological feedback loops must be considered as part of evolutionary explanations.[8,9,52–54] More globally, human actions (and that of other biological entities, e.g., the great oxidation event) significantly influence planetary dynamics, for example by introducing various antimicrobial substances into the environment.[11,55] The evolution of AMR is therefore best explained by drawing on sociohistorical disciplines that help us track our societies' influence on the Earth System[56,57] as a whole. Interestingly, the related global-level dynamics involve intricate patterns of genetic migrations, where distinct spatial scales involves different MGEs.[28,58,59] This gives biogeography also a crucial role in evolutionary studies, where the spatial structure of populations and metapopulations must be properly understood *before* modeling population dynamics. These insights underscore the need for evolutionary studies to transcend genetics (and its derivative fields such as population genetics), expanding into socioenvironmental contexts.

REPRESENTING EVOLUTIONARY PROCESSES WITH EVOSYSTEMS

The traditional perspective suggests that evolution amounts to changes in heritable variation across time within Darwinian populations or lineages. This viewpoint partially explains the phenomenon under scrutiny. The gene family *bla*$_{NDM}$ forms a lineage and it does change across time, and so do the lineages of associated bacteria. The problem is that many crucial elements of the phenomenon (most of what was just exposed) are left out if we stick to this constraining perspective (see Table 1). Hence, we ask: is evolution that which happens within a lineage, or does it refer to the ever-changing set of interactions that compose an evosystem?

This comes down to choices regarding how we define evolution, evolutionary entities and the field intended to investigate them, but if definitions are to echo the work being done in practice and the phenomena under inquiry, then the standard definitions are found lacking. In the case of *bla*$_{NDM}$, a critical "thing" that evolves is the evoystem, a network of interacting entities at various levels of organization (parts of genes coming together to form new genes; various functionally integrated genes; transposons; plasmids; cells; microbial communities; macrobes; macrobial communities, abiotic components of the environment). Its evolution is irreducible to changes in the distribution of variation within a single Darwinian population. Studying the said evosystem requires tools from population genetics, phylogenetics and the other disciplines associated with the Modern Synthesis, but these are insufficient. To understand the spread of *bla*$_{NDM}$ (and AMR evolution more broadly), we must at least draw insights from ecology, Earth system sciences, biogeography, sociology, history, anthropology, network sciences and the medical sciences.[60,61] The study of evolution, if reduced to evolutionary biology, offers a partial perspective, which our approach to evolutionary *studies* expands.

CONCLUDING REMARKS

In this paper, we made two related claims. First, evolutionary biology is biased towards its core disciplines (mainly population genetics and phylogenetics), and this leads to a partial approach to evolution where the study of the selective environment and its complexity is blackboxed (but not left out). This generates important loss of information and an incomplete representation of evolutionary phenomena, as we illustrated with a case of AMR evolution. Consequently, we believe there is an urgent need to redefine the phenomenon under inquiry (i.e., evolution). Our second claim is that the evosystem concept best captures evolutionary phenomena and best represents the work of evolutionary scientists. For instance, our analysis of the case study echoes the urging need to address AMR evolution by focusing on interlevel interactions and the nestedness of biological entities, as expressed by Baquero in his 2010 Garrod lecture.[51] We believe the evosystem concept adequately complements the ontology outlined in that paper, as it can also be made mathematically tractable using network modeling. We believe that establishing a novel conceptual cornerstone for the field, redefined as evolutionary studies, will renew its potential to contribute to our understanding of complex and socially important issues, such as the evolution of AMR. We also hope this may foster novel outlook on phenomena that evolutionary biology has historically struggled to explain, such as altruism, symbiosis broadly construed, or multilevel evolution.

TABLE 1 Evolutionary biology (the standard approach to evolution) and evolutionary studies as sketched in this paper.

	Evolutionary biology	Evolutionary studies
The target of explanation	- A Darwinian population (homogeneous population, usually of genes or organisms) or a lineage. - The selective environment is external to what evolves, i.e., to what is studied.	- Evosystems: Heterogeneous systems composed of entities at different levels of organizations and their various interactions. - Evosystems include Darwinian populations and their selective environment.
Evolution	Changes in the frequency of heritable variation.	Changes in the frequency of entities and interactions; changes in the nature and topology of interactions.
Disciplinary boundaries	- As defined by the Modern Synthesis and its legacy (although flexibility is and has always been allowed): population genetics (mathematics and genetics), phylogenetics (taxonomy), paleontology form the core. - Developmental biology and ecology were marginalized and their inclusion is to this day contentious (especially that of ecology). - Earth System sciences and social sciences are excluded.	Includes the disciplines traditionally associated to evolutionary biology, as well as developmental biology, molecular biology, ecology, Earth system sciences, history (and other social sciences), medicine, infectiology, epidemiology, etc.
Acknowledged drivers of evolution	- Natural selection. - Drift (neutral evolution). - Point mutation. - Other drivers are often acknowledge by working scientists but absent of summaries of evolution.	- Natural selection. - Drift (neutral evolution). - All processes that lead to genetic variation. - All processes that lead to phenotypic variation. - All processes that change the interactions between and within populations. - The very attempt to provide an exhaustive list would be absurd, hence our desire to stay away from any claim of a new synthesis or of an extended one.

AUTHOR CONTRIBUTIONS

F.P. and L.P.H. conceptualized, wrote, and revised the paper together. F.P. conceptualized and realized Figure 1. F.P. conceptualized the graphical abstract image. E.B. and F.N. extensively revised the manuscript and provided structural concepts and ideas.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

No datasets were generated or analyzed during the current study. No computer codes or algorithms were used to generate results.

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