Molecular Ecosystems

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Abstract

Biologists employ a suggestive metaphor to describe the complexities of molecular interactions within cells and embryos: cytological components are said to be part of "ecosystems" that integrate them in a complex network of relations with many other entities. The aim of this essay is to scrutinize the *molecular ecosystem*, a metaphor that, despite its longstanding history, has seldom been articulated in detail. I begin by analyzing some relevant analogies between the cellular environment and the biosphere. Next, I discuss the applicability of the molecular ecosystem concept in actual scientific practice.

1 Introduction

Biologists often adopt a suggestive metaphor to capture the complexities of molecular interactions within cells and embryos: cytological components are said to be part of *ecosystems* that integrate genes and proteins in a complex network of relations with many other gears of the cellular machinery and with features of the environment.

The practice of employing ecological concepts to describe cytological interactions has a long history that traces all the way back to the work of early embryologists. In his celebrated textbook, *Principles of Development* (1939), Paul Weiss introduced the expression "cellular ecosystem" to describe Gurwitsch (1910) and Spemann's (1921) *morphogenetic fields*, that is, groups of cells whose position and fate are specified with respect to the same set of boundaries. With

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the rise of the genetic approach, pioneered by the Morgan School, morphogenetic fields and other embryological concepts were eventually set aside (Gilbert et al. 1996). Yet, following the "rediscovery" of developmental biology in the last few decades of the 20^{th} century, Weiss' ecological metaphor has been revived in contemporary molecular research and systems biology. Over seventy years after Weiss' influential publications, it is now once again customary for researchers to describe living organisms and their components as embedded in *cellular* or *molecular ecosystems*:

> Living systems are autonomous self-reproducing "molecular ecosystems" defined as a collective of self-organized communities of dynamic, interdependent, interacting, and computing molecular species. (Lee et al. 1997, 491).

> Once a protein is made, it becomes part of a larger level of organization. For instance, it may become part of the structural framework of the cell, or it may become involved in one of the myriad enzymatic pathways for the synthesis or breakdown of cellular metabolites. In any case, the protein is now part of a complex "ecosystem" that integrates it into a relationship with numerous other proteins. Thus, several changes can still take place that determine whether or not the protein will be active. (Gilbert 2006a, 137).

> The activation, growth and death of animal cells are accompanied by changes in the chemical composition of the surrounding environment. Cells and their microscopic environment constitute therefore a cellular ecosystem whose time-evolution determines processes of interest for either biology (e.g. animal development) and [*sic*] medicine (e.g. tumor spreading, immune response). (Chignola et al. 2006, 1661)

> Evidence is accumulating that microorganisms do not live as isolated individuals, but as populations of cells that are continuously producing, sensing and responding to chemical signals, which allows them to communicate and cooperate. (...) [T]hese advances lay the foundations to investigate the dynamic nature of molecular ecosystem networks in time and space. (Raes and Bork 2008, 697-98)

The general intuition underlying the the metaphor is evident. Molecular mechanisms and processes, such as gene expression, have often been depicted as rigid, self-regulated, deterministic gears, where every little piece has its specific and independent role that is unaffected by the cellular and environmental context in which it is embedded. This picture, however, is misleading. To paraphrase a humorous analogy from biologist Susan Lindquist, while protein interactions are typically depicted as dancers performing in a spacious ballroom, a more accurate representation would be something akin to the famous "stateroom scene" from the Marx Brothers movie *A Night at the Opera*, where every action and reaction is heavily constrained by the crowded environment. The ecosystem concept is intended to capture and represent the complexity of cytological systems, the interdependence of its various components, and the fact

that cells and organisms are not insulated; changes at the molecular level both influence and are influenced by changes in the surrounding environment.[1]

While the ecosystem metaphor is routinely applied to the cellular environment, the extent and respects in which the molecular microcosm resembles the ecological macrocosm is a question that is seldom addressed explicitly. Analogies between ecological and molecular systems are commonly assumed, but rarely articulated or discussed in detail.[2] A possible explanation for this omission is that the application of ecological concepts to the molecular realm is straightforward: the analogy requires no further analysis because it is self-explanatory. Upon further scrutiny, however, this response becomes rather puzzling. *Prima facie*, developing organisms and their components are very different from portions of the biosphere. For one thing, organisms are more cohesive, compartmentalized, and in equilibrium than environments and, as a result, their individuation is much more straightforward.[3] Moreover, whereas tracking the diachronic development of organisms—their birth, growth, senescence, and death—is relatively unproblematic, making sense of the "survival" and "evolution" of ecological environments is no trivial matter. Finally, the clear and intuitive distinction between biotic and abiotic ecological components—between living organisms, such as plants, fungi, and bacteria, and inorganic entities like rock, soil, and air—is meaningless at the molecular level.[4] In short, cells and developing organisms look nothing like ecological units; if some kind of analogy exists, it needs to be cashed out explicitly, it cannot be simply assumed. On the other hand, it might be objected that the concept of the molecular ecosystem is "just a metaphor," and, as such, we should not be too demanding in evaluating the correspondence. The problem with this response is that our choice of scientific metaphors matters: it informs both theoretical and experimental work. We are thus left with the following question: is the molecular ecosystem metaphor well-grounded? And, if so, what precisely does it purport to capture?

[1] It is important to address right away a potential confusion. As clearly emerges in the passages quoted above, biologists apply the ecological metaphor to both *individual cells* (or unicellular organisms, such as bacteria) and *collections of cells* (e.g. tissues). Following this widespread convention, I refer to both kind of systems as "molecular ecosystems." Whether the target of the analysis are intra-cellular or inter-cellular interactions should be made obvious by the context of the discussion. (I am grateful to Kim Sterelny and an anonymous referee for bringing this ambiguity to my attention.)

[2] Consider, for example, the first passage quoted above, which is the opening statement of a chemical biology article (Lee et al. 1997). The term "ecosystem" figures three more times in the article (once more in the introduction, once in the conclusion, and once in the title.) Yet, what exactly turns "self-organized communities of dynamic, interdependent, interacting, and computing molecular species" into an *ecosystem* is never explicitly discussed. Some of the other quoted works spell out the concept in greater detail; yet they all fall short of explaining the analogy between ecological and molecular environments.

[3] Determining whether and to what extent ecological environments are cohesive, compartmentalized, and in equilibrium is a substantial issue that, however, I shall set aside. The important point, for present purposes, is that organisms approximate closed systems much more closely than environments.

[4] To be sure, whether proteins, ribosomes, membranes, nucleotides, etc. should be classified as "living" or "nonliving" is far from clear. However, these entities are on a par: either they are all treated as biotic, or as abiotic; there is no intuitive way of drawing the line.

