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Modeling the evolution of interconnected processes: It is the song and the singers

Tracking units of selection with interaction networks

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Abstract

Recently, Doolittle and Inkpen formulated a thought provoking theory, asserting that evolution by natural selection was responsible for the sideways evolution of two radically different kinds of selective units (also called Domains). The former entities, termed singers, correspond to the usual objects studied by evolutionary biologists (gene, genomes, individuals, species, etc.), whereas the later, termed songs, correspond to re-produced biological and ecosystemic functions, processes, information, and memes. Singers perform songs through selected patterns of interactions, meaning that a wealth of critical phenomena might receive novel evolutionary explanations. However, this theory did not provide an empirical approach to study evolution in such a broadened context. Here, we show that analyzing songs and singers, using patterns of interaction networks as a common ontology for both, offers a novel, actionable, inclusive and mathematical way to analyze not only the re-production but also the evolution and fitness of biological and ecosystemic interconnected processes.

KEYWORDS

earth system science, evolutionary biology, evolutionary systems biology, interactions networks, units of selection

INTRODUCTION

Recently, Doolittle and Inkpen introduced a thought provoking hypothesis about evolution by natural selection, entitled "It is The Song, Not The Singers" (ITSNTS).[1] This hypothesis generalizes the condition for evolution by natural selection (ENS), a major scientific concept introduced by Darwin in 1859 to explain the evolution of species.[2] ITSNTS expands this critical theoretical framework way beyond the evolution of monospecific populations to further address the evolution of processes, for instance, functions realized by communities within ecosystems. Thanks to ITSNTS, evolutionary biology can now seek to make sense not only of the history of species, but also of the history of processes or patterns of interaction such as stable and recurrent biogeochemical cycles, for example, nitrogen fixation, operated by interactions between biotic and abiotic components.[1] The evolution of such patterns of interaction, sustaining functions, information, or even memes,[1] had long been considered to fall under the scope of what evolutionary biology, or eventually cultural evolution, should intuitively be able to explain, yet struggled to. ITSNTS recently appeared as a powerful way to fill in this important theoretical gap.

When formulating their hypothesis, Doolittle and Inkpen were very careful to highlight both its unique scientific and philosophical scopes. The key point of ITSNTS is that some processes could now be understood as bona fide units of selection, which are different from recognized higher level entities that emerged by selection through evolutionary transitions,[3] for example, from smaller units giving rise to a higher level biological organization, as genomes would emerge from genes, or as eukaryotes would have emerged from an endosymbiosis between two prokaryotic partners.[4] Such cases are typically accounted for in the context of multi-level selection.[5,6] According to Doolittle and Inkpen, biogeochemical cycles, metabolic functions or other functions realized by communities of individuals, information, and even memes, *qua* processes, can be described as patterns of interactions between components (typically, in their biological examples, such components were entities, such as genes, organisms, or species.[1]) Processes (see glossary) are consequently defined as the dynamic results of interactions between components of a system, and can accordingly be described using networks to represent the patterns of interactions that sustain the targeted process. Such networks might, in many cases, only be proxies for the phenomenon we mean to explain, for example when co-occurrence networks are used to infer molecular or organismal interactions that perform the function of a system.[7] Whereas the Darwinian theory of ENS could explain how replicated components could be selected,[8] until ITSNTS was proposed, a major theory explaining how interactions between components could, eventually, also be the result of natural selection was lacking.[9] To embrace ITSNTS wording, Darwinian ENS successfully explains the evolution of singers (basic individual entities), yet it could not easily explain the sideways evolution of another Domain of selective units: the songs (processes resulting from interactions between potentially heterogeneous individual entities).

In particular, ITSNTS is distinct from ENS, because songs are not made of singers (in the same way that genomes are made of genes), but rather songs are performed by singers.[1] At first sight, this distinction stressing the difference in nature between a song and its components seems to leave little opportunities for songs to expose traits upon which natural selection could act. This traditional reading suggests that only singers may be the real outcomes of evolution by natural selection, whereas songs might be at best a fortuitous evolutionary by-product of selection operating at a narrower level.

To this perspective, Doolittle and Inkpen oppose a process-based approach to evolution, explicitly grounded in process-based metaphysics.[1,10] In this line of thought, songs are processes and can feature the necessary coherence to be conceived as persisting individuals, that is, as defined by ITSNTS, fitness bearers emerging from components in evolutionary dynamics. Doolittle and Inkpen write: “Conversely, process ontologists see processes as primary, [material] things as their manifestations. For ITSNTS, this would mean, in effect, that taxa and the communities they form are adaptations of the processes they implement, not the other way around. And of course we, as multicellular individuals, are processes: few of our cells are “the same” as those with which we were born, and our identity is sustained throughout our lives by the continuity of developmental and regenerative processes, not the atoms or cells in our bodies at birth.”[1] Doolittle and Inkpen insist that some songs can be selected for themselves (i.e., songs are selectable patterns of interaction).[1] While, they sketched the importance of topological descriptions of interaction structures susceptible to get selected, however, they did not elaborate upon the practical, empirical outcome of their theory for evolutionary studies.

Here, we further develop ITSNTS to provide a method for possible empirical tests for the evolution of patterns of interaction, aiming to distinguish processes that can evolve by natural selection from those that cannot. We agree with Doolittle and Inkpen that any given song (e.g., a geochemical cycle such as nitrogen fixation) is not made of singers but performed by singers. Yet, we feel that it could be even more productive to stress that there is in fact no fundamental ontological divide between singers and songs, in other words that evolution by natural selection is about patterns of interactions, all the way down. Our model, called ITSATS (for It Is The Song *And* The Singers) is more closely related to process-based metaphysics than ITSNTS. Indeed, while ITSNTS holds that both processes (songs) and entities (singers) are mandatory to understand evolution, ITSATS stresses that the whole biological hierarchy can be fruitfully described using patterns of interaction, aligning with contemporary advocates of the relevance of process-based metaphysics for biology. Typically, Nicholson and Dupré wrote: “we propose that the living world is a hierarchy of processes, stabilized and actively maintained at different timescales. We can think of this hierarchy in broadly mereological terms: molecules, cells, organs, organisms, populations, and so on. Although the members of this hierarchy are usually thought of as things, we contend that they are more appropriately understood as processes.”[10]

