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# ON THE POSITION OF BIOLOGY IN SYSTEMS BIOLOGY

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ABSTRACT. Although the term “systems biology” describes a wide range of diverse research projects, a common feature of systems approaches in biology is that they rely on contributions from various non-biological disciplines. Inspired by Ernst Mayr’s concerns about biological autonomy, this essay explores the status of biology within this evolving, multidisciplinary scientific landscape. After briefly considering competing theoretical views about the optimal role of biology in systems biology, the focus turns on two examples that illustrate distinct strategies for its implementation. On the basis of these examples, I argue that traditional biological concepts remain essential for elucidating meaning from the mathematical models used to represent the experimental results, both in top-down and in bottom-up versions of systems biology. The paper concludes with a discussion of the philosophical implications of the preceding analysis for the normative issue regarding biological autonomy: should biological autonomy be maintained for systems biology to fulfill its aims? The viability of the alternative cannot be excluded *a priori*. The observed effectiveness of pluralistic explanation in current systems biology, however, suggests that the continuing contributions of an autonomous biology, with its own irreducible concepts and methods, would not obstruct the development of an integrative systems approach but would rather advance its agenda.

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KEY WORDS. Biological autonomy, systems biology, reductionism, complexity, explanatory pluralism.

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## 1. INTRODUCTION

Ernst Mayr opens his first essay in *Toward a New Philosophy of Biology* with this remark: “All recent volumes on the philosophy of biology begin with the question: ‘What is the position of biology in the sciences?’” (Mayr, 1988, 8). He goes on to argue that a battle has been waged over the status of biology between those who do not see it as essentially different from physics and are consequently anticipating its eventual reduction to physics, and others who claim that it differs fundamentally from the physical sciences in its subject matter, conceptual framework, and methodology, thus meriting full status as an autonomous science.

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Concerns similar to Mayr's, regarding the status of biology, constitute the primary motivation for this paper. The scope of the investigation, however, is narrower here: the issue at stake is not the position of the discipline in the sciences, in general, but specifically its role within systems biology (SB), an emerging multidisciplinary approach to the study of biological systems. More precisely, the main objective is to examine the relevance of concepts and methods—traditionally used to demarcate biology as an autonomous science—for the scientific inquiry currently conducted under the umbrella of SB; for a set of diverse research projects which could themselves be characterized as biological. In what sense could this characterization be claimed to be accurate? Is SB biological merely due to its subject matter? The answer to this question has implications both for the direction of development of SB and for the fate of biology as a special science.

To position my efforts to address this problem within a recent discussion, but also to clarify the way in which terms such as “conventional biology” will be used in the present context, I feel compelled to refer from the outset to Michel Morange's (2011) remarks concerning the difficulty to postulate absolute criteria for defining the boundaries of the biological domain. Although he recognizes that distinctions between biology and physics are bound to remain contingent because scientific disciplines are historical objects that evolve perpetually, Morange claims that history itself has “moulded and stabilized forms of explanations [and] ways to address questions that can be unambiguously called ‘physical’ or ‘biological’” (Morange, 2011, 139). The observation that cell and molecular biology are already replete with descriptions and methods that we clearly recognize as physical, he adds, shows that the relationship between physics and biology is complicated since this presupposition is already built into our understanding of what we have come to designate as biological. As a result, molecular explanations and mechanisms, despite having originated from physics, are now taken to be integral parts of the scientific inquiry that I will call “conventional,” “classical,” or “traditional” biology, using these terms interchangeably throughout this essay. Following Morange, I adopt the view that the intertwining of concepts and methods such as those that Mayr describes as genuinely biological<sup>1</sup> with contributions from physics constitutes a well-characterized feature of the identity of classical biology. My preoccupation is to examine how this relationship might be changing when the limits of molecular explanation—and, therefore, of classical biology itself—appear to be reached and new approaches to biological problems, such as SB, emerge in response to its insufficiency. Morange (2011) argues that, under the conditions described, additional opportunities for physics to contribute to the explanatory process are created. What I seek to address in more detail is what we might learn from

the case of SB about how the roles of explanations that could be described as conventionally biological and others that may be regarded as physical, or of some other non-biological type, are being redistributed today within the permanently evolving domain of biology.

In what follows, I argue that a consideration of the current state of affairs in SB reveals that researchers continue to rely on conventional biological concepts for the elucidation of meaning from biological systems, as they proceed with the study of their more complex features. The discussion begins in section 2, which seeks to introduce the reader to various theoretical perspectives about the proper place of biology in the context of SB's multidisciplinary landscape. In section 3, two examples—representing top-down and bottom-up incarnations of the program of SB, respectively—are provided to illustrate the persistent centrality of contributions from molecular biology for the current implementation of the systems approach in the laboratory. A critical assessment of the results of these case studies and of additional examples leads to the conclusion (in section 4) that SB remains biological, not only in a nominal sense but also in virtue of the role that those who practice it still reserve for molecular explanations, as well as for other methods, concepts, and language which are in Mayr's terms biological. Whether this observation has normative implications, i.e., whether it tells us anything about the necessity of preserving biology as an autonomous science in the context of a pluralistic SB, is a question that arises naturally from the proposed analysis. It ought to preoccupy both philosophically inclined biologists and philosophers of biology, since it concerns the epistemological status and the scientific legitimacy of the discipline. The normative side of the subject of biological autonomy must, therefore, also be addressed in this essay (section 5) through the lens of our conclusions regarding the explanatory role of biological concepts in contemporary SB.

## 2. COMPETING VIEWS ON THE PROPER ROLE OF BIOLOGY IN A MULTIDISCIPLINARY APPROACH

Within the past two decades, SB has emerged as an ambitious and putatively new approach to the study of complex biological systems. The approach is innovative, its proponents claim, because in contrast to traditional molecular biology, which capitalized on the analysis of organisms and the investigation of the properties of their constituent elements, it shifts the emphasis to the consideration of properties at the system level, promising to fulfill the role of a holistic alternative to the dominant reductionist scientific paradigm (Kitano, 2001; Nielson, et al., 2004; Calvert and Fujimura, 2009).