The aim of this article is to explore structural parallels between ecological units and cellular modules metaphorically called "ecosystems." The following section argues that the cellular *milieu* is analogous to the biosphere in important and surprising respects. I begin by drawing a methodological continuum in the individuation of ecological and molecular systems. Next, I maintain that the cytological machinery instantiates characteristic ecological relations, such as predation, competition, mutualism, and density-dependent effects. Finally, I spell out some similarities between ecological and molecular environments. These considerations will suggest a more perspicuous characterization of molecular ecosystems. The second part of the essay discusses how the molecular ecosystem concept can be fruitfully applied to actual biological research.

2 Fleshing Out The Metaphor

Following Tansley's (1935) original suggestion, ecologists typically define ecosystems as communities of organisms in their physical environment. More precisely, ecosystems are constituted by the totality of biotic elements enclosed within a spatial region, together with the abiotic physical components of the territory in which these organisms interact, such as air, soil, water, and sunlight. Despite the intuitive appeal of this broad definition—which is routinely encountered in both popular and technical literature—from a philosophical perspective, the ecosystem is notoriously one of the most elusive biological concepts and one of the hardest to analyze.[5] Consequently, I shall not attempt to directly define the molecular analog of a concept whose precise characterization is still left wanting. Instead, I focus on criteria that scientists employ to individuate and describe ecological units and emphasize some remarkable—and, perhaps, surprising—parallels with the cytological environment. Specifically, I consider three features of ecosystems: the delimitation of their boundaries, the community structure, and the concept of the environment.

In order to draw an explicit parallel between the molecular microcosm and the ecological macrocosm, it is necessary to provide a preliminary specification of the cytological correlates of basic ecosystem components, such as organisms, populations, and species. In what follows, I treat cells, proteins, and other individual cytological components as the analogs of biological *organisms*. Accordingly, cellular and molecular kinds correspond to biological *species*, while local aggregates of type-identical cells or molecules correspond to *populations*, i.e. communities of conspecific organisms. To avoid potential confusion, uppercase variables range over molecular types and indexed lowercase letters pick out individual token entities. Thus, $\{p_1, p_2, p_3\}$ are all molecules of type P. With this in mind, we can now proceed to examine the characteristic features of molecular environments.

[5] This widely-recognized vagueness, however, does not thwart the theoretical fruitfulness of the ecosystem concept, or its empirical testability (Odenbaugh and de Laplante ming).

2.1 Ecosystem Boundaries

Ecologists do not search for ecosystems in the same way that paleontologists dig up fossils. The typical first step is rather to circumscribe a certain territory, generally delimited by physical discontinuities—like a forest, grassland, or a pond—and pose a series of diagnostic questions such as: which species inhabit it? What kind of intra-specific and inter-specific relations do populations engage in? How do organisms interact with the abiotic environment? Addressing these and similar issues helps determining the characteristic ecosystem structure displayed by the portion of the environment under scrutiny. In short, on the very first pass, ecosystems are circumscribed, not discovered.

As an illustration, let us consider a classic contribution to the history of ecosystem ecology: Lindeman's trophic-dynamic approach to the study of ecosystems. Raymond Lindeman and his wife Eleanor spent five years examining the small Cedar Bog lake in Minnesota. After painstakingly sampling the lake's biota, water, and bottom sediments, in addition to monitoring the distribution of littoral vegetation and vertebrate animals and comparing data across different seasons, the Lindemans provided a detailed analysis of the ecosystem structure of the small lake.[6] The historical and theoretical significance of Lindeman's (1942) trophic-dynamic perspective is well documented (Golley 1993) and need not be discussed here. The relevant point, for our purposes, is his methodological approach, which instantiates the procedure described above. The investigation begins with the circumscription of a relatively well-defined system (a small lake), followed by a thorough analysis of characteristic interactions between biotic and abiotic components, and concludes with a general assessment of ecosystem structure—a concept introduced by Tansley less than a decade earlier. For the sake of brevity, I refer to this mode of boundary-individuation based on physical discontinuities as *physiognomic individuation*.

The physiognomic mode of individuation is particularly effective when the system to be circumscribed is relatively small and uniform, as in the case of small lakes or woods, where most species tend to populate the entire region. In contrast, it is much less functional when applied to larger and heterogeneous systems, such as oceans, forests, or grasslands, where each community typically inhabits only a portion of the territory.[7] How can one individuate these sub-ecosystems embedded within larger units? Note that the physiognomic approach might not be applicable. If the altitude of a mountain or the depth of a lake increase gradually, there will be no cut-off point to mark transitions; as a result,

[6] Aspects of lacustrian trophic dynamics discussed by Lindeman (1942) include qualitative food-cycle relationships, productivity (the general rate of production of the concerned food groups), biological efficiency with respects to lower levels, and the ratio between the biomass of predators and prey.

[7] To wit, shallow-water fish only dwell the coastal regions of an ocean or vast lake, whereas certain algae only grow at depth; similarly, mountain ranges cover huge and diverse territories, but coniferous trees only survive below a certain altitude. While both fish and algae clearly belong to the great lake ecosystem and *Coniferae* are part of the Alpine ecosystem, for certain purposes, it will be useful to focus on a smaller portion of a larger environment, where only particular species are found.

it will not be clear where boundaries should be drawn. A possible solution lies in the adoption of an altogether different mode of system individuation: instead of circumscribing an entire region by relying on physical discontinuities, one can track the activity of organisms and then plot their distribution inside the territory. Succinctly put, the idea is to, first, select the relevant population(s) and, next, to "draw the boundary" by circumscribing the inhabited area, in case a single population is selected, or by conjoining these potentially overlapping regions, if multiple populations are selected. The result is a nested hierarchy of partially overlapping ecosystems, ranging from small regions containing a single population to the totality of the biosphere. This *component-specific* mode of individuation allows for the boundaries of each sub-system to be traced even in the absence of clear physical discontinuities. For instance, we can restrict our attention to the mountainous regions colonized by the Norway Spruce, the Silver Fir (or both) even if nothing else isolates these areas from each other and from sections of the mountain ranged inhabited by other species.