Yet, an important difference remains between ITSATS and traditional process-based metaphysics, which maintains that entities and processes are opposed notions, sustaining mutually exclusive approaches to the description of science’s subject matter. ITSNTS maintains the distinction, but rejects the idea that the corresponding views of evolution are mutually exclusive. In contrast, ITSATS claims that embracing a common ontology, according to which *all* evolving entities can be described as patterns of interaction[9] provides a scientifically operational framework, inspired by work in systems biology as well as novel approaches in evolutionary biology.[11–13] More explicitly than ITSNTS, ITSATS thus emphasizes the hierarchical structure of systems, pointing out that at any level objects (singers) interacting to produce a song can be modeled as songs themselves, performed by other interacting objects (singers) at the next level down. Singers and songs become labels to be applied contextually. For example, a singer, such as a unicellular organism part of population dynamics or symbiotic interactions, can become a song in an explanation focused on processes resulting from more inclusive interaction networks.

Also, ITSATS emphasizes how interacting sets of objects (songs) may evolve in various ways, both neutrally and by natural selection operating through persistence rather than reproduction. This allows testing (and possibly rejecting) the ITSNTS explanation of some processes, for instance, when patterns of interaction are not repeated, since then a song is not re-produced. Moreover, interaction patterns can be mathematically characterized, their topological variants can be described in terms of centrality and path analyses,[14–16] which provides a mathematical framework to study the fitness of a song,

BOX 1 Fitness and patterns of interactions in the context of ITSATS

ENS occurs in population where there is variation, differential fitness and heredity. Because ITSATS is meant to augment the scope of evolutionary biology, it must show, among other things, that some patterns of interactions can indeed be fitness bearers, increasing their frequency in a population as a result of selection. We suggest that the fitness of songs is intimately related to the notions of resilience and robustness, which can be illustrated as follows.

First, some biological phenomenon can be represented as a network of interaction. There are countless methods available to achieve this, as the tools of network sciences inform evolutionary biology in a many ways. In the case of microbial communities, for example, co-occurrence networks can be used to infer interaction networks (see Box 2 and the work of Faust and Raes.[50])

Second, once an interaction network has been generated, it is possible to identify patterns of interaction (subgraphs) and measure their fitness, just like this can be done with traditional units of selection. An important distinction, however, is that traditional ENS reduces fitness to the reproductive output of units of selection, while ITSATS takes a more inclusive approach, in which fitness refers to the persistence of a system. Persistence of a system can be realized in two ways: when patterns of interactions are robust and when they are resilient. In Figure 1, we illustrate both phenomena in a multilayer network. Such a multilayer network describes topologies of interaction networks at different time points, each layer being constructed using the method presented in Box 2. Figure 1 shows two different occurrences of the same pattern of interaction (a triangle). One of these (red) is used to illustrate robustness, as the pattern remains the same across time; the other (blue) illustrates resilience, as the pattern is perturbed and then re-produced. Selection on persistent or resilient systems can thus increase the fitness of a pattern of interaction.

Accordingly, the fitness of “traditional organisms” has already been studied through topological considerations on the (functional) interactions of organismal components. This methodological treatment can be found in the literature on ageing, because, precisely, ageing is defined as a decrease in fitness. For instance, Gavrilov and Gavrilova [70] proposed that organismal fitness reduces through a process of redundancy exhaustion, ultimately leading to a system with components connected in series, so that any cumulation of new defects in the components can only lead to organismal death, leveling off mortality rate of the organisms in the meantime. Thus, organismal fitness would benefit from redundant singers (playing the same part in the song) that reduce the chances of having defects in the connected series. Furthermore, Kriete[71] proposed that negative feedbacks between organismal components can introduce some robustness in networks, before non-heritable damage results in catastrophic system failure (death). In other words, specific patterns of interactions can be critical to stabilize organismal fitness. Likewise, Kiss[72] proposed to analyze fitness using the notion of network evolvability, that is, the capacity of the system to change its own patterns of interactions. Beyond robustness, organismal fitness requires some flexibility in the interactions between its singers. Literature on gut microbiome and ageing provides additional examples in which interactions between host-associated microbes are correlated with host fitness (healthy ageing)[73]. Such studies consider the fitness of “traditional” organisms, as resulting from broader, dynamic, and eventually tipping structured interaction networks involving microbes.

that is, the appearance and increased re-production of new interaction patterns over time/space.

Below, we develop the scientific pay-offs of ITSATS modeling.

Both singers and songs can be described as patterns of interaction

ITSNTS stressed that songs are distinct units of selection from the singers performing them. Doolittle and Inkpen wrote that: “whatever biological processes are made of, it is not the same kind of stuff as the things (genes, cells, organisms, species) that implement them.”[1] Thus, ITSNTS seems to oppose two kinds of entities: patterns of interactions (the songs) and other entities (the singers), while acknowledging that both kinds can evolve sideways. The relationships between singers and songs are however complicated. On the one hand, Doolittle and Inkpen underscore a strong relationship of dependence between songs and singers. They write that “because there is a song, there are singers,”[1] and that “because there are singers, there is a song.”[1] On the other hand, ITSNTS is rooted in the fundamental possibility of a decoupling between the evolution of singers and songs: the singers could change and the song persists, since songs can be real units of selection. Because these aspects of the ITSNTS hypothesis are complex, they can easily become a source of confusion, in particular because singers (being more traditional objects of studies in evolutionary biology than songs) may still seem to be the more fundamental entities through which to understand evolution, and songs might continue to be overlooked (in evolutionary biology).

We propose therefore, and in contrast with ITSNTS, that it would be fruitful to stress the lack of fundamental ontological distinction between songs and singers. Singers, like songs, can be real units of selection, in the very sense that even the most basic material entities, familiar to biologists, such as genes or organisms can also be seen as emerging from patterns of interactions.

Let’s consider a seemingly very basic component of life, an entity to which it seems intuitive to assign the role of singer: a gene. From a biochemical perspective, a gene can also be seen (and modeled) as the result of chemical, physical and spatial interactions between DNA bases. In that case, according to ITSATS, because a gene re-produces by re-assembly of a collective of DNA bases in interaction, a gene function associated with this pattern of interaction can be selected for. In other words, a gene can also be seen as a song performed by a pattern of interactions between singers (its DNA bases). This example is a direct extension of ITSNTS at the molecular level of biological organization: because there is a given gene function that can be selected for, there will be a specific re-assembly of DNA bases, and because there are specific interactions between DNA bases, there will be a given gene function.