The terms "reductionism" and "holism" are historically situated in an old philosophical debate, which is now being revisited on the occasion of

renewed interest in the problem of complexity. The history of their usage within this debate has loaded them with multiple meanings. As a result, by simply invoking the goal of a holistic understanding of biological systems, the issue concerning the precise identity of SB cannot be settled unequivocally. Instead, the variation in what is understood by the term “holistic,” in combination with overstatements as to the degree to which traditional molecular biology is genuinely reductionist, gives rise to confusion with respect to the character and the methodology of contemporary systems approaches (Gatherer, 2010). The ambiguity is exacerbated by the fact that, as SB continues to develop, its specific practical objectives are constantly reexamined and rearticulated. Some systems biologists, for instance, explicitly claim that their objectives remain fundamentally reductionist in nature, which further complicates the relationship between SB and reductionism (Calvert and Fujimura, 2009). As a consequence of this lack of consensus regarding SB’s specific objectives and the optimal mental strategy for attaining them, a rigorous formal definition of its methodology has yet to be provided (Aebersold, 2005; Joyner and Pederson, 2011).

Given the notable difficulty in reaching a widely accepted definition, Fischbach and Krogan (2010) are justified in proclaiming that “systems biology means different things to different people” (Fischbach and Krogan, 2010, 1). And yet, when we turn our attention to the applied side of SB, certain basic features of the approach that are shared among the diverse examples of its application can be clearly identified. An immediately discernible feature of SB in its practice is that it enlists contributions from multiple disciplines, not only from biology and its branches, but also from others, conventionally regarded as non-biological, such as computer science, engineering, and mathematics. Additionally, it seeks the formalization, quantification, and integration of data concerning the properties of biological systems, and employs computational modeling to achieve their visualization (Klipp, et al., 2005). Thus, SB is not only characterized by the integration of vast amounts of data, or by bringing together multiple disciplines, but it also constitutes “merging [of] modeling strategies (supplemented by new mathematical procedures) from data-poor fields with data supply from a field that is quite deficient in explanatory modeling,” namely, from the data-rich “omic” disciplines (Krohs and Callebaut, 2007, 181).

The main task that lies ahead in this essay is to characterize the contributions of biology—its current position—within the multidisciplinary landscape of SB. Before taking on this task, however, let us consider briefly the question regarding the role that biology would have to assume in the context of an optimally implemented new program for the study of complex biological systems. Thus far, the answers put forth to this question

stem from two distinct theoretical conceptions of SB, each corresponding to a different vision about the proper role of traditional biological disciplines within the developing systems approach.

O'Malley and Dupre (2005) point out that this division of SB into two main streams has been described in several earlier published evaluations of the field (e.g., by Haubelt, et al., 2000; Huang, 2004; Levesque and Benfey, 2004; Westerhoff and Palsson, 2004). What these accounts have in common is that they distinguish between molecular biology-based SB, aiming at a large scale integration of experimental data, versus system theory-based approaches, which are less reliant on conventional biology and more dependent on a mathematics and physics-oriented perspective. Advocates of the latter vision of SB maintain that the emphasis should no longer be on biology but must rather be placed on a broader study of those properties that are shared among systems in general. In order to achieve this shift of focus, they argue, principles and methods originating from disciplines such as computer science, physics, chemistry, and engineering—all of which may be rigorously formalized using mathematical expressions—should not only be adopted by SB but, even further, they must assume the primary role in its development <sup>2</sup>.

The view according to which classical biology need no longer be at the center of investigations concerning complex biological systems is clearly expressed in the work of the proponents of network biology (e.g., Barabasi and Oltvai, 2004; Albert, 2005). Some of them, in fact, prefer to avoid the term “biology” altogether when referring to this scientific endeavor, subsuming it instead under the more inclusive designation “interdisciplinary field of networks” (Dorogovtsev and Mendes, 2003). Their argument begins from the observation that biological systems can be conceptualized as biological networks, which share organizational features with non-biological networks, “such as the internet, computer chips, and society” (Barabasi and Oltvai, 2004, 101). This, in turn, indicates that the behavior of all these diverse networks could be predicted and explained by an appeal to similar laws and mathematical formalisms. When having to account for the properties of biological networks, therefore, mathematics would fulfill the primary explanatory function, according to the theoretical stipulations of network biology.

Since its inception, the theory that focuses on the common properties of networks has had an impact on the development of SB <sup>3</sup>. Aebersold (2005) goes one step further, proclaiming that the networks perspective is not merely influential for SB; it rather constitutes one of its branches. Network biology, however, has come to be regarded as more than a mere subdivision of SB; network-centered thinking is to some degree integrated into both top-down and bottom-up programs for the study of complex biological systems, and so is the biology-rooted perspective. Thus, in the

discourse about SB's methodology the division between network-oriented and biology-oriented accounts of the approach is substituted by a new distinction, between top-down and bottom-up versions of SB (see, e.g., Bruggeman and Westerhoff, 2006). The former dichotomy is superseded by the latter. At the same time, however, the older divisions are also included into the new terms of the debate. Integration of disciplines and perspectives is at the heart of SB, but ideological tensions about its methodological orientation, such as those identified above, are preserved in the background and remain philosophically relevant.

We will examine more closely top-down and bottom-up conceptions of SB below, with the help of case studies. We shall then be able to assess the implications of the evidence for thinking about the position of biology in contemporary SB.

### 3. THE TOP-DOWN AND BOTTOM-UP VERSIONS OF SB AS CARRIED OUT IN THE LABORATORY

Those who perceive and practice SB as a top-down approach start by using network theory and preexisting knowledge about the biological system under investigation in order to infer a preliminary comprehensive model of the relations among its molecular components. The model guides the research and is ultimately amended by being tested against data about the system's components and their interactions, collected via the high-throughput, system-wide experimentation which is characteristic of the "omics" analyses that have initiated and continue to propel the systems approach in biology (Bruggeman and Westerhoff, 2006). Conversely, the proponents of bottom-up SB apply the principles of physical chemistry in order to first characterize the interactive behavior of each manageable system part (Hyman, 2011). They then employ mathematical methods to integrate the obtained data into a dynamical model that predicts the behavior of the entire system (Bruggeman and Westerhoff, 2006). For example, in a project that seeks to organize the genes of a given biological system into a functional hierarchy, top-down approaches begin from fixing the hierarchy—represented in the form of a network—by interpreting with the help of algorithmic methods the previously available information about what each gene does. In contrast, bottom-up strategies count on the obtained data about how genes interact with each other in order to ultimately extract, through mathematical processing, a probabilistic hierarchical network of their functional organization (Fraser and Marcotte, 2004).

The described dichotomies with respect to the optimal strategy for reaching the objectives of the systems approach are encountered primarily in the context of theoretical analyses of SB. When it comes to practice,

however, a great deal of complementarity is revealed and productive collaboration seems to be possible. Typically SB is not implemented as a purely top-down or a purely bottom-up strategy. That said, significant methodological differences between the two perspectives do exist and they do manifest themselves in examples of predominantly top-down or predominantly bottom-up oriented experimental projects.