In sum, we can distinguish between two models of ecosystem individuation: a physiognomic approach—which begins with a preliminary circumscription of the system and then works "inwards" to explore the ecological structure of the territory—and a component-specific approach, which starts by selecting the population(s) of reference and then works "outwards," looking at their distribution and the totality of their interactions.[8] With all of this in mind, let us set ecology aside and focus on a different area of biology. Recent advances in genetics and molecular biology revealed that development is the product of a series of discrete and interacting modules, which allow the tinkering of finely-tuned and complex processes without wreaking havoc to the entire organism (Bolker 2000; Schlosser and Wagner 2004). I argue that our two modes of ecological individuation—physiognomic and component-specific—correspond to two distinct strategies for

[8]This distinction between models of individuation is closely connected to the interpretation of another important (and equally controversial) ecological concept: the ecological niche. Elton's (1927) classic definition—according to which a niche is a particular way of making a living in an ecological community—fits in well with the traditional view of the environment as posing selective pressures on organisms, triggering a process of adaptation. Functionally-defined Eltonian niches exist independently of the organisms that occupy them and the same niche can be occupied by different organisms in different communities, as long as these organisms fulfill the same causal role. For instance, the "large carnivore niche" is occupied by lions in the African Savannah and by tigers in the Indian subcontinent. According to a more recent definition, however, niches are volumes in an abstract multidimensional space, whose dimensions correspond to environmental quantities relative to a certain population (Hutchinson 1965). To illustrate, the dimensions of marine fish niches are likely to include variables such as water temperature, water salinity, rates of predation, availability of resources, foraging range and so forth. Building on Hutchinson's insights, Lewontin (1978) suggested that the very nature and identity of niches depends on the organisms that occupy them. The niche's characteristic dimensions vary quite drastically once we vary the species of reference; consequently, attempting to define a niche independently of its occupants is problematic. Niches, Lewontin says, are made, not found. The upshot is that there are two opposing concepts of ecological niche, and this distinction fits in naturally with the two forms of boundary identification isolated here. Eltonian niches are individuated physiognomically, on the basis of physical parameters independent of their occupants. In contrast, the individuation of Hutchinsonian niches crucially depends on the populations of reference and their relationship to the environment.

individuating developmental modules.

Developmental modules are often constituted by tissues, limbs, and organs (e.g. muscles, legs, hearts), or the underlying morphogenetic fields, that is, the collection of all the cells committed to the formation of the trait in question (e.g. the cardiac field or the limb field). In such cases, where the "unit of ontogeny" straightforwardly corresponds to the anatomical part, the individuation of the module runs parallel to the physiognomic mode presented above: researchers pick a particular phenotypic trait and proceed with the investigation of the molecular process underlying its growth, from early embryonic stages to the adult phenotype. While contemporary biology is still very far from a comprehensive, let alone complete, explanation of ontogeny, remarkable progress has been achieved over the last few decades: many genes, molecules, and processes responsible for organogenesis have now been identified with precision. Developmental units, however, do not always correspond to entire anatomical traits. Here, two different cases ought to be kept distinct. The former class of examples is constituted by molecular modules that are much smaller than traits and develop independently of them, such as enhancer regions of genes (Gilbert 2006b).[9] A different class of units that do not correspond to entire functional parts is constituted by developmental units that cross-cut anatomical ones, a good illustration of which is provided by the preliminary segmentation of the fruit fly *Drosophila* into *parasegments*.[10]

These two classes of examples raise an important problem: how do we individuate ontogenetic modules when they do not straightforwardly correspond

[9]Enhancer elements are DNA sites that bind with specific transcription factors (regulatory proteins) to selectively control gene expression, that is, whether and in what quantity the coding sequence is transcribed into protein. Altering the structure of the enhancer may block the transcription of the gene or, alternatively, determine its expression at a given time or in a different areas, with obvious consequences for development. Some gene enhancer elements contribute to the formation of many different parts of the organism. So-called "toolkit genes," for instance, do not underlie specific traits, but contribute to the formation of various different parts of the organism. Furthermore, such genes or gene elements can be virtually identical across phylogenetically distant species, as in the case of *homeotic genes*. A splendid example of the evolutionary significance of enhancer modularity is provided by Kingsley's analysis of the evolution of three-spined stickleback fish. (For a clear presentation and discussion of these results, see Gilbert and Epel 2009, 337-41). The fascinating details of enhancer modularity need not concern us here. The relevant implication, for present purposes, is that these molecular units are smaller than and functionally independent of the tissues that they generate.

[10]Succinctly put, the fruit fly larva is divided into repetitive developmental units called *segments*, which govern the identity of the cellular nuclei that they contain. Each segment (or segment group) corresponds, at least approximately, to specific anatomical traits. For example, segments located in the posterior areas of the embryo develop the abdomen, segments located in the central region generate the thorax, while anterior segments develop into the head. Segmentation, however, does not occur right away; segments derive from an earlier division of the larva into functional units called *parasegments*, which are defined by the expression of *pair-rule* genes after gastrulation. Parasegments fulfill a central and complex role in the development of the fruit fly, which we can set aside (for an insightful but accessible discussion, see Gehring 1998). The important point here is that segments and parasegments do not correspond; each segment is constituted by the posterior half of one parasegment and the anterior half of the following one. As a result, parasegments are fundamental units of insect design that do not directly map onto distinct anatomical components.

to anatomical ones? As noted, when the developmental module coincides with a discrete trait, the boundaries of the module simply are the boundaries of the trait itself: the cardiac field, for instance, is constituted by all and only the cells that will eventually form the heart. But what about tiny gene enhancer elements, or *Drosophila* parasegments, which cross-cut developmental units? The key to individuating these modules is to select their triggering mechanism (typically, but by no means always, a cluster of genes or gene products) and to identify their "habitat" or "niche," i.e. the various components with which the mechanism interacts to differentiate particular areas of the organism. These habitats generally include a network of genes, various kinds of proteins—such as transcription factors, paracrine factors, and adhesion molecules—as well as signal transduction cascades, and many other cytological gears. Hence, when the developmental unit cannot be individuated by focusing on anatomical discontinuities, the system's boundaries can still be delimited by selecting characteristic elements of a mechanism and tracking their distribution and activity inside a larger system, such as an organism or an embryo. This investigative strategy corresponds to the component-specific mode of ecosystem individuation discussed above. There we began by selecting species or populations of reference and then worked outwards to determine their distribution and activities in the territory; here the preliminary step is to mark a certain macromolecular component and determine its diffusion and activity in the developing organism.[11]

In sum, I distinguished between two modes of individuation. The first, *physiognomic* mode, circumscribes a system in terms of physical discontinuities. The second, *component-specific*, mode focuses on the distribution and activity of selected populations embedded within a larger system, allowing a more fine-grained individuation of units, even in the absence of real or alleged "natural boundaries." These two approaches can be employed both in ecology and in molecular-developmental biology. To be sure, the physiognomic mode is more widely employed in ecology, where units are often characterized by physical discontinuities. In contrast, the component-specific approach is typically encountered in the molecular sciences, where experimental manipulation is more readily available. Yet, anatomical discontinuities are important guidelines in developmental investigations, and the finer-grained individuation of systems in the absence of physical discontinuities is fruitful in ecological research as well. I thus conclude that these common modes of preliminary boundary delimitation constitute a first important analogy between the theoretical structure and

[11] When the molecular system is simple enough—that is, when a relatively small number of genes with a clear functional role are involved—these processes can be studied in vivo, by tracking the expression of a gene or the activity of a protein in different cells or parts of the organism. This is typically done with the use of fluorescent markers in the living organism (hence the expression "in vivo"). However, in vivo techniques become impractical, if not flatly impossible, in more complicated systems where genes and proteins are involved in several different interactions across a variety of cell types. When this is the case, these molecular networks must be studied in vitro, by cultivating and isolating cellular colonies in test tubes or on petri dishes. This allows researchers to investigate the behavior of molecules and the development of cells independently of the myriad interactions and processes occurring in the developing organism.

experimental practice of both disciplines.