Empirically, this takes notable importance when genes and their functions are generated by the recruitment of genetic material coming from different gene lineages. For example, more than three hundred composite genes were identified in haloarcheal lineages, 126 of which were formed with genetic material coming from bacterial lineages.[17] This process, importantly, is distinct from lateral gene transfer, where complete genes are being transferred from one lineage to the next. In contrast, composite genes arise when smaller DNA segments associate to form new genes, and are said to be phylogenetically chimeric when these genes stem from genetic material issued from distinct host lineages.

Composite genes are, from an empirical standpoint, extremely telling: they highlight the complexity of evolutionary dynamics that give rise to evolutionary novelties such as the adaptation of haloarchea to high salinity environments. From a conceptual standpoint, they are just as important: not only can genes be described as patterns of interactions between bases, but their components are potentially obtained from distinct lineages, such that genes can lean towards having “too many parents.”[1] While tracking even smaller bits of DNA, or even lineages of nucleotides, might become tempting in order to compensate for the increasingly recognized messiness of gene lineages,[17–19] this would only transpose the difficulty one level down (genes are songs composed of smaller singers, which are songs composed of yet smaller singers, etc.). In the end, when DNA sequences such as genes are tracked, for example, by phylogeneticists, it is not as material monoliths that they attract attention and yield results, but rather as re-produced selectable sets, that is, patterns of interaction or songs. Hence, gene lineages feature the same kind of stability found in other patterns of interactions that ITSATS identifies as *bona fide* units of reproduction.

Modeling gene evolution with dynamic interaction patterns

There are several pay-offs to consider the function of a gene as a pattern of interaction. First, this view seems consistent with the Dawkinsian model of evolution,[20] a popular description of evolution by natural selection. The Dawkinsian model stresses the success of replicators, that is, lineages of immortal genes, bearing a replicated information. In this model, genes grow into families of selfish genes, through rounds of rather faithful replications. Although the material of the ancestral gene itself is rapidly replaced by new bases, reassembled according to the initial template, the information (or, according to ITSATS, the song) carried out by that gene persists. Accordingly, it is tempting to summarize the evolution of a replicator and the evolution of its information using an evolutionary tree, which represents how substitutions accumulate within a gene family as new copies of the selfish genes are produced by replication. Such an evolutionary tree is more conventionally called a gene phylogeny. Such a standard tree-based formalism offers a natural way to display and to analyze the evolution of a gene function and is furthermore consistent with the practices of phylogeneticists as well as with the Darwinian and the Dawkinsian views of evolution by natural selection.

However, molecular biologists and phylogeneticists are well aware that such gene trees can only partially capture gene functional evolution.[21] Namely, a gene phylogeny represents the succession of substitutions in the primary sequence of homologous genes over time, which uncontroversially constitutes an essential part of the history of the genes. But from that tree pattern it is impossible to fully predict the function of each gene variant that evolved. The reasons for these are well established. During evolution, some base substitutions can be neutral with respect to the gene function: the standard notion of synonymous substitution illustrates that an “A” can be replaced a “T” in the primary sequence of the gene without affecting the gene function, or more exactly that of its encoded protein(s). By contrast, other mutations can alter the gene function, for example, a non synonymous substitution at a base encoding the active site of a protein might change the function of that gene and thus its song. Yet, this functional knowledge depends on interactions between bases forming a gene, and also on interactions of that gene and its encoded products with other molecular components.[12,22] This means that describing the evolution of functions, or of information, remains a non-trivial issue, which cannot systematically be solved by a simple mapping of changes in a tree-pattern of descent with modification.[9,21]

Interestingly, conceiving of a gene as a pattern of interactions rather than as a singer allows an expansion of the ways to describe the evolution of songs beyond the canonical phylogenetic trees/replicators approaches. For example, when DNA bases enter into novel interaction patterns as a result of a gene fusion, a new song (or function) can evolve and be selected for (gene fusion does not necessarily lead to a new function, but it can).[23,24] This is the case for so-called fused genes with emergent properties, such as the AtGRXS16 S-gene family in *Arabidopsis thaliana*, formed by the fusion of components from the GIY–YIG and GRXS domains, encoding amino-acids between which an intramolecular disulfide bond can be formed, an interaction with functional consequences that would not exist in absence of that gene fusion.[18] Because the origination of songs by fusion involved (at least) two distinct sources (e.g., in the case of AtGRXS16, DNA from two distinct gene families), the evolution of that kind of information cannot by definition be described by a tree. Indeed, trees have single roots, where fused genes phylogenies would require multiple roots.[25] This simple example, coupled with the chimeric genes example provided earlier, reiterates the central tenet of ITSATS, which is that the evolution of a song (e.g., a function sustained by interacting DNA bases) is a more general issue than the description of the changes occurring on singers (e.g., the substitutions of DNA bases) by a branching pattern. Evolution of novel songs has also to do with the variation of the outcomes of interactions between components, even for entities traditionally conceived as singers.

Moreover, a gene or a gene product interacts with other genes and other genes products. These interactions are well known in systems biology,[12] and described for example in the form of gene regulatory networks,[22,26,27] or protein-protein interaction networks.[28,29] These networks associate genes whose interactions result in a particular re-producible phenotype,[30] and such interaction networks are therefore also songs. More precisely, since the ITSATS model already considered genes – and their products, for example, a folded protein, resulting from a recurrent pattern of interactions between amino-acids under physical, chemical and environmental constraints – as songs, ITSATS sees a gene regulatory network as a larger song made of smaller songs, that is, as an opera performed by specific interactions between songs. Because there is a gene regulatory network (opera), there are genes (smaller songs) that occasionally change interactions, for instance when the promoter of a gene is subjected to a mutation that affects how that gene (or its products) interact with other genes (or other gene products) in interaction networks.[27] We are not eliminating singers here, but we do highlight that every singer is a song with respect to the next level down, while still playing the role of a singer with respect to the next level up, and both roles are critical to the hierarchical view. The status of singer and song is defined by the context being considered. As such, ITSATS appears as a fractal and unifying model relying on a single, shared ontology: patterns of interactions (songs *and* singers).