### 3.1. TOP-DOWN SB ILLUSTRATED BY A CASE STUDY

An early example of the implementation of the top-down strategy in SB was published by Ideker, et al., in the May, 2001 issue of *Science*. Their paper reports the methods and results of a project aiming at the characterization of the behavior of the network of genes and gene products that participate in an enzyme cascade: the yeast galactose-utilization (GAL) pathway. The researchers detected, recorded, and quantified the effects of controlled perturbations on the system with the help of relatively new at the time technologies for large-scale mRNA and protein response measurement. They then integrated and processed the acquired data using an algorithmic computer-based approach, which permitted the visualization of the GAL pathway as a complex network-like structure of interacting proteins and genes<sup>4</sup>. In summary, the experimental process began from the construction of a model governing the interactions among the molecular components that, on the basis of previous research, were known to be involved in yeast galactose metabolism. Once this initial task was carried out, the protocol called for the perturbation of each pathway component “through a series of genetic (i.e., gene deletions or over-expressions) or environmental (e.g., changes in growth conditions or temperature) manipulations” (Ideker, et al., 2001, 929). Twenty such perturbations were effected, both on the molecular components of the pathway and on the environment in which the system was situated. DNA-microarray technology helped determine the results of these perturbations, leading to the identification of 997 genes whose expression (mRNA) levels were significantly different from those recorded in a non-manipulated control yeast strain. A statistical method based on maximum-likelihood estimation was essential for evaluating the data and reaching this conclusion. In addition, the changes in mRNA levels were correlated to changes in the abundance of corresponding proteins. The integrated picture obtained suggested that a correlation exists between changes in protein abundance and changes in respective mRNA levels in response to the perturbations carried out. Isotope labeling techniques and tandem mass spectrometry, followed by computational analysis of the tandem mass spectra, were employed in order to obtain these protein abundance data.

The recorded changes in mRNA and protein abundance as a result of perturbations could not be accounted for in their totality by the initial network representing the GAL pathway. The next step in the experimental process consisted, therefore, in processing these results in a way that would permit the modification of this network. Specifically, Ideker, et al. elected to integrate the mRNA/protein abundance data with previously available physical interaction (protein-protein and protein-DNA) data, pertaining to those molecular components whose expression was affected by at least one of the perturbations performed in the study. As a result of the aforementioned integrative step, the preliminary GAL pathway was expanded and transformed to a complex network of interconnected proteins and genes (figure 1).

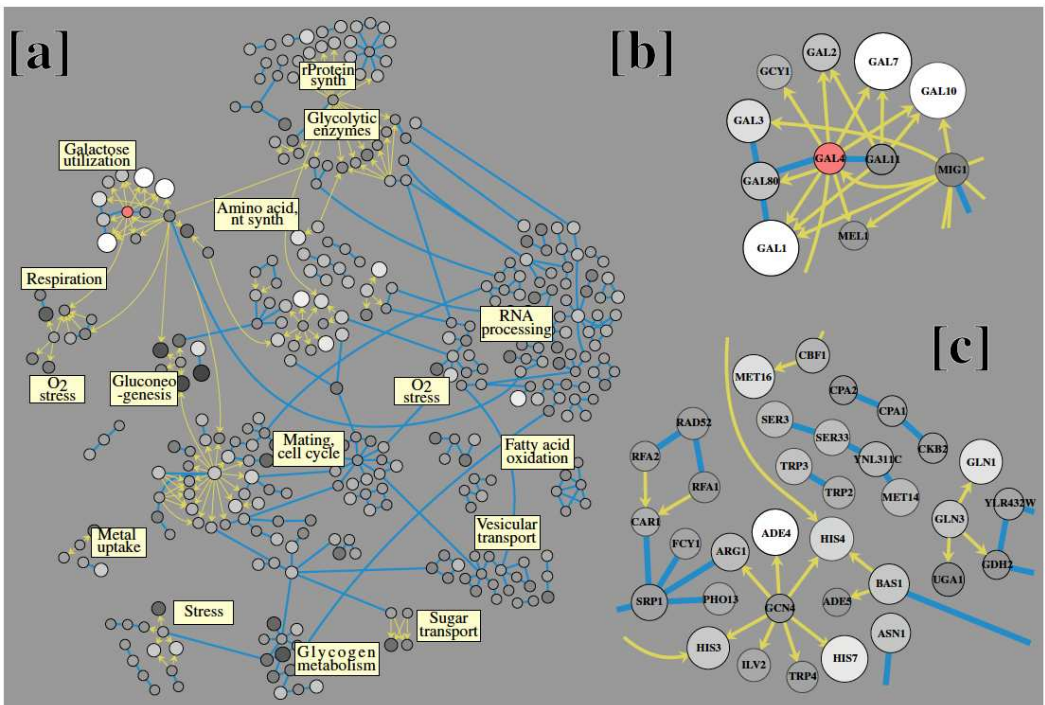


FIGURE 1

The last step in the top-down strategy of SB prescribes the generation of new hypotheses regarding the system's function on the basis of the acquired network structure. It also requires iteration: the design of experiments that are again based on systemic perturbations, in order to test these



hypotheses and to refine the latest model. In this case, Ideker, et al. report the results of a single iteration of the process. They do conclude, however, with a promissory note that acknowledges the need for “more directed experimental processes” (Ideker, et al., 2001, 933) in order to test their interpretation of the data and to produce a deeper understanding of the system studied.

In the years since these findings were published, SB has advanced considerably. New or updated techniques for measuring experimental results and more powerful mathematical and computational tools for analyzing and visualizing them are now at the disposal of researchers. A consideration of more recent examples of top-down SB (see, e.g., Baliga, et al., 2004; Carrera et al. 2009; Needham, et al., 2009; Street, et al., 2011), however, suggests that the basic objectives of SB, as well as the steps for attaining them, have been largely conserved throughout the decade during which this approach has been actively pursued.

### 3.2. AN ALTERNATIVE TO TOP-DOWN SB: BOTTOM-UP SB ILLUSTRATED BY AN EXAMPLE

To illustrate the main methodological features of bottom-up SB we appeal to the example of a study of gene regulation in the bacterium *E. coli*, published in 2006 by Nicholas Guido, et al. The examination of a more recent case could have provided insight into the latest experimental techniques used in the field, but this particular study was chosen instead because it constitutes a rather clear interpretation and a faithful implementation of the strategic plan of bottom-up SB. The authors explicitly declare from the start that they will be taking a bottom-up approach toward the subject of their study. They also describe the general objective of their work by stating that it seeks to show that “the properties of regulatory subsystems can be used to predict the behavior of larger, more complex regulatory networks” (Guido, et al., 2006, 856).