2.2 The Community Structure

A further analogy between the the macrocosm and the microcosm emerges as soon as we switch from ecosystem ecology to a different biological subfield: community ecology.[12] In particular, let us focus on the characteristic structure of ecological communities, which typically exhibit a wide range of interactions, at various levels and of various kinds. Some of these interactions are defined in terms of the causal role of the interactors, i.e. independently of the precise identity of the relata. Predator-prey relations, for example, are instantiated by a variety of different populations—rabbits and foxes, birds and moths, etc.—all of which fulfill a particular functional role: intuitively, predators need to feed on prey. In contrast, other forms of interaction structurally depend on the particular organisms that instantiate them and on their living conditions. These are the interactions that determine the specificity of particular environments. To wit, the living conditions of organisms vary substantially across the biosphere: mountain lakes are quite different from tropical rainforest. Accordingly, particular modes of interaction, such as whether inhabitants graze in a grassland, fly in the air, or swim under rocks depend, at least in part, on the kind of available resources. This cornucopia of ecological relations can hardly be replicated within a single organism, let alone a single cell. Yet, simple molecular systems instantiate many of the interactions that characterize the community structure of ecological units. In order to substantiate this claim, I focus on functional interactions that abstract away from the precise identity of the interactors and the specificity of their living conditions. The following examples illustrate how ecological relations, such as competition, predation, mutualism, and metabolic cooperation have cytological analogs in regulatory mechanisms and protein modification processes.

To begin, consider ecological *competition*, which can be characterized, in general, as an interaction between two organisms or species that result in a fitness gain for one and a fitness loss for the other. Now, surely, whether and how it is possible to talk about the "fitness" of genes and other molecular types is a controversial matter that I shall not address here. Setting the issue of fitness aside, however, cells, proteins, and other macromolecules engage in forms of non-intentional competition, where different cellular or molecular species "compete for the same niche." Chignola et al. (2006) observe that cells bordering a growing tumor mass exploit their acquired capability to resist to more acidic environment and to uptake more nutrients than non-cancerogenous cells in order to invade the surrounding tissue. Analogous forms of competition are also

[12] In this article, I do not enter the dispute over the fundamentality of ecosystems or communities as ecological units. Following the practice of many molecular biologists, who frequently appeal to properties of communities to describe the structure of cytological systems, I treat the community-structure as a central feature of molecular ecosystems. Admittedly, it is curious that many of the most characteristic features of molecular "ecosystems" are borrowed from community ecology rather than ecosystems ecology.

known to commonly occur at a smaller scale, between cytological components. In the same paper, Chignola and colleagues note how the survival and expansion of B lymphocytes depends upon specific interactions between antigens and immunoglobulin receptors. Hence, specific B cell clones compete and are selected by the foreign antigen. A similar effect is due to the fact that molecular systems typically contain a greater variety and quantity of reactants than is strictly necessary for a certain reaction to occur, ensuring that the effect remains stable under a broad range of circumstances. Thus, when there is much transcription factor in a system but only a limited number of binding sites, the result is a form of molecular competition (Nathan 2012a).

Next, consider *predation*, a biological interaction in which a hunting organism (a predator) attacks and feeds on another organism (its prey), typically resulting in the death of the prey and the predator's absorbing the victim's tissues. Microbiologists frequently talk of bacterial populations resembling canonical predator-prey interactions. For instance, Balagaddé et al. (2008) describe the construction of a synthetic ecosystem consisting of two populations of *E. Coli* where "The predator kills the prey by inducing the expression of a killer protein in the prey, while the prey rescue the predators by eliciting expression of an antidote protein in the predator." (p. 1) Talking about cells "hunting" and "feeding" on each other might seem counterintuitive, at first blush.[13] Yet, this model satisfies the broader definition of predation (for a two-species ecosystem), where the prey suffers from the growth of the predator, and the predator benefits from the growth of the prey. Consequently, the periodic fluctuations in community size and the variations in concentration rates display similar dynamics governing density-dependent forms of population control.

Bacterial populations constitute a particular and relatively understudied kind of ecological communities. However, despite their peculiarity and the substantial differences with canonical models, it should be promptly noted that they do not form *molecular* ecosystems, but rather familiar (ecological) ecosystems—communities of organisms in their physical environments.[14] In order to find examples of predation in a molecular ecosystem proper, one needs to looks at models whose constituents are not individual organisms, but are parts of larger, self-standing organisms. An interesting example of intra-cellular predation occurring in a molecular ecosystem is constituted by macrophages, phagocytes that contribute to the vertebrate immune system by engulfing and digesting cellular debris and pathogens (as well as stimulating the action of lymphocytes and other immunological responses). Analogous interactions can also be found at the sub-cellular level, for example by looking at catalytic reactions that modify the structure of proteins, effectively inhibiting their capacity to perform their

[13] Indeed, the authors hasten to add that their bacterial system differs from canonical ecological models in two respects. First, instead of acting as a food source, the prey in the bacterial ecosystem provides an "antidote" against the programmed death of the predator. Second, predator-prey competition for nutrients in a co-culture is generally absent from ecological systems.

[14] To be sure, Balagaddé and colleagues talk about "synthetic ecosystems," not "molecular ecosystems."

normal function. To illustrate, consider the (reversible) process of phosphorylation, which consists in the addition of a phosphate group to proteins and other organic molecules, with several important effects, including the (de)activation of enzymes and receptors. Just as increasing the number of predators in a territory (e.g. foxes inhabiting a field) will increase the selective pressure on prey (say, rabbits), the number of bacteria in an organism or active proteins in a cell is proportional to the number of macrophages or enzymes that modify the protein structure. To emphasize, macrophages and enzymes do not "feed" on microbes and proteins in the same way foxes feed on rabbits—phagocytes and molecules do not gain vital nutriment or energy from these interactions. However, the phagocytation of microbes and the deactivation of enzymes mirrors the causal role of ecological predation, namely, to control the size of specific populations.