ITSATS provides a single, empirically testable, ontology for evolution

We have argued that evolution by natural selection, understood as the evolution of songs, that is, patterns of interaction with selectable properties, provides a universal model across all biology – from molecules[12] to ecosystems[31–34] – and points towards a shared network-based ontology to analyze the history of life. Bringing forward this network-based ontology for evolution by natural selection is fruitful for many reasons. First, networks are powerful analytical models. Networks allow for topological analyses of the evolution of songs, for all levels of biological organization. Take for instance the case of a metabolic cycle: a series of reactions (e.g., transformation of A into B, transformation of B into C, etc.) performed by enzymes (e.g., 1, 2, 3, etc.) hosted by microbial cells (Figure 2). This cycle is the direct outcome of interactions between enzymes (biotic components) and substrates. As the classic ITSNTS hypothesis described, this metabolic cycle does not require that all singers come from a monogenic population, for example, the enzymes could be carried by different microbial hosts, as illustrated in cases of metabolic hand-offs.[35] This metabolic cycle is a song, if it is re-produced over time, even though different singers (different enzymes, or enzymes from different hosts for a given step) could be involved in the different occurrences of the metabolic cycle. This metabolic cycle would even be possibly positively selected for if its frequency increased over time. Moreover, as ITSATS stresses, the topology of that metabolic cycle can be characterized by centrality and path analyses.[14–16]

This latter point brings out the second advantage of the network-based ontology: the evolution of songs by ITSNTS is empirically testable. ITSNTS was originally motivated by the striking observation that some ecosystems show recurrent dynamics that are difficult to explain, such as the debated re-production of microbial communities observed in coastal marine plankton time-series by ecologists,[36] or the reproduction of microbiomes observed in human guts by clinicians and metagenomicians.[37] ITSNTS addressed this challenge by providing a framework that explained such re-occurring natural phenomena, by arguing that the re-production of an entity opens the possibility to consider this entity as a *bona fide* unit of selection.

Differential fitness, along with heredity and variation, is a minimal condition for ENS.[8,38] Traditionally, fitness has been reduced to the reproductive output of units of selection. Populations, in this perspective, evolve by means of natural selection when some of their components reproduce more than others, thereby increasing the ratio of their type (gene family, species, phenotype, etc.). Building upon the work of various authors that have shown this approach to fitness to be highly insufficient to account for biological evolution, even in the context of Darwinian evolution.[1,39–44] ITSNTS argues that patterns of interaction can be fitness bearing entities (songs) even if they do not have traditional reproductive output. In this sense, Doolittle and Inkpen use Bouchard's notion of fitness as persistence: fitness refers to the *persistence of lineages* (or more generally songs) across time. This persistence can be achieved by the sheer stability of a song, or by it being re-produced across time, by different singers. In cases of re-production, that is, recruitment of singers performing a song, there need not be material continuity between the singers of a song. But as Doolittle and Inkpen put it: "This is true but not fatal to ENS (for either memes or community metabolisms) as long as there is some causal connection between populations over time, a relationship between implementations of a process [song] now and in the future such that the former can be seen as necessary for the latter."[1]

In other words, Doolittle and Inkpen banked on the fact that songs can persist through re-production,[41] that is, the recurrence of a pattern of interaction. If this is to be translated empirically, however, more needs to be said on how we can measure song fitness. In Box 1, we show how the notion of fitness applies to patterns of interaction using the notions of network robustness and network resilience within multilayer networks, constructed from longitudinal data. In short, song lineages can persist in two ways: either a given song resists change, it is then said to be robust; or it fails to resist perturbations, but its topology tends to be re-produced across time. Patterns of interactions thus re-produced can be said to be resilient. Importantly, this means that reproduction is a specific case of re-production, which is itself a specific way for persistence of systems to be realized. To take a fitness-as-persistence approach to ENS thusly helps us expand the scope of evolutionary biology in a unified way, centered on patterns