The regulatory subsystem in question is a synthetic gene network under the control of a promoter that was engineered so that it could be activated and repressed in a complex pattern within *E. coli* cells. The fact that the subsystem under scrutiny was the product of human design is a distinctive feature of this particular project. In contrast to what holds true for many pathways and processes found in living organisms, in the present case the components of the subsystem, as well as its structure, were fixed by the researchers. Precise information about the ground level of this subsystem was, therefore, fully available from the beginning of the experiment, facilitating both model construction and the targeted testing of its behavior under various conditions: in the absence of regulatory molecules, in the presence of repressors only, in the presence of activators only and, finally, in the presence of both repressors and activators. Quantitative data

regarding gene expression under these conditions were collected. In addition, a deterministic mathematical model predicting the *in vivo* behavior of the modular system was generated. The model simulates the expected mean transcriptional response of the three regulated systems (repressor-only, activator-only, repressor-activator) and it is based on formal expressions of the kinetics of their components under conditions of equilibrium. The transcriptional data obtained by the researchers in the laboratory were fitted to these expressions, which were derived theoretically, in order to generate an estimate of the mean transcriptional response of the system under each of the conditions tested (figure 2). This task was accomplished by means of computer software designed to solve non-linear least squares problems through the application of a gradient-based optimization algorithm (Guido, et al., 2006, Supplementary Information, 5). With the help of additional algorithm-based computational methods, once more, the initial deterministic model of this modular subsystem was ultimately extended to include stochastic effects. This processing enabled the model to predict quantitatively the behavior of a more complex system which involved regulatory feedback. Experimental evidence supporting the accuracy of the predictions made on the basis of the extended model (figure 3), is presented by Guido, et al. in the conclusion of their paper.

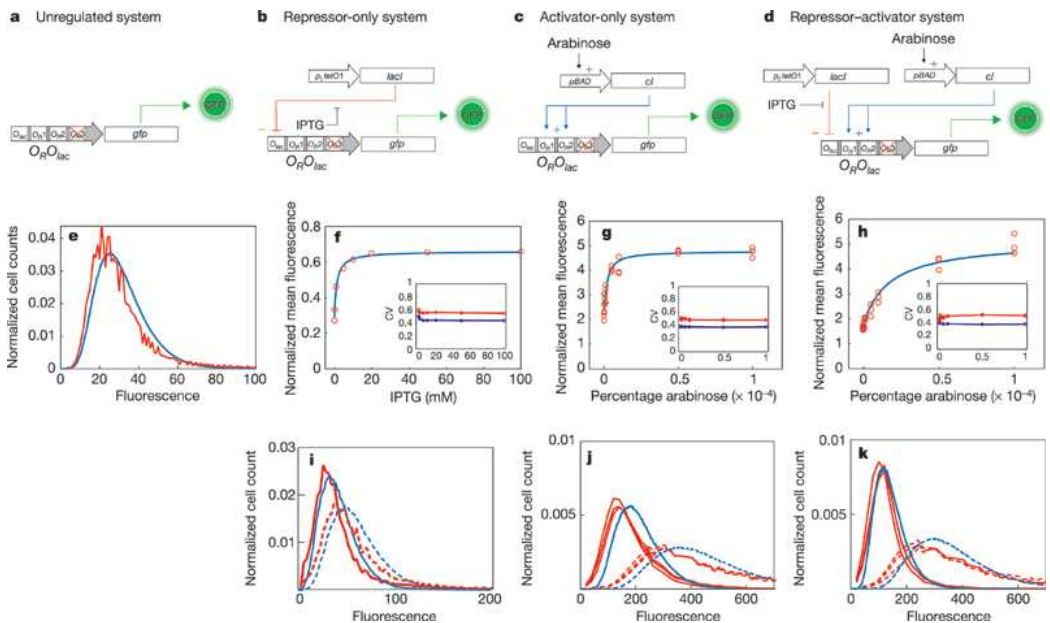


FIGURE 2

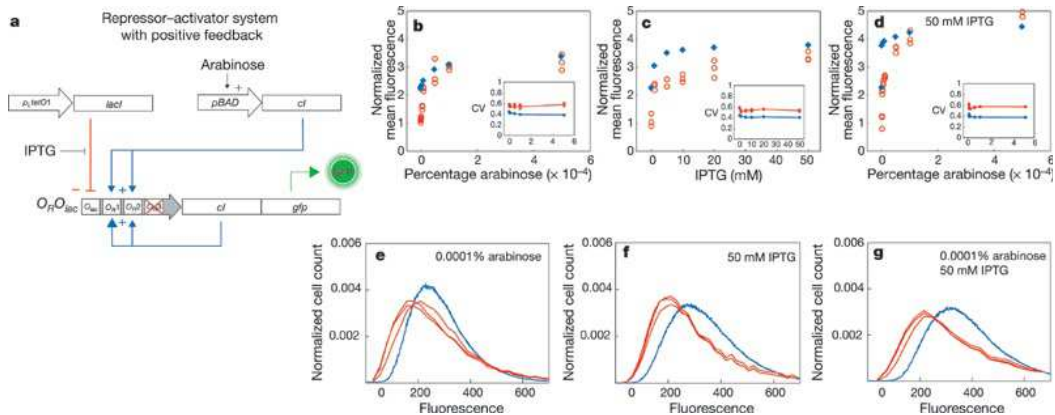


FIGURE 3

The mathematical calculations that underlie the models used in this project are reported by the authors in a separate addendum to their article. They concern primarily the chemical kinetics of the transcription factors binding to the promoter that controls gene transcription in the synthetic network whose characterization was the focus of the investigation by Guido, et al. The supplementary information found in the addendum is exceedingly technical, yet it is instructive for us because it confirms the foundational role of mathematics, physical chemistry, and computation for the developing systems approach in biology; a role which, as we can discern from this case study, is not confined to the top-down version of SB but also extends to its bottom-up version.

What are then the implications of these observations for the role that biology might still have to play in this context? The issue that has motivated the present inquiry can no longer remain in the background.

#### 4. ASSESSMENT OF THE PHILOSOPHICAL IMPLICATIONS: THE BIOLOGICAL STATUS OF SB

Having examined examples illustrating the two most prevalent contemporary approaches to the implementation of SB, we are in a position to address a question that is only slightly modified from the one cited by Mayr: “What is the position of biology within SB today?” There is a problem with this formulation, however: it implies, *a priori*, that biology constitutes a distinct part of SB. To avoid making unwarranted assumptions, one could ask instead a related question about whether SB is biological and, if so, then

to what degree. However, there are difficulties with this alternative question, no matter how exactly it may be articulated. In particular, asking it seems redundant at first: is it not true that any kind of biological inquiry must be biological by definition? Moreover, is there any sense in suggesting that a science that is indeed biological could possibly be only partially biological? Some qualification of the use of the term “biological” as used in the present context is in order before proceeding.