A third example of an ecological relation that is frequently displayed at the molecular level is *mutualism*, which occurs when organisms belonging to different species interact in a way that each derives a fitness benefit (i.e. increased or improved reproductive output). Interactions between adjacent tissues during organogenesis, such as *reciprocal embryonic induction*,[15] constitute a good molecular example of obligate mutualism—a form of mutualism where the interaction does not merely raise the fitness of each interactor, but where one species cannot survive without the other. Like competition and predation, mutualistic relations can also be observed on a smaller scale, for instance, in the process of *cooperative binding*—whereby a molecule attached to a DNA site facilitates the binding of molecules of the same type—or in the case of *molecular chaperones*, proteins that assist the folding an assembly of macromolecular structures. The analogy between mutualism at the molecular and ecological level becomes even more evident when we shift from proteins to genetic structures, since the former do not autonomously reproduce (proteins are synthesized from DNA templates). Genes, in contrast, are more similar to organisms in virtue of their ability to directly affect their own replication, by synthesizing the right kind of molecule. To wit, consider cases of feedback and feedforward loops in gene regulation, where the binding of a transcription factor at an operator ensures that a certain gene is expressed, while the expressed gene synthesizes more transcription factor of the same kind, effectively enhancing its own replication. This form of cytological mutualism is closer to its ecological analog because, through its own expression, the gene itself improves its chances of being transcribed, while the transcription factor increases its replication rate by interacting with DNA. To be sure, genetic mutualism is not identical to ecological mutualism since, as noted, the concept of fitness does not straightforwardly apply at the molecular level, and there are several other significant differences between the two domains. The point is simply that genetic mutualism is closer to its ecological

[15] Reciprocal embryonic induction occurs when the formation of two organs requires a complex interaction between different tissues that, without such interaction, do not develop correctly. To illustrate, consider an example, borrowed from Gilbert and Epel (2009). When the presumptive retina of the mammalian eye meets the presumptive lens, the lens "instructs" a bulge of cells from the forebrain to develop the retina. In turn, the presumptive retinal cells instruct the placodal epithelium of the developing head ectoderm to generate the lens.

counterpart than similar relations between proteins or tissues.

Finally, various forms of *metabolic cooperation* can be found both at the bacterial level—for example, in the process of *quorum sensing*, a stimulus-response system employed by many bacterial species to coordinate gene expression according to local population density, which feeds back on the structure of the population—and at the molecular level, in the form of complementary pathways (e.g. groups of blood proteins, usually activated by antigen-antibody complexes, which mediate specific antibody responses) and the active/passive transport of metabolites in and out of the cell. This fourth analogy between ecological and cytological communities has a plausible explanation. Like ecological systems, molecular environments are highly sensitive to density-dependent interactions, such as variations in population size. This affects not only the dynamics of the system—as noted in the above discussion of as competition, predation, and mutualism—but also the structure of the system itself. In sum, the heterogeneity of the local habitat determines the range and nature of possible interactions in molecular environments, like it does in the biosphere. Just as a diverse environmental structure allows a great variety of interspecific interactions (compare rainforest with deserts), a complex developmental system enables a broader range of molecular interactions and a more nuanced array of responses to stress-induced reactions and other environmental conditions.

2.3 The Environment

The third feature of ecosystems that I discuss is the concept of the environment. Ecological ecosystems encompass both communities of living organisms and the physical milieu in which these organisms thrive, reproduce, compete and, more generally, interact. As noted at the outset, the distinction between biota and abiota is hard to spell out at the molecular level since there seems to be no principled way of drawing the line between living and non-living entities. Then how are we to conceive of the molecular environment? I contend that it is possible to individuate various types of molecular environment even without a clear separation between organic and inorganic components.

In the context of a lucid analysis of adaptation, Robert Brandon distinguished between three different concepts of environment: external, ecological, and selective (Brandon 1990; Brandon and Antonovics 1996). Simply put, the *external environment* encompasses the sum of all physical factors (biotic and abiotic) surrounding the organism. While clear and intuitive, this notion is extremely broad. Obviously, not every element of the external environment has an impact on the life of every organism in the system. For example, the average PH of the soil is unlikely to directly affect the growth of a population of foxes. Hence, for the purposes of investigating the development and evolution of particular organisms, a more specific notion of environment is required. Brandon defines the subset of the external environment that directly affects the global reproductive output of an organism, population, or species as their *ecological environment*. In a nutshell, the ecological environment of a species is constituted by all and only the features that affect the survival and reproduction of

that species. While this concept of ecological environment is much more specific than the all-encompassing external counterpart, relative to some research projects, even this more restricted notion of environment is excessively broad. The ecological environment measures the scale of environmental heterogeneity, that is, the performance of an individual across a variety of different (external) environments. But suppose that one is interested in isolating only the differential reproductive output of a population in a particular habitat; what is needed are the factors that make an actual difference in fitness—how the environment affects the organisms' contribution to the next generation. In this case, only a fraction of the totality of the physical elements constituting the ecological environment of that population will be salient; this subset will constitute the population's *selective environment*.

In short, Brandon identifies three concepts of the environment, ranging from the all-encompassing external environment to the restricted selective one. I maintain that, by selecting cells, proteins, and other individuals macromolecular gears as the cytological correlate of organisms and species, a similar distinction can also be applied to cellular environments. For instance, the *external molecular environment (ExME)* of a protein corresponds to the totality of the system's components, including all other molecules, proteins, enzymes, DNAs, RNAs as well as other kinds of entities, such as cellular membranes, microtubules, mitochondria, and organelles. Just like its ecological counterpart, the ExME of a protein is extremely comprehensive, including elements that do not (directly) interact with the molecule at hand. For example, the synthesis of P-protein might be unaffected by the presence or absence of enzymes that catalyze Q-reactions. By restricting the ExME to all and only those components of the system that affect the function or replication of P-molecules, we obtain P's *ecological molecular environment (EcME)*. The EcME of P is constituted by the collection $p_1 \dots p_n$ of all P-molecules, together with all molecules $Q, R, S \dots$ that react with P, enzymes that catalyze P-reactions, DNA operators to which P can bind, the transcription factors that "compete" with P in binding to these sites, etc. In short, the EcME of P-molecules is the subset of P's ExME that (actually or potentially) interact with P. Finally, by restricting P's EcME to all and only those cytological gears that affect P's synthesis or replication, we obtain P's *selective molecular environment (SME)*.[16]

In conclusion, Brandon's tripartition of the ecological environment concept into external, ecological, and selective can be applied to cellular systems, despite the lack of a straightforward distinction between biotic and abiotic components. As we shall see in the following section, these distinctions play an important role in the explanation and understanding of biological systems.

[16]It should be obvious that the EcME and SME of a molecule typically overlap, but they seldom coincide. To wit, repressors and other inhibiting factors that bind DNA, inhibiting the transcription of P are part of both P's EcME and SME. In contrast, stretches of nucleotides to which P binds to regulate the expression of genes that do not encode P itself belong to the EcME but not to the SME.

2.4 Mapping Ecology Onto Cytology: The Molecular Ecosystem

Let us take stock. Genes, molecules, and other cytological gears do not act in isolation, but form a complex network of interactions which display remarkable similarities with the characteristic features of ecological ecosystems. First, there is an analogy between two modes of individuation: physiognomic and component-specific. Second, cytological structures display some relations typically found in ecological communities, such as competition, predation, mutualism, and metabolic cooperation. Third, Brandon's trichotomy of the environment-concept maps onto a clear subdivision of molecular environments. With all of this in mind, we are now in a position to characterize molecular ecosystems more precisely. Mirroring the standard ecological definition—a community of organisms together with its physical environment—one can define a *molecular ecosystem* as *a collection of interacting molecular gears, exhibiting a characteristic community structure, together with its external molecular environment.* Such systems can be identified either *physiognomically* (on the basis of physical or anatomical discontinuities) or in a *component-specific* fashion, by focusing on the distribution and activity of a selected subset of organismic or embryonic elements.