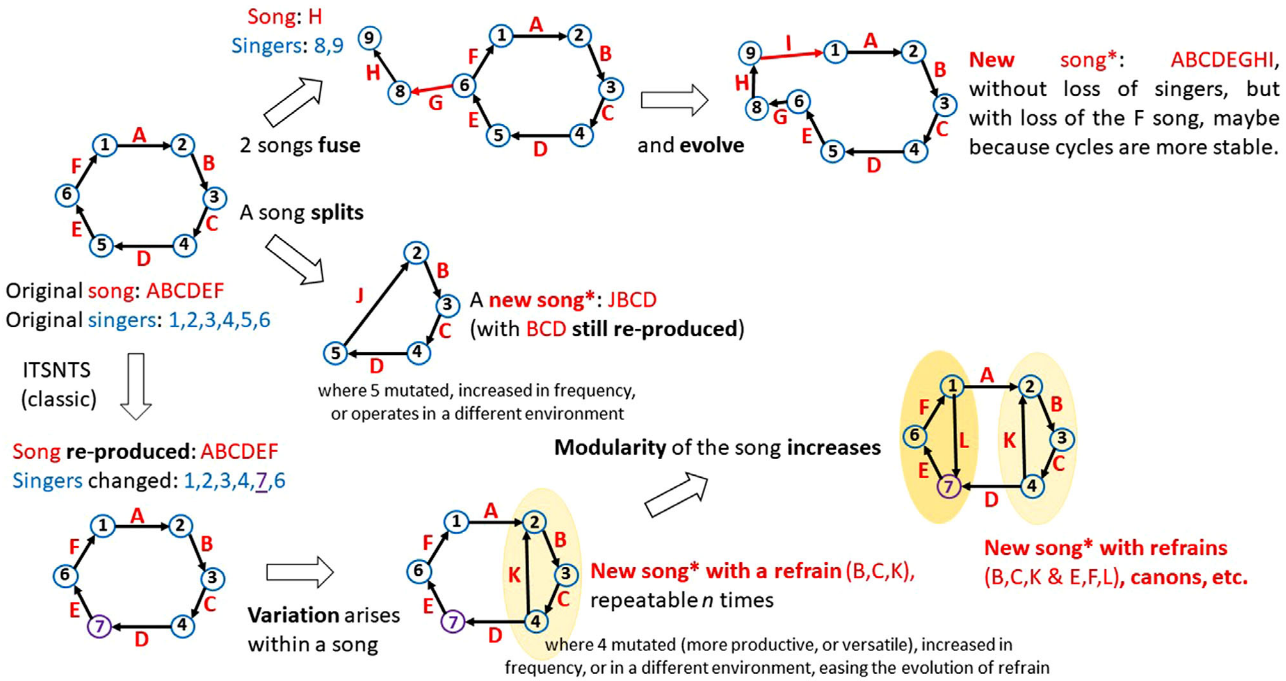

FIGURE 1 Possible schematics for the evolution of the "A,B,C,D,E,F" song. Singers are in blue circles, and their interactions are represented by directed edges. The song corresponds to the succession of red steps along the interaction pattern. For example, component 1 performs the transition from step "F" to step "A," while component 2 performs the transition from step "A" to step "B"; the interactions of components 6 & 1 & 2 therefore plays a part of the complete song: "A,B,C,D,E,F." As the patterns of interaction change, the songs evolve or persist. The evolution of new patterns offers an additional description of evolution, supporting network studies of evolution, according to ITSATS. *refers to case where, if the new song increases in frequency with respect to the "ABCDEF" song, in some environments, then the new song can be positively selected for. Anytime, new song get selected because a singer changed the song, niche construction can occur

of interaction. Indeed, the fitness of a song can be diagnosed by quantifying the frequency at which a given pattern of interaction appears in a population (Figure 1), for example by analyzing –omics data produced in time series. In Box 2, we detail how evolutionary inquiries framed by ITSATS can be realized and Box 3 shows how this can inform contemporary debates in evolutionary biology. These discussions help understand the various ways in which novelty can be introduced into patterns of interactions or, more generally, how songs can change by splitting, or fusing, or by experiencing variants of their patterns of interactions, and more fundamentally songs can change when the interactions between singers change (Figure 2).

Modeling the evolution of ecosystems using dynamic interaction patterns

This opens up many empirical possibilities to test insights that go beyond the work of Doolittle and collaborators, and to frame them in the unifying vocabulary of ITSATS. For example, Lenton and collaborators[45–48] have in the past decades suggested that ecosystems can be units of selection, that is, entities featuring traits that could be selected for and thusly form populations that evolve by natural selection.

This claim has been put to the test recently by Blouin and collaborators[7,49] who designed experiments of artificial selection to act on microbial communities standing in as ecosystems. Specifically, Blouin et al. recently highlighted that CO_2 emissions of microbial ecosystems could be artificially selected. Interestingly, this ecosystemic trait was correlated with patterns of interactions between the constitutive microbes. "A first objective of this study was to bring an experimental proof of principle that community structure, especially the structure of interaction networks of communities, are significantly affected during the artificial selection procedure. A second objective was to document how far we can go in changing ecosystem phenotype by artificial selection." [7] In order to achieve this, their experiments featured six independent lines of thirty microbial communities each (a control set of microbial communities similarly structured was also used to contrast artificial selection with random selection). The communities were left alone for twenty-four hours and their CO_2 emissions were then measured. In each independent line, the three communities that produced the least CO_2 were selected on this basis, pooled together to produce a source from which thirty new communities were created. More precisely, each new community is created from a sample of 50 μL of the source pool to which 750 μL of sterile liquid medium was added; and the communities were cultivated in 96-deep-well microplates.

After twenty such selective events (twenty-one generations), the biodiversity of the communities was characterized on the basis of the