Etymology alone would appear to constitute sufficient evidence for concluding that “systems biology” is fundamentally biological. Besides, its subject matter is the study of living beings: SB is an inquiry into the function, structure, and behavior of complex biological systems; in that respect it must also be considered biological. In addition to these parameters, however, the conceptual framework and the methodology adopted by a given science are at least as important for defining its identity. To return to Mayr, biology in particular is defined by certain unique, “biology-specific concepts or principles” (Mayr, 2004, 28). From this point of view, any inquiry that lacks or ignores such concepts cannot be regarded as properly biological, even if it does concern itself directly with biological problems.

In the discussion that follows I adhere to this more rigid conception of what counts as biological. Of course, the classical notion of biology is challenged—and with good reason, given the discipline’s continuous evolution—in an era when biological problems are addressed from an integrative systems perspective<sup>5</sup>. To adopt Mayr’s understanding of the term “biological” in order to address the task at hand is not a choice made because of an uncritical commitment to such an understanding. On the contrary, it is demanded by the critical nature of the task; only under this condition—namely, that biology is understood as an autonomous discipline with its own concepts and methods—is it philosophically productive to ask a question like the one Mayr asks about the position of biology in the sciences, this time in the narrower domain of SB. The question would be pointless if any biologically oriented inquiry counted as biology, given that SB itself constitutes such an inquiry. Moreover, to ask about the extent to which SB is biological also becomes possible upon adopting Mayr’s understanding of the term “biological.” Answering this question is, in turn, a prerequisite for evaluating his claims regarding the need for preserving the autonomy of biology.

After these obligatory clarifications, more needs to be said about those concepts and methods which I will take, following Mayr, as the signposts of a distinctively biological science in the subsequent assessment of SB. Many of the concepts that are unique to biology are owed to the complexity of biological systems. Their complexity is at the basis of properties such as metabolism, reproduction, regulation, growth, and hierarchical organi-

zation, which are not encountered in non-living systems and for which biology must be able to account (Mayr, 2004). In addition, the capacity of organisms to evolve is singled out by Mayr as another exclusively biological property. Biological systems have a historical dimension—they change and adapt to changing environments over time—and this must also be reflected in biological explanations. The concepts of evolution, natural selection, and adaptedness, are among those that capture the historicity of living beings. The catalog of concepts that are essential to biological thinking also includes, according to Mayr (2004), the notions of genetic program and population. The concept of teleology, which for Ayala was indispensable for some biological explanations “that cannot be reformulated in non-teleological form without loss of explanatory content” (1968, 208), is excluded from the list offered by Mayr (1988), who includes instead a notion closely linked to the aforementioned concept of program: teleonomy.

Besides these conceptual standards, a methodological feature allegedly distinguishing biology from the other physical sciences that merits individual attention because of its implications for the discipline’s scientific legitimacy is that, whereas for the latter formal laws play the primary explanatory role, explanations in biology are primarily based on generalizations drawn from descriptions and observations (Brent, 1999). That which has served as the basic criterion for the modern notion of what counts as “true science,” however, is precisely the capacity to provide explanations of natural phenomena in the form of deterministic laws. As a result, the paradigm of the exact physical sciences came to be regarded as the blueprint for science in general. Correspondingly, by setting it apart from physics, biology’s apparent lack of explanatory generalizations that could indisputably be called laws put in question its scientific credibility.

Whether any of the law-like regularities encountered in biological systems could be described uncontroversially as laws of nature remains a matter of philosophical debate. Mayr was among those who consistently defended the view that in the domain of biology claims of universality, such as laws, fail due to the inherent complexity, variability, and contingency of organisms <sup>6</sup> (Hamilton, 2007). He did not, however, regard the purported absence of laws from biology’s explanatory framework as a deficiency. Instead, he considered the descriptive nature of biological explanations to be well-suited to the aforementioned special features of the discipline’s objects of study. Other scholars, nevertheless, have either proposed that it does make sense to speak of laws in certain biological contexts (see, for instance, Winther, 2006; Hamilton, 2007), or challenged the epistemological value of the very question about whether strict laws play an explanatory role in biology (Mitchell, 1997; Woodward, 2003).

These philosophical disagreements aside, the idea that in order for biology to establish its status as a legitimate science it ought to become

more like physics, seeking law-based explanations of biological phenomena rather than continuing to rely on informal concepts, has long been influential on the direction of the discipline's evolution. With the rise of molecular biology, biochemistry, and genetics, elements from the method of the physical sciences started to play an important role for the study of life (Westerhoff and Kell, 2007). This, in turn, signaled a transformation of the traditional character of biology, which continues with the emergence of approaches such as SB. More specifically, systems approaches are creating opportunities for the participating physical sciences to further push the boundaries of biological explanation, this time beyond the limits set by molecular biology (Morange, 2011). Some systems biologists and theoreticians have suggested that these efforts to expand SB's explanatory power in order to address problems of biological complexity must also include a strategy for the identification of organizing or design principles: mathematically expressed law-like generalizations that could account for the organization of biological systems in general (Mesarovic, 2004; Braillard, 2010; Green and Wolkenhauer, 2013).

Braillard (2010) borrows the term "design explanation" from Wouters (2007) but uses it in the specific context of explanation in SB. Design explanations, as Braillard defines them, do not show how structure produces function but rather illustrate why certain functional constraints determine the presence of specific structures in biological systems. In contrast to mechanistic explanations, these accounts are not causal: "while the function determines the structure, it does not cause that structure" (Braillard, 2010, 50-51). To provide a design explanation for a given biological structure, one must presuppose that general design principles are to be found in biological systems. Design principles capture mathematically the functional constraints required for design explanations and, since they are understood as law-like generalizations, they are also taken to have little dependence on evolutionary contingency. The introduction of such principles to the conceptual framework of SB is intended to facilitate explanation by generalizing the results obtained through standard mechanistic approaches at a biological system's molecular level. At the same time, however, it constitutes a new challenge to the notion that biology is a science of fundamentally contingent systems and processes, drawing attention once again to the question regarding the extent to which SB might be said to remain biological from Mayr's traditional perspective. I will discuss what an upgraded explanatory role for mathematical formalisms, such as organizing principles or design explanations, could imply for answering this essay's central question with the help of an example later on in this section.