Before moving on, an important clarification is in order. The observation that molecular networks exhibit an ecosystem-like structure is by no means novel, and the successful application of population ecology models to animal cells has been widely discussed (Bajzer et al. 1997). Furthermore, the concept developed here displays noteworthy similarities with previous analyses.[17] Yet, the present definition constitutes an attempt to identify more perspicuously the characteristic features of cytological systems, the preliminary modes of identification, the ways in which molecular communities "function together," and the various environmental components. In addition, I attempted to spell out the analogy between ecological and molecular structures more explicitly and systematically. To be sure, my general characterization is not intended to provide necessary and sufficient conditions to determine exactly which cytological systems constitute ecosystems. Spelling out a precise operational definition of the ecosystem—at either level, ecological or molecular—is a daunting task that cannot be undertaken here. The upshot of the preceding discussion is simply that the widespread practice of employing ecological concepts to describe the molecular milieu is more than just a suggestive metaphor. Conceptualizing the complexities of molecular interactions as embedded within ecosystems captures some important features of the cytological environment.

[17] Raes and Bork (2008, 693), for example, define a microbial ecosystem as "a system that consists of all the microorganisms that live in a certain area or niche and that function together in the context of the other biotic (plants and animals) and abiotic (temperature, chemical composition and structure of the surroundings) factors of that niche."

3 Applications

This section provides a critical discussion of whether—and to what extent—the molecular ecosystem concept articulated in the first part of the article can be fruitfully employed in current and future biological research. I begin by examining the potential application of ecological concepts in systems biology. Next, I consider their impact on our understanding of the structure of cytological communities and molecular environments.

3.1 Eco-Systems vs. Ecosystems Molecular Biology

Recent years have witnessed a significant methodological shift in molecular biology, from reductionist approaches—which analyze the structure and function of individual or small groups of molecules in relative isolation—to holistic approaches that purport to explain the behavior of entire systems without breaking them down to their component parts. Initially, these "wholes" consisted of a handful of genes embedded in a network, which capture how these genes respond to external stimuli, influences, and signals. Steady advances in robotics and computation, however, enabled the creation of complex models reproducing the wiring of complete cells and microbial organisms (Kitano 2002; Joyce and Palsson 2006). In the meanwhile, the next step in this rapidly progressing field has already been targeted: the long-term goal is to extend models that capture the behavior of individual cells and simple organisms to models capable of analyzing the complexity of entire ecosystems (Raes and Bork 2008). An assessment of this ambitious project transcends our present purposes. The question that I want to address is: can the molecular ecosystem concept shed light on our understanding of biological systems?

Prima facie, the relevance of the ecosystem concept to systems biology might seem obvious. As an illustration, imagine that, over the next few decades, the systemic approach will fulfill its most optimistic promises and advance to the point of unravelling the molecular complexities of entire ecological environments. On the envisioned scenario, scientists will be able to provide complete, or reasonably complete, molecular descriptions of the physical interactions underlying large portions of the biome, such as lakes or mountain ranges. Following Raes and Bork (2008), the result of this extremely ambitious project—which, to emphasize, is still very far from being undertaken, let alone accomplished—can be called "eco-systems biology," for the system to be mapped corresponds to an ecosystem. Thus, one might argue, the molecular ecosystem is the ideal explanandum of molecular biology, the object of future systemic approaches.

Upon further scrutiny, however, this suggestion appears to miss the target. To see why, consider the role of the ecosystem concept in this science-fictional enterprise. The appeal to ecosystems serves to draw the boundaries of the system under consideration, not to characterize its molecular structure; the explanandum of eco-systems biology (i.e. the result of future molecular investigations) is the complete mapping of a relatively large portion of the biome. But, note, "ecosystem" here refers to the traditional ecological concept: the

totality of biotic elements enclosed within a spatial region, together with the abiotic components of the system. In contrast, the molecular ecosystem concept described above is a different kind of entity, which purports to serve an independent purpose, namely, to describe and represent the interactions in cellular systems. To wit, when Lee and colleagues suggest that "living systems are autonomous self-reproducing 'molecular ecosystems,' " or when Gilbert maintains that the transcribed protein becomes part of a "complex ecosystem," the point is not that organisms coincide with ecological units or portions of the biosphere. The claim is rather that the cellular environment and its characteristic interactions are analogous, in important respects, to the ecological environment and, consequently, can be described as such.

The ecosystem concept thus fulfills two different conceptual roles in biological investigations. On the one hand, it may figure as the *explanandum* of current (or, more likely, future) explanations, which aim the individuation and modeling of entire portions of the environment. Alternatively, the ecosystem can function as the *explanans* of the systemic approach, whereby the ecological metaphor serves the purposes of characterizing the nature of cytological interactions. To avoid any confusion, I suggest that we refer to the molecular study of ecological units as *molecular eco-systems biology*, while restricting the expression *molecular ecosystems biology* (unhyphenated) to the application of ecological concepts to the characterization of molecular systems. To be clear, the upshot of this discussion is not a quick dismissal of the general relevance of ecosystems ecology for systems biology. The moral that we ought to draw is rather that, for the *molecular ecosystem* concept to play a substantive role in scientific practice, its contribution has to fall within the domain of ecosystems biology—as opposed to eco-systems biology. We now turn to precisely this endeavor.

3.2 Cytological Communities

If the metaphor developed here cannot be employed to capture the explananda of systems biology, let us focus on its role as explanans. A natural suggestion is to apply the molecular ecosystem to the study of cytological communities from an ecosystem perspective.[18] But what does it mean, precisely, to study a molecular system from an ecosystem perspective? Intuitively, one might define a full-fledged ecosystem approach as a detailed specification of the wiring and connections of a large system's components. Yet, thus conceived, it becomes extremely hard to distinguish the ecosystem perspective from the traditional systemic one. Now, surely, this is not necessarily a problem since, as noted, systems biology is a thriving subfield of contemporary life sciences. However, the conflation of systems and ecosystems obscures the advantages of importing

[18]The importance of studying molecular interactions from an ecological standpoint is explicitly acknowledged in the scientific literature. To wit, Raes and Bork (2008, 693) suggest some molecular issues that could be approached at the ecosystem level, including "estimating the relative importance of ecosystem members in ecosystem functioning and productivity, the effect of nutrient availability on species composition or the resilience of the ecosystem to disturbances."

ecological concepts into molecular studies.