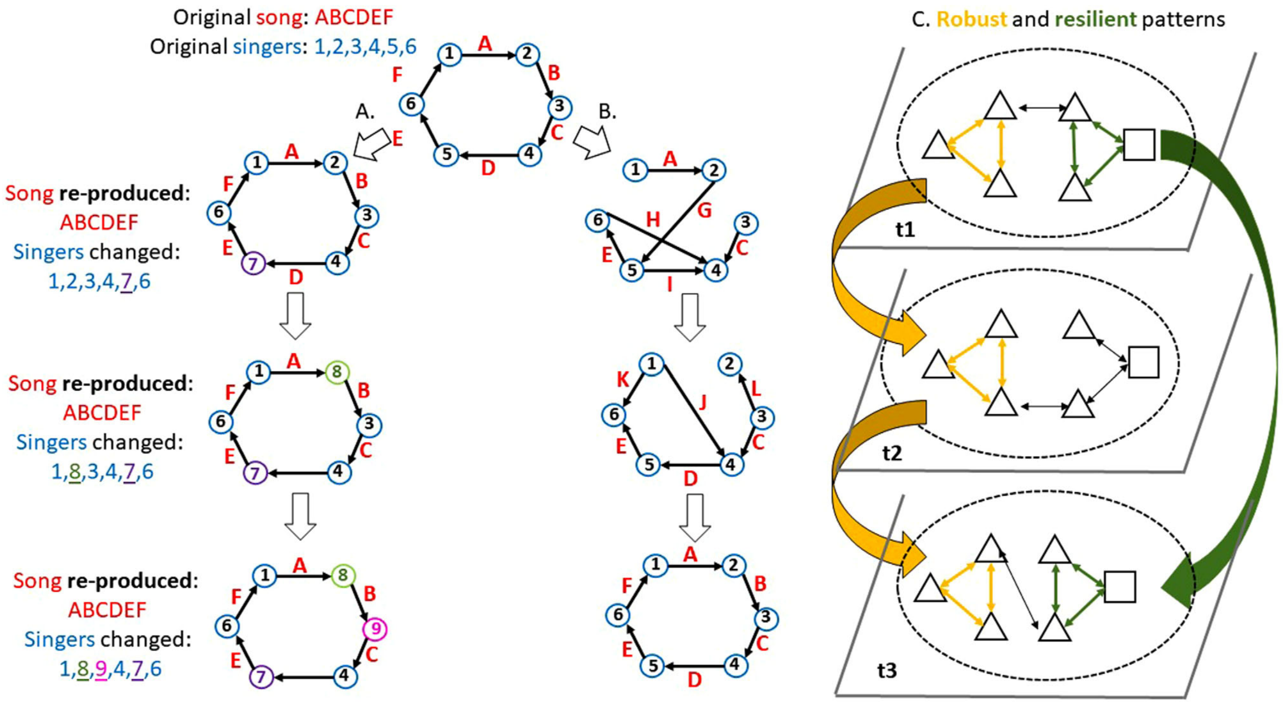

FIGURE 2 Further description of songs' properties. Same colour code as Figure 2. The frequency of recurrence of the song provides a basis to determine (A) whether a song is robust to the change of singers (singers switch a lot, the song stays) or, inversely, (B) whether a song is fragile (Singers are there, rarely the song). (C) Formal modeling using a multilayered network, where each layer (gray area) corresponds to the state of a system (delimited by a parallelogram) at a given time *t*. Nodes are (biotic or abiotic) components of the system, and the two-ways arrows that link them represent interactions (e.g., inferred from co-occurrence networks). This specific multilayered network was built to illustrate the resilience and robustness of patterns of interactions. In orange, a triangular pattern of interaction remains the same across time; it is robust. In green is another occurrence of a triangular pattern of interactions that features resilience: it disappears in the second layer, but is re-produced in the third. In this light, maximizing robustness and re-producibility are two ways for songs (in orange and in green), and for a system, to maximize their fitness

T-RFLP-defined genetic units in presence. This characterization was then used to infer interaction networks (as in Faust and Raes,[50]) correlating lower CO_2 emissions with structural features of the communities. Notably, low CO_2 emission was thusly correlated to low interaction richness (i.e., the total amount of pairwise interactions), low connectance (i.e., the ratio for realized to possible interactions) and low average degree (i.e., the average amount of interaction of nodes present in the network).

This insightful work can be interpreted constructively in the terms of ITSATS: ecosystems are patterns of interactions, which can be acted upon by selection. As in ITSNTS, this statement implies that ecosystems (songs) can evolve by means of natural selection, but it *does not* deny the possibility of the singers, in this case the microbes, to evolve sideways. On the contrary, both evolutionary dynamics appear to be complementary, in the sense that both must be taken into account if biodiversity is to be properly assessed and its underlying dynamics understood.

Basically, ITSATS means that a theoretical framework is now available to mobilize the inferential power of network sciences in ways that could increase our knowledge of evolutionary dynamics. In MLNs, analyses of community structure, and in other uses of network-based tools in evolutionary biology, network comparison holds the keys to a more inclusive understanding of evolution. It becomes testable for instance that songs follow general topological principles over evolutionary time (e.g., an increase in modularity,[14]) if the topology of the past interaction networks differs from the topology of subsequent interaction networks, as the result of introduction of particular motifs over time.[12,51] It is also possible and testable that evolving processes fell prey to the evolution of other competing processes. If new interactions become favored by selection (e.g., step A being no longer followed by step B, but being more frequently followed by step C, so the song lyrics evolves from "AB" to "AC"), then a song can be re-oriented in a novel evolutionary direction.

ITSATS can model the evolution of interconnected processes

A third pay-off of stressing the common network-based ontology to describe evolution by natural selection is that it makes this modeling especially inclusive. As Doolittle and Inkpen noted when they focused on the nature of the singers, songs can be performed by biotic and abiotic components in interactions.[1] This diversity allowed ITSNTS to model the evolution of ecosystems, whereas the inclusion of abiotic material, which by definition does not replicate, as a part of an evolving system usually makes the notion of evolution of the ecosystem as a whole irrelevant for traditional evolutionary theories.[41] Focusing on interactions between *and* within singers, ITSATS proves that ITSNTS can be understood as being even more inclusive.

BOX 2 Investigating the origins of symbioses with the ITSATS framework

How to analyze songs practically? What type of data do we need? What does it bring compared to a more traditional approach? A thought example illustrates what could currently be achieved to shed light on the origins of symbioses, a distinct research avenue from traditional phylogenetic studies on the origins of species.

Patterns of prokaryotic interactions over time (featuring some microbial songs) can be inferred using state-of-the-art microbial co-occurrence networks construction methods. For example, using 16S environmental data from time series, such as a series of seawater samples, receiving increasing amounts of freshwater from the melting ice in Arctic sea, one can build networks, in which nodes correspond to OTUs and edges correspond to statistically significant, weighted correlations in OTUs distribution after a given duration of fresh and sea waters mixing. Producing such temporal networks requires several steps.

In brief, first, sequence reads (from transcriptomics or metagenomics) must be denoised, filtered to remove chimera, and clustered into sequence variants to generate OTUs (for example using DADA2 v1.1.5.[74]) Second, for samples from the same time point (15 samples being considered as a decent starting point), OTUs abundancy tables can be analyzed using Sparse Inverse Covariance Estimation for Ecological Association and Statistical Inference v0.1.2 (SPIEC-EASI)[75] to compute correlation strength, and/or using Weighted Gene Co-expression Network Analysis (WGCNA), to compute co-occurrence patterns (e.g., Maffei et al. 2017.[76])

The resulting temporal series of microbial co-occurrence networks tracks how and which OTUs interact over time. These networks may feature robust interactions (persistent sets of edges and nodes in networks from consecutive sampling times) or resilient interactions (re-produced sets of edges and nodes, in networks from disjoint sampling times; see Box 1). Network comparisons to identify statistically significant matching subgraphs between pairs of microbial co-occurrence networks can take further advantage of edge weights to test for general or local reinforcement dynamics of interactions. For instance, at t_1, when freshwater first meets sea water, the resulting mix of microbial communities may be described by microbial co-occurrence networks, with a diversity of weakly correlated interactions, whereas when the mixing of waters have been ongoing for a longer time period, if the microbial communities become more structured, their microbial co-occurrence networks will present some stronger correlations, a different distribution of edge weights, and the recurrence or persistence of some sets of edges and nodes past time t_n. Thus, emerging microbial symbioses (or more generally any emerging patterns of interactions) could be identified by finding subgraphs that become robust with time (i.e., are present in the co-occurrence networks past t_n, possibly with increasing edge weights, and representing an increasing proportion, or absolute number, of the reads present in each sample). Such reinforced patterns of microbial interactions, suggestive of microbial symbioses, would be compatible with a form of selection, acting beyond a single OTU level. Analyses designed to impose selective constraints on ecosystems (see main text) could further demonstrate causal connections between a given selection regime and the emergence of reinforced patterns of microbial interactions (songs). By showing that some symbioses can be selected, such analyses would go beyond traditional approaches that tend to analyze OTUs evolution independently, and test ITSNTS, that is, whether different sets of microbes (singers) can take part into similar songs.