Although the last remarks concerning the search for organizing and design principles in SB suggest that this might be changing, thus far biology

has rarely appealed to non-causal generalizations for the explanation of biological phenomena. Nevertheless, in the course of its historical development it has relied increasingly on the identification of causal mechanisms for fulfilling this purpose<sup>8</sup>. Machamer, et al. (2000) define mechanisms as “entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions” (Machamer, et al., 2000, 3). They also contend that, “to give a description of a mechanism for a phenomenon is to explain that phenomenon” (Machamer, et al., 2000, 3). Biologists had generally espoused the ideas contained in both of these propositions well before philosophers made them explicit. After the advent of molecular biology, in particular, few biologists would challenge the contention that to explain protein synthesis, for instance, it suffices to describe the mechanism of this process.

In assessing the nature of basic mechanistic explanations in biology, Bechtel (2011) notes that one of their important features is that they characterize sequential processes qualitatively. Accordingly, the mechanism of protein synthesis specifies the operation of transcription of DNA into mRNA by identifying the parts involved (the gene being transcribed, the mRNA, RNA polymerase, etc.) and their chemical structure without, however, providing a quantitative account of the possibly varying rate of transcription (Bechtel, 2011). Furthermore, in contrast to what is the case for the deductive-nomological framework of explanation, which is dominant in sciences like physics, for mechanistic explanations in biology it is not essential to formulate the relevant laws in order to account for a particular phenomenon. Despite the fact that laws could be invoked occasionally, the specification of a mechanism depends primarily on the determination of its parts, the operations that they perform, and the pattern of their organization. This observation further supports the claim that, thus conceived, mechanistic explanation does not signify a radical departure from biology, i.e., from a discipline in which laws have limited explanatory function but qualitative accounts remain at its forefront.

The recent emergence of SB may be regarded as the latest step taken in the direction of an eventual alignment of the methodology of biology with the program of the physical sciences. In terms of epistemic aspirations, at least, some systems biologists see themselves as more strongly committed to the methods of physics than molecular biologists have ever been. Calvert and Fujimura (2011) provide support for this claim by reporting a series of statements gathered in the process of interviewing scientists who work in this multidisciplinary field. Indicatively, one of the interviewees predicted that with the development of SB, “the ‘intuition or naïve understanding’ of molecular biology, will be replaced with ‘rigid mathematical or computational understanding,’” while another “acknowledge[d] that biology currently lies ‘half-way between history and physics,’ but hope[d]

that systems biology will bring biology closer to physics" (Calvert and Fujimura, 2011, 159). The same anticipation that SB will bring about the transition from a largely qualitative and descriptive biology to a rigorous science that integrates the analytical tools of the physical sciences is also shared by systems biologist John McCarthy (2004). Several other leading figures of the field, however, emphasize the centrality of biology for SB, subscribing to the view that "systems biology is driven by biology" (Calvert and Fujimura, 2011, 161). Both in terms of language and with respect to the questions asked, another scientist among those interviewed by Calvert and Fujimura states "SB is biology" (2011, 161). Thus, some of the interviewees conclude that SB does not represent a paradigm shift; it rather constitutes a more complex biology. What can be inferred from this diverse collection of views, more generally, is that the sociological perception of the status of SB by the scientific community is quite complex and ambivalent itself. How does this picture of epistemic expectations and methodological preferences match the one that emerges from the analysis of the two examples from the practice of SB considered earlier in this essay? This is the relevant question that must be addressed as we proceed.

One might argue that a strong commitment to the mechanistic methodology familiar to classically trained molecular biologists is still an integral part of bottom-up applications of SB. Closer examination of the case study of gene regulation in *E. coli* that was presented in section 3 provides support in favor of this claim. As seen before, bottom-up approaches start with an effort to shed light on the mechanistic details that concern the function, interaction, and organization of the lower-level components of biological systems. In our case, the elucidation of the behavior of the promoter that controls a synthetic gene network under variable conditions gave rise to a mechanistic model of its regulation, in which causal relations were represented schematically. To the extent that it involves mechanistic models, the bottom-up approach in SB does not seem to deviate significantly from the methodological prescriptions of molecular biology. Judging solely on the basis of this criterion, it would appear that bottom-up SB is in any way methodologically more relevant than old-fashioned biology; there is not much that is more traditional in biology today than the methodology of molecular biology.

Even so, bottom-up SB is certainly not merely conventional biology. Besides relying on mechanistic thinking, it also depends on computational techniques, on quantification and formalization of biological phenomena, on the input of physics and chemistry, as well as on mathematical modeling. The mechanism accounting for the simple regulatory system initially studied by Guido, et al. (2006) could not have been specified without theoretical contributions from physical chemistry and mathematics, combined with computational analysis. Moreover, this deterministic model



had limited power. It only allowed predictions about the repression and activation of gene expression in a genetic sub-network. In order to predict the behavior of a more complex regulatory network, which involved non-linear (cyclical) regulation by positive feedback, the original model had to be extended to include stochastic effects. For the purpose of generating such a stochastic model, the data obtained through basic biological methods were supplemented with the results of mathematical analysis, a task that required once more computational processing. The described methodological features may be taken to support the plausibility of the view that the practice of bottom-up SB complies with a theoretical agenda similar to the agenda of network biology, which, as some of its proponents envision it (see section 2), aims to eventually substitute the explanatory contributions of conventional biology with explanations from non-biological sciences. Nevertheless, as noted earlier (footnote 2), formalization, the application of computational methods, and the inclusion of contributions from mathematics or from other sciences, such as physics and chemistry, does not automatically amount to marginalization of the role of conventional biology. In the Guido, et al. (2006) example, in particular, the formalisms employed, as well as the methods borrowed from non-biological sciences, appear to complement the explanatory role of biological methods and concepts rather than to undermine it. Consequently, biology seems to retain its explanatory relevance despite the upgraded role played by the physical sciences in contemporary bottom-up SB.

Consideration of the case of top-down SB reveals a similar picture regarding the status of biology in systems approaches. In contrast to the preliminary models of bottom-up SB, which are deterministic, the models employed in top-down systems approaches are characterized by Bruggeman and Westerhoff (2006) as phenomenological. They are not based, that is, on mechanisms or on precise knowledge about the relations between the components of the system that they simulate; they rather present a comprehensive picture of the system in its complexity, which highlights the frequently non-linear and non-sequential relations between its functional and structural components. As seen in the study of galactose utilization in yeast by Ideker, et al. (2001), these networks are mainly generated via computational processing of massive data sets, allowing for simulations that are rooted in mathematical formalisms. By means of an iterative process, the researchers pursued the goal of refining the phenomenological model of the pathway of galactose metabolism. The model inferred through this process was intended to produce an understanding of the overall state of this complex network without having to first characterize the causal mechanisms that describe the interactions among its parts. Such characterization may become possible after the schematic representation

of the system is provided by means of a directed graph. Ideally, the refined model should be able to predict the behavior of the yeast galactose metabolism system in the event of future perturbations. Thus, in top-down SB answers to biologically relevant questions depend on global representations of the system that are produced through predominantly non-biological methods.