One way to distinguish the ecosystem approach from traditional systems biology is to focus on its increased complexity. Simply put, the idea is that, while determining all the regulatory interactions in relatively small cellular circuits can be already quite challenging, focusing on larger portions of the biome introduces further levels of complexity, such as ecological interactions between organisms (competition, predation, etc.) and structural interactions, like mat formation (Raes and Bork 2008). The thesis that, in general, the broader and more sophisticated the system, the more levels of complexity arise is important, albeit hardly controversial. Consequently, reducing the motivation underlying the molecular ecosystem concept to this truism threatens to trivialize the whole analysis. To successfully establish that the very idea of a molecular ecosystem plays a substantial role in biological practice, we must understand the payoff of describing cytological communities in *ecological* terms, not just as a complex system. In other words, it must be shown that (and why) a detailed examination of the structure of large molecular systems is enhanced by a careful mapping of cytological relations onto ecological ones. To this effect, let us briefly consider some concrete examples.

In a recent article, Fujii and Rondelez (2013) describe the construction of a bottom-up assembly of chemical systems that reproduce *in vitro* the specific dynamics of ecological communities. The authors experimentally observed molecular behaviors—such as predator-prey oscillations, competition-induced chaos, and symbolic synchronization—that, it is argued, will foster a better appreciation of the molecular origins of biological complexities and "may also serve to orchestrate complex collective operations of molecular agents in technological applications." (p. 27) Setting the fascinating details of this remarkable work of engineering aside, what role do ecological concepts play in modeling the macromolecular world? In order to answer this question, it is important to note that, while molecular gears and microorganisms display a typical community structure, such description is, strictly speaking, unnecessary. In principle, it would be quite possible to map the relevant cytological interactions without appealing to ecological concepts at all. This is evident in Fujii and Rondelez's discussion, who note that, in the system under consideration, the three characteristic relations of predator-prey systems—prey growth, predation, and decay—can be fully described at the molecular level by employing the standard language of biochemistry. To wit, consider first *prey growth*, which expresses the autocatalyzing reaction of a molecule: prey N triggers its own generation in a simple loop. In DNA biochemistry, such reactions correspond to an isothermal amplification scheme based on repetitive enzymatic extensions, nicking on a dual-repeat DNA template. Next, let us move on to *predation* reactions. At the chemical level, the growth of predator through the consumption of prey can be expressed as a replicator with exponential dynamics, such as the DNA polymerase-catalyzed elongation of a primer on a template.[19] Finally, *decay*

[19]More precisely, this DNA polymerase-catalyzed elongation may be conceptualized as a form of "predation" only provided that it satisfies three conditions: (i) the predator P must

simply requires that all molecular species have a limited lifetime, which (from a thermodynamic perspective) ensures the existence of bounded attractors and prevents a runaway of the system.

While Fujii and Rondelez focus on intra-cellular interactions, similar considerations can be straightforwardly applied at the inter-cellular level. To illustrate, consider, once again, Chignola and colleagues' (2006) discussion of cellular proliferation and tumor growth. The major limitation of complex models, they note, is the enormous number of microscopic details that one should factor in order to develop a realistic model of an entire cellular ecosystem. To circumvent the problem, the authors develop a stochastic model that captures the main features of the interactions between cells and their environment. The details of the proposal need not concern us here. The important point, for present purposes, is that cellular states are subsumed under into three simple categories—*quiescent*, *active*, or *dead*—and the environment is subdivided into discrete niches, classified as either *favorable* or *unfavorable*. The resulting stochastic model is clearly an oversimplification, albeit one that provides a succinct—yet accurate and predictive—description of the growth and proliferation of tumor spheroids, by employing ecological concepts such as competition, predation, and selection.

If the cytological machinery can, at least in principle, be fully described at the biochemical level, what is the payoff of characterizing the entire system as a "molecular ecosystem"? A possible answer emerges through the recognition of two advantages of shifting from macromolecular language to a higher level of description. First, while a fully biochemical account would render the model long and cumbersome, analyzing these molecular reactions in ecological terms provides a perspicuous depiction of the system's fundamental structure. Referring to a sophisticated replicator with exponential dynamics as "the growth of predators through the consumption of prey" provides a compact description that abstracts away from several unnecessary details. More importantly, a relatively general description of the intricate networks of chemical reactions, molecular processes, and spatiotemporal organization allows researchers to identify and study similar conditions across various systems, which might encompass different macromolecular gears in different environments.[20]

Setting descriptions and explanations aside, a second advantage of ecological notions concerns the *engineering* of complex systems. Relations from community ecology presented in the first part of this article, which have been extensively analyzed through decades of mathematical modeling and experimentation, provide the conceptual guidelines for picking out and recreating analogous structural interactions in other, more sophisticated molecular systems. This role of ecological notions as templates for replicating basic structures with different

have a center of symmetry, that is, a palindromic sequence, in its sequence; (ii) the prey N must be long enough to prime the polymerase; and (iii) P must be short enough to significantly dissociate into monomeric species at the experimental temperature.

[20]To be sure, the biochemical details of these reactions are important and cannot be avoided in a specification of a complete (or relatively complete) causal-mechanistic explanation of the interactions. Yet, such explanations do not exhaust the range of scientific explanations: biochemical details become irrelevant in the context of comparative work that identifies analogous structures across different systems (Nathan 2012b).

components is explicitly noted by Fujii and Rondelez (2013, 33), who claim that "Contrary to small-molecule oscillators, however, our approach is general in the sense that many systems with various reaction network topologies can be built using the same design principles".[21]

The moral that we ought to draw is that ecology inform molecular biology in two important ways. First, ecological relations provide a useful framework for describing complex molecular interactions in simple, perspicuous, and relatively abstract ways, an endeavor which allows researchers to *refine* and *compare* existing models. Second, ecological structures provide a "masterplan" for *replicating* specific cytological conditions in the process of engineering new artificial systems.

3.3 The Molecular Environment

Finally, let us apply the molecular ecosystem concept to the study of molecular environments. Over the last few decades, our understanding of the relation between organisms and their environments has undergone a major theoretical shift. While biologists traditionally conceived environmental changes as independent of the development of organisms and the evolution of populations, in a series of seminal essays, Richard Lewontin (1978, 1983a,b) famously argued that biological and environmental changes are really a function of each other. Lewontin's insights had a major impact on ecology, inspiring a number of new approaches to the field, such as *niche construction* and *ecosystem engineering*.[22]

[21] A similar emphasis on engineering is also present in Balagaddé and colleagues' (2008) synthetic ecosystem consisting of two *E. coli* populations, which communicate bi-directionally through quorum sensing and regulate each other's gene expression and survival *via* engineered gene circuits. The authors begin by noting a key challenge for synthetic biology, namely, "to identify general, scalable strategies that enable *construction* of increasingly complex gene circuits with reliable performance, as well as to develop novel technological platforms for quantitative circuit characterization (...)" (1, emphasis added). As noted above, this is not a molecular ecosystem proper, but rather a traditional (ecological) ecosystem, constituted by microbial communities in a synthetic environment. Yet, this work provides a nice illustration of the role of the ecological apparatus in comparing the structure of different mechanisms. As in the previous example, the value of adopting an ecosystem perspective lies not (only) in the accuracy with which it describes or explains molecular mechanisms—after all, biochemical descriptions are also, in principle, available. Rather, ecological concepts provide conceptual guidance for the *engineering* of complex systems. "The generic nature of our system design makes it portable to other ecological interactions, including mutualism, competition, commensalism, and amensalism (...) The virtually unlimited configurations that are possible with these basic elements will allow us to further examine the interplay between the environment, gene regulation and population dynamics. With additional control over population mixing or segregation, it will be possible to program bacterial populations to mimic development and differentiation in multicellular organisms." (Balagaddé et al. 2008, 6).