First, our approach can reconcile neutral evolution,[52–54] ITSNTS and evolution by natural selection. The evolution of interactions is indeed central for the evolution of songs. According to ITSATS, re-produced interactions can also be seen as songs, possibly within a larger song. But critically, not all interactions are the result of natural selection. Constructive neutralism (also called pre-suppression)[52–55] explains how some interactions can (irremediably) arise in absence of positive selection for them. For example, the complexity of the ribosomal machinery may first evolve neutrally, as a result of pre-suppressed mutations introducing dependences between ribosomal proteins.[56] Likewise, dependency relationships between microbes are expected to evolve by a ratchet mechanism in nature.[55]

Typically, some biological interactions likely arise by chance: by pre-suppression or even by drift (within populations with small effective sizes).[52] This kind of evolution probably typically affects gene regulatory networks. Thus, “the regulator first hypothesis” holds that many components of a gene regulatory network are neutrally recruited by association with the recruitment of a promoter, rather than based on particular selective advantages carried by each component of a gene regulatory network.[57] In this model, neutral connections are not counter-selected, new edges are expected to accumulate neutrally in gene regulatory networks, producing “fatter” patterns of interaction (longer songs) than expected by chance alone. Consequently, gene regulatory networks feature a mix of connections, some of which are essential for their new functions, whereas some other connections (the regulated genes and edges recruited by association with a newly acquired promoter) are a neutral, by-product of the mode of network growth.

Just like Doolittle and Inkpen introduced abiotic components as *bona fide* singers of songs, ITSATS introduces neutrally evolved songs (neutrally evolved interactions) as *bona fide* components of operas. What seemed like a non-starter for evolution by natural selection (constructive neutralism) becomes an acceptable evolutionary process, able to produce stable, re-producible patterns of interaction between

BOX 3 ITSATS informs contemporary debates in evolutionary biology – the case of host-mircobes interactions

ITSATS also informs contemporary debates in evolutionary biology.

For example, the evolutionary potential of symbioses generated by interactions between a macrobial host and its associated microbes is currently a hotly debated issue.[77–83] While multispecies symbiotic communites that include a macrobe have been shown to be functionally integrated in ways that influence the components' fitness, theoretical arguments have been proposed to deny most of these symbiotic assemblages the status of unit of selection because of their lack of fitness-based unity[79,84] or their incapacity to reproduce as wholes.[5] Other authors have defended the opposite, banking on the interactor/replicator distinction[81,82] or by stressing the functional continuity of such assemblages across generations.[85] Doolittle and Inkpen, with ITSNTS, highlighted the possibility that some of such assemblages are songs, and hence units of selection. Most empirical models that were developed to assess the evolutionary potential of these consortia, as seen in the work of Roughgarden,[81,86] describe host-microbe interactions on the basis of taxonomic composition, a promising approach in itself, but that leaves aside the study of the interactions among these taxa.

ITSATS provides another line of empirical inquiry to assess the evolutionary potential of host-microbes associations. For example, co-occurrence networks (see Box 2) of constitutive singers (hosts and microbes) could be used to infer if some patterns of interaction qualify as specific candidate holobionts. Importantly, this requires establishing criteria for comparing networks of interactions, such as homomorphy, connectance, average degree of nodes composing the network, and so forth. This type of inquiry can test hypotheses regarding structures of interactions deemed more fit than others, and could highlight topological traits of host-microbe associations that are targeted by selective pressures. It could, for example, stress the centrality/preferential connections of few nodes in the network and hence weaken the case for whole community-level selection, yet identify critical subsets of robust or resilient interactions between hosts and microbes (i.e., smaller holobionts).

This echoes recent work by Suárez,[85] who suggests that host-microbes symbioses are evolutionary relevant, if their boundaries are set by identifying the microbial genes that contribute, through interactions, to the persistence of the symbiosis across time. In his approach, the whole macrobial genome is included in the functionally delineated symbiosis, while only essential genes of microbes are to be considered. This perspective could be strengthened by demonstrating which macrobial and microbial genes are central in the patterns of interaction that characterize host-microbe symbioses, thereby acknowledging their privileged role for explaining the resilience and robustness (i.e., fitness) of the interactions at work. ITSATS offers a methodology to test such hypotheses. Alternative network analysis methods (e.g., Boolean network analysis,[87]) might also be used to analyze the dynamics of interactions.

Thus, ITSATS allows to assess the evolutionary potential of the *interactions* that sustain symbioses rather than the evolutionary potential of the taxonomic collections that compose them. By providing this additional outlook, ITSATS opens up the possibility to identify shared topological structures, present in different putative holobionts in the form of conserved networks of interactions composed of singers.

components (songs), embedded in a broader picture of evolution (operas). For example, the complexity of the ribosomal machinery may first have evolved neutrally, but because ribosomes contribute to perform a step of a larger re-produced cycle, the cell cycle, since there is a cell cycle, a complex ribosomal machinery is also re-produced. A neutrally constructed song can be co-opted as part of a selected opera.

Second, modeling the evolution of operas, as allowed by ITSATS, is desirable to understand the evolution of processes in a realistic way, since processes are typically interconnected. Not only can larger songs be made of smaller songs, but songs can also intersect as shown in countless examples in ecology and in systems biology.[58–60] Niche construction[61] is a neat example for such interconnectedness with evolutionary significance. When the outcome of a metabolic network (song 1) is a component, used in an interaction to perform a step of a geochemical cycle (song 2), then a song (the metabolic pathway) contributes to another larger song (the geochemical cycle), which in turn contributes, by niche construction, to the success or failure of the singers (enzymes and host taxa) that performed the metabolic song. Thus, a metabolism like denitrification, producing N_2 thanks to a final reaction involving the gene *nosZ* will ultimately enhance the fitness of the *nosZ* gene if the Nitrogen cycle, of which N_2 is a component, is fully realized. However, if microbes use the Annamox variant path, from NO_2^- to N_2, within the Nitrogen cycle, this alternative path (i.e., song) would favor the *hzo* gene over the *nirS/K*, *norB* and *nosZ* genes[62] (Figure 3). In that sense, ITSATS makes it possible to model how interconnected pathways (which may have appeared at different geological ages) may compete in different environments. Importantly, it adds perspectives based on -omics approaches (very common in biology) and evolutionary approaches (very fundamental in biology) to the study of processes such as elemental cycles, as well as to the ever-more present eco-evolutionary approaches to the study of various phenomena.[63–69]

The ontology of evolution as patterns of interactions promoted by ITSATS thus brings evolutionary biologists way beyond the classic ENS model, since, according to Darwin: "natural selection cannot possibly produce any modification in any one species exclusively for the good of another species,"[2] and encourages them to analyze the interconnectedness of pathways.