Upon careful reflection, however, it becomes evident that such a description of top-down SB is underestimating the role of biology for its success. The directed graph Ideker, et al., obtained by applying mathematical methods—i.e., the galactose utilization network—constitutes a more elaborate simulation of a biological system that was previously understood in terms of a significantly less comprehensive pathway. Such richer representation signifies a marked improvement over the previously available mechanistic model, but only to the extent that it can become intelligible; that it can convey meaning about the biological processes that are being studied. This condition of intelligibility is a prerequisite for attaining the main objective set to be accomplished by SB: the accurate prediction and controlled manipulation of the behavior of complex biological systems.

The limited capacity of the graph-based representations currently used for the visualization of the results of top-down SB to depict the system in an intelligible manner constitutes a significant shortcoming of such approach. Visualization programs have been developed, Alan Aderem remarks, because “human minds are incapable of inferring the emergent properties of a system from thousands of data points, but we have evolved to intelligently interpret an enormous amount of visual information” (2005, 511). Nevertheless, those seeking to interpret what the network-like structures that we encounter in contemporary SB tell us about the system cannot extract meaning directly from them by simply looking at the graphs any more than they could by looking at the raw data. There is, therefore, the need for additional, secondary means of analysis—a process of interpretation—in order for such models to become readily intelligible. For this purpose, the mathematical formalisms used in model construction in SB may not suffice without some recourse to familiar concepts which could help render them meaningful<sup>9</sup>. Classical biology is well-qualified to serve as the source of such concepts.

In fact, the scientists who practice SB in the laboratory today seem to rely routinely on residual classical biological concepts. In the cited case of glucose utilization in yeast, for instance, the model assembled becomes intelligible and scientifically relevant only when interpreted as a scheme of interactions between genes or proteins—i.e., molecules with specific biological functions, properties, evolutionary origins, and evolutionary potential—and not simply as a collection of interconnected nodes of

precisely quantified intensity and magnitude. Moreover, the system itself, as a whole, must be conceptualized as a biological process with a specific role—the metabolism of glucose—within the context of a living organism, before the measured variations in quantifiable properties of its components can be successfully translated into a meaningful predictive model of its behavior. These observations suggest that top-down SB remains rooted in biology; in its current implementation it appears that it must retain informal biological concepts—evolutionary, functional, and teleonomic—in order to fully benefit from the perspective afforded to it by the introduction of the formal methods of mathematics into the study of organisms.

In short, both bottom-up and top-down approaches to SB share a deep reliance on biological methods and concepts. On the one hand, bottom-up SB continues to invest on the mechanistic methodology of reductionist molecular biology and counts on it for enabling it to eventually address questions about the whole system by means of mathematical strategies. On the other hand, top-down SB enlists traditional biological concepts and biological language in order to give meaning to the holistic models that it builds via mathematical and computational processing of system-wide data. Besides, biological terminology and the corresponding biological concepts remain as dominant in bottom-up approaches as they are in top-down SB. In addition, mechanism-based modes of explanation are clearly still present not only in bottom-up but also in top-down SB. This observation further supports the assessment that explanatory methods similar to those employed in molecular biology remain relevant for SB.

The idea that conventional biological explanations still have an important role to play in SB is put to the test, however, by recent systems approaches that seem to depend heavily on organizing and design principles for carrying the explanatory weight. In emerging fields such as synthetic biology and evolutionary systems biology, for example, researchers seek to capitalize on the explanatory force of mathematically expressed general system principles, many of which were first uncovered in the context of engineering. This methodological choice challenges directly the classical view of living beings as contingent and consequently of biology as a science without generalizations. The study of chemotaxis in bacteria serves as a good example for illustrating how design explanations produce an understanding of the robustness of this biological process that could not have been attained by an exclusively mechanistic systems approach (Braillard, 2010). At the molecular level, chemotaxis-guided movement in bacteria is a well-characterized phenomenon. The molecular interactions causing the bacteria to move either toward greater concentrations of attractants or away from high concentrations of repellents have been described to a high degree of mechanistic detail. But the mechanistic account of chemotaxis is limited in its capacity to explain certain features

of this phenomenon such as its robustness. As Braillard (2010) points out, the mechanism suffices for understanding *how* bacteria sense differences in concentration for a variety of ligands and *how* these differences produce specific changes of flagellar motion, but it cannot fully explain *why* the function of this system remains relatively stable when subjected to large variations in its parameters. Progress in addressing the latter question was made only when Yi, et al. (2000) analyzed the mechanism mathematically by applying a principle originating from the engineering strategy of internal feedback control. Their analysis suggested that the process of adaptation in bacterial chemotaxis is robust due to inherent structural features of the system, namely, the feedback loop that was shown to be part of the mechanistic model of chemotaxis. In this case, therefore, a control principle first identified in non-biological systems—the principle of integral control—serves as a theoretical tool for analyzing a biological system’s behavior and providing a non-causal design explanation for it. A similar strategy is described by Alon (2007), who shows how simple formal principles, extracted from the recurring patterns of interaction in small sub-circuits across various regulatory networks, could be transferred into the practice of SB in order to help explain complex biological functions for which causal mechanisms alone have thus far failed to account adequately. Examples of the search for principles of organization can also be encountered in the emerging field of evolutionary systems biology. For instance, Jaeger and Crombach (2012) study the evolutionary dynamics of the gap gene system in dipterans, a network involved in regulating segmentation during early insect development, by using modeling formalisms together with quantitative experimental data to reverse-engineer the network in different species. They then compare the inferred gap gene circuit models to gain “general insights” (Jaeger and Crombach, 2012, 114) that could be applied for explaining the evolutionary constraints in other developmental gene regulatory networks.