[22] In brief, niche construction is the idea that "organisms, through their metabolism, their activities, and their choices, define, partly create, and partly destroy their own niches." (Odling-Smee et al. 1996, 641). In turn, "Ecosystem engineers are organisms that directly or indirectly modulate the availability of resources (other than themselves) to other species, by causing physical state changes in biotic or abiotic materials. In doing so, they modify, maintain and/or create habitats." (Jones et al. 1994, 374). The relationship between these two—partly overlapping—theories constitutes an important question that, however, I shall set aside. For the sake of simplicity, following Pearce (2011), I treat ecosystem engineering as any

While these theories were initially developed with respect to ecology and evolution, recent research revealed that, just as organisms construct their own niches (beaver dams modify the structure of lakes and rivers, earthworms alter the chemical composition of the soil, symbiotic microbes induce gene expression in the host's gut epithelia, mutually benefiting both the host and themselves, etc.) cells and molecules also engineer their own niches. This molecular niche construction process is much less documented than its ecological analog, yet we now have clear and convincing examples of niche construction at the inter- and intra-cellular level, such as the cytological niches described above, and even in the development of mammals:

> Mammalian development is a case par excellence of an organism creating a niche and having the niche modify and permit the development of the organism. Mammalian embryos construct their niche by instructing the uterus to alter its cell cycles and its adhesion proteins and by inducing angiogenesis and a barrier to the immune system. The placenta induces the decidua reaction in the uterus, causing the uterus to become a habitat for the developing embryo. In so doing, the placenta instructs the uterus to bring food vessels into the fetus. Hormones from the embryo itself help construct an embryonic from the developmentally plastic anatomy of its mother reproductive tract. The uterus reciprocally helps induce the formation of the placentive tract. (Gilbert and Epel 2009, 395).

This simple example sketches how the kinds of molecular environment isolated above map onto actual developmental distinctions.[23] The cells constituting the mammalian placenta are embedded in a broad *external molecular environment*, which includes both the surrounding uterus and other environmental signals. Yet, only a subset of the uterine features directly affect the development of the organism. The cytological mechanisms employed by the embryo to construct its habitat—such as mechanisms responsible for the alteration of cell cycles and adhesion proteins, the induction of angiogenesis, and the triggering of decidua reactions—constitute the embryo's *ecological molecular environment*. At an even finer-grained level, focusing on mechanisms governing the growth of the embryo, the replication of its cells, and the encoding of genetic information in gametes, we obtain a *selective molecular environment*.

Distinguishing between different kinds of molecular environment through an analogy with ecological environments provides a convenient way of systematizing different embryonic components and classifying their different contribution to the development of the organism. Can these cytological analogs of the ecological environment make developmental explanations and models more per-

modification to the environment caused by organisms, including the physical consequences of their trophic activities. In turn, niche construction is here understood as a particular kind of ecosystem engineering where the modification of the environment feeds back to the engineering organisms.

[23]Of course, if we view mammalian development as an *individual* embryo constructing its own niche, then there is no need to appeal to molecular ecosystems; the traditional notion of niche construction will do just as well. The advantages of the molecular ecosystem concept emerge when we distinguish and analyze the specific role and mechanisms underlying the various parts and stages which contribute to the growth of the entire embryo.

spicuous? Can they be employed in guiding the manipulation and control of developing embryos in experimental settings or in recreating these processes in vivo or in vitro? These are important questions that cannot be addressed a priori. The present discussion suggests that—just like competition, predation, and mutualism—external, ecological, and selective environment might be fruitfully applied in developmental research. However, a precise assessment of their contribution must await their application in the production of models and the engineering of synthetic systems. Only once these abstract concepts have been put to work, will we be able to fathom their true potential.

4 Concluding Remarks

The aim of this article was to analyze the striking resemblance between the cellular environment and the biosphere. In the first part, I focused on three analogies between the ecological macrocosm and the molecular microcosm. First, I distinguished two approaches for the individuation of ecological and molecular systems—*physiognomic* and *component-specific*. Second, I showed that molecular environments display several processes and interactions characteristic of ecological communities, such as competition, predation, mutualism, and metabolic cooperation. Third, I applied Brandon's distinction between external, ecological, and selective environment to cytological systems. On the basis of these considerations, I suggested a more general definition of *molecular ecosystem* than those found in the extant literature. The second part of the essay focused on some potential applications of the concept to current or future biological practice. More specifically, I discussed how the molecular ecosystem sheds light on systems biology, cytological communities, and molecular niches.

We are now in a position to formulate a tentative conclusion. If the molecular ecosystem concept is viewed as a biological *explanandum*, its impact on biological practice is rather modest. The ambitious goal of systems biology to model the microstructure of entire portions of the biosphere does not require a "molecular" notion of ecosystem. Similarly, if the purpose of the metaphor is simply to debunk the obsolete view that molecular mechanisms and processes are rigid-self regulated, deterministic gears, then there is no real reason to appeal to *ecosystems*; the simpler notion of a *system*—with its traditional apparatus, including feedback, feedforward loops, etc.—will do just as well. The real value of applying exquisitely ecological concepts to molecular biology emerges when we focus on their role as *explanantia* in comparative research and in guiding the production of complex models, both *in vitro* and *in vivo*.

But do we need a self-standing notion of *molecular* ecosystem at all? Couldn't we get along with the familiar ecological notions of ecosystem, niche construction, predation, competition, mutualism, etc.? In this article, I suggested a negative answer. As noted at the outset, developing organisms and their components are very different from portions of the biosphere. Familiar ecological concepts—which take self-standing *organisms* (and their physical environments) as their interactors—do not straightforwardly apply to cellular and sub-cellular

entities. More importantly, despite the striking analogies between macrocosm and microcosm, the complexity of the molecular realm deserves to be analyzed via the employment of a perspicuous set of tools that models its specificity. The notion of molecular ecosystem developed here purports precisely to offer a general framework for such endeavor. To be sure, unravelling the full potential of the molecular ecosystem concept requires a much more detailed analysis that cannot be fully undertaken here and must await further experimental progress. The modest goal of this essay was to show that the foundations of the metaphor are solid and to begin to address a more general question: *how can ecological concepts inform molecular research?*

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