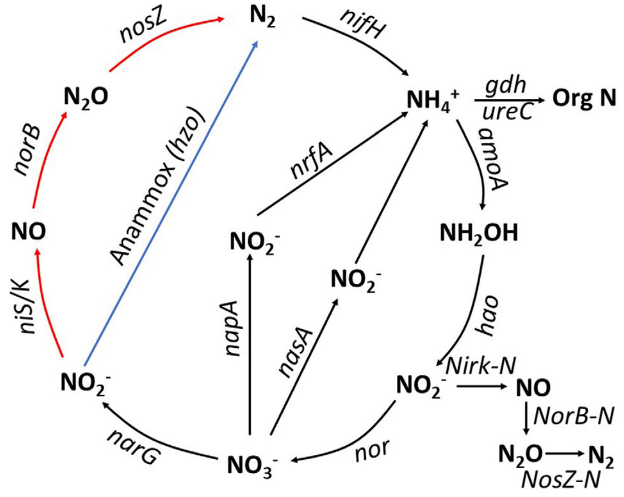

FIGURE 3 Simplified representation of gene-based interactions and phylogenetic diversity in the Nitrogen cycle. The cycle is inspired from Carter et al. 2012. While this representation does not take into account thermodynamic drivers of the cycle, it allows for -omics based comparative studies of the gene sets involved in N cycling over space and time. Components of the Nitrogen cycle are indicated in bold. Genes performing the different steps of the cycles are indicated in italics. Denitrification (a song) is underscored in red, Annamox (another song) is underscored in blue. These two songs may compete with one another. The realization of Denitrification rather than the Annamox pathway may result in niche construction, when N_2 production favors the completion of the Nitrogen cycle, which in turns enhances the fitness of organisms carrying, for example the *nosZ* gene

CONCLUSIONS AND OUTLOOK

None of the above is at odds with the ITSNTS hypothesis. However, ITSATS makes it more salient that inclusive evolutionary studies are possible when evolution is fundamentally analyzed, and fruitfully so, as stabilized (or unstable) dynamics of patterns of interaction. By stressing that singers are not fundamentally different from songs, when singers are considered at a finer analytical grain unraveling their fundamental processual nature, then singers appear to be themselves decomposable into smaller musical parts. Hence, ITSATS posits that larger songs, larger delineated patterns of components in interactions, are composed by the interplay of smaller songs, because components of the larger songs (a.k.a. singers in ITSNTS) are themselves the result of patterns of interactions between smaller components. This precision matters: ITSATS thus underscores how diverse and complex the phenomena that could evolve by natural selection are. For example, it allows evolutionary biologists to embrace, under the legitimate scope of evolutionary explanations by natural selection, the evolution of “operas” as re-produced interaction patterns involving components, which are themselves processes, and the evolution of partly neutrally emerging collectives. Moreover, ITSATS provides a description of this complex evolution currently amenable to scientific studies based on network analyses. Therefore, we invite evolutionary biologists to construct such networks in order to analyze the interactions in the systems on which they work, and, 160 years after the Origin of Species,

Glossary

It’s the song, not the singer (ITSNTS): a theory developed by Doolittle and collaborators that is meant to augment the scope of evolution by means of natural selection, claiming that it applies to patterns of interactions (processes) *as well as* to traditional objects of evolutionary biology, such as genes or organisms.

It’s the song *and* the singer (ITSATS): the theory we defend in this paper; it is an extension of ITSNTS. We argue that patterns of selection can indeed be selected for, and that this allows one to model the evolution not only of songs, but also of singers. ITSATS defends a unified view of evolution, downplaying the importance of the distinction between songs and singers, and proposes that network methods offer a generic way to assess, empirically, the evolution of patterns of interaction.

Songs: as defined in this paper, songs are patterns of interaction that are also fitness bearers. Such patterns of interactions form lineages whose evolution is sustained by natural selection. Genes, geochemical cycles, multispecies symbiotic assemblages, and so forth. can be described as patterns of interaction, and their fitness can be measured based on their robustness or resilience.

Singers: as defined in this paper, singers are the components of songs. A gene, for example, can be a singer with respect to a larger song such as an organism or a multispecies assemblage. The same gene, in an alternate situation, will itself be considered a song, as it is also a fitness-bearing process resulting from the interaction of its components (domains, nucleotides, etc.), that is, a pattern of interaction that features selectable resilience and/or robustness.

Process: dynamic phenomena sustained by interactions of components, that is, a pattern of interaction. Typically, functions, mechanisms as well as complex entities can be conceived as processes. Processes can be described based on the interactions that sustain them and accordingly modelled using networks. The philosophical notion of process goes back to Heraclitus (535-475 B.C.) and is rooted in a rich philosophical tradition. Recently, its usefulness for biology has been underscored to draw the attention of researchers towards neglected objects of inquiries (namely, in the case of evolutionary biology, patterns of interactions that sustain phenomena of interest).

Fitness: as defined in this paper, the fitness of a biological entity is its capacity to sustain or increase the ratio of similar entities within an evolving population. When applied to patterns of interactions, fitness is translated by the network’s robustness (its capacity to resist change) and resilience (its capacity to be re-produced).

purposely tackle the broader and deeper issue of the evolution of processes.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

É.B & FP wrote the MS and produced Figure 1. EB produced the other figures.

ADDITIONAL INFORMATION

No datasets were generated or analyzed during the current study.

No computer codes or algorithms were used to generate results.

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