The prominence of non-causal and non-mechanistic explanations in these examples could tempt the reader to conclude that any input conventional biology might still be able to contribute has already been rendered explanatorily irrelevant in certain SB approaches. Contrary to this interpretation, I take the emerging picture of the explanatory landscape in SB to be pluralistic. Proponents of early general system theories, including Ludwig von Bertalanffy, Mihajlo Mesarovic, and Robert Rosen, were motivated to seek general system principles that could be introduced in biology primarily because they recognized the limitations of reductionist methods for addressing problems of biological complex organization. Far from intending to reduce biological concepts to abstract formalisms, they aimed instead to provide a thoroughly scientific alternative in which general system principles would complement descriptions at the molecu-

lar level of the biological systems in order to give biologists a better understanding of the whole organism. Similarly, I understand the present quest for organizing principles in SB as an effort to enrich and expand its explanatory repertoire as well as to strengthen its predictive capacity by integrating rather than eliminating descriptive biological methods and causal mechanistic explanations with non-causal, mathematical formalisms. The goal is model enrichment, not model replacement, Braillard (2010) remarks. By employing both general system principles and causal mechanisms SB aspires to bridge the explanatory gap between descriptions at a biological system's molecular level and abstract high-level models. Alon (2006) concurs with the idea that invoking design explanations in SB is consistent with integration rather than with the elimination of molecular biological contributions, stating that the quest for general principles depends on molecular experimentation. Finally, the emerging field of evolutionary systems biology constitutes itself a paradigm of methodological pluralism given that it aims to broaden the scope and the predictive capacities of SB by integrating the latter's modeling techniques with the explanatory concepts of evolutionary biology (O'Malley, 2012).

Regardless of whether we are approaching biological systems from top to bottom or from bottom to top, or we enlist abstract organizing principles to account more adequately for their complex features, biology remains indispensable, albeit no longer exclusively responsible, for providing meaning to the experimental data and to the models constructed. Biological thinking retains a prominent place within contemporary SB, even if many non-biological disciplines are vital to its success. If this interpretation of the evidence gathered from this survey of SB in practice is accurate, the implications about the status of biology are clear: it retains an important explanatory role as an autonomous science within the constantly evolving pluralistic landscape of SB. Furthermore, as Mayr emphasizes, the fact that the domain of biology overlaps with the domains of several other sciences in the context of SB does not qualify as an argument against biological autonomy. Autonomy does not entail complete separation of biology from the other sciences (Mayr, 1988, 8). Rather, biology can be said to be constitutively autonomous as a science in so far as it remains free to determine its own constitution: the questions and problems that pertain to biological inquiry, as well as the terms and methods required for addressing them.

##### 5. THE NORMATIVE QUESTION

The conclusion according to which the case of SB supports the continued autonomy of biology amounts to a claim about its current state of affairs but it does not answer the related normative question: should biology

retain its autonomy in an ideal scenario about the future of SB? In order to be treated properly, this issue would have required separate consideration in a different study. Because of its importance and its close connection to the subject of our investigation, however, we will engage with it here. Our discussion will be limited by the extent to which the preceding assessment of the present status of SB can permit us to speculate about the optimal role of biology within a fully developed systems approach.

Let us begin by considering a hypothetical question: what if SB evolved through a reductionist process involving substitution of informal biological concepts by their formal counterparts? Although there is no indication that eliminative reductionism is currently taking place in SB, or that this is likely to occur in the future, if such a scenario were to materialize, then biology would cease to play its role as the source of concepts needed for understanding complex biological systems. A more fundamental science would have to supply them instead. It is not inconceivable that ways to efficiently translate informal biological concepts into formal expressions may eventually become available. For the accomplishment of such a task, however, the boundaries of the physical sciences will have to expand to accommodate newly formalized concepts, presently thought to have no place within the domain of science. The physical sciences themselves would, therefore, have to be transformed from their current constitution. Whether such a transformation is feasible and in what exactly it should consist, remains unclear.

Although his intention, as mentioned earlier, was not reduction but rather to pave the way for a holistic understanding of biological systems, Bertalanffy (1968) identified the formalization of concepts of the kind just mentioned as the primary goal of General System Theory (GST). A certain formulation of the concept of finality, for instance, retains an essential role within the mathematical description of systems that GST seeks to provide. It is a notion of finality devoid of anthropomorphic connotations or of any foresight of the goal. It involves, that is, only causal forces that act from behind and whose overall effect is to direct the system to a certain end. However, GST did not succeed in providing a satisfactory formal expression—i.e., the “final-value” mathematical formulas that Bertalanffy had promised—of this teleonomic concept.

Some of the examples discussed earlier indicate that steps in the direction of successfully formalizing concepts required for the characterization of biological and other complex systems have already been taken. It remains unclear, however, whether mathematical formalisms would suffice for resolving the range of explanatory problems inherent in the project of understanding biological complexity. When considering the process of explanation, translation, and interpretation in other non-scientific contexts—but even in physics, mathematics, and certainly in biology—a

conclusion that consistently emerges is that informal concepts are indispensable for the extraction of meaning and its communication. Therefore, reducing biological concepts to formal expressions—e.g., to general system principles—is not likely to increase explanatory efficiency, as this initiative would also inevitably entail the introduction of additional informal concepts for contextualizing the contributions of these new formalisms. The demand for providing context for mathematical formalisms might ultimately amount to a demand for reintroducing notions familiar to biologists, including causality, finality, purposefulness, or function; the very notions, that is, that the formal principles would have been expected to replace.

It is not at all clear, therefore, that the pursuit of a SB purged entirely of biological concepts would constitute a fruitful endeavor. On the contrary, our speculative argument suggests that in order for SB to fulfill the goal of providing new insights into the complex function and structure of biological systems, the continuing contributions of an autonomous biology, with its own irreducible explanatory concepts and its own methods, remains a prerequisite. Moreover, our examination of the ways in which SB is practiced by the scientific community indicates that, thus far, the influence of the radical view according to which explanation in biology does not require anything beyond the proper application of the appropriate physical and mathematical methods has not been decisive in shaping its development. Although non-biological disciplines are becoming increasingly integrated into the frame of SB and their contributions are crucial for improving our capacity to tackle the unsolved biological problems of complex organization, the picture emerging is a pluralistic one: SB includes a variety of potentially complementary explanatory strategies<sup>10</sup>. In this multidisciplinary framework, the autonomous operation of biology guarantees the possibility of explanatory pluralism by accommodating different models of explanation, each of which is suitable for addressing a distinct level of the system's organizational hierarchy. We can therefore enlist non-causal, non-mechanistic, inferential models to approach highly complex, non-linear processes at the top of the system's organizational hierarchy, while using in parallel classical mechanisms to account for linear interactions between the components at the bottom of the system. Biological concepts and formal principles from the physical sciences are not mutually exclusive but together they serve as connecting links between these models and render them informative with respect to the issues at stake; issues pertaining to the behavior of biological systems and, in virtue of this distinction, necessarily falling under biology's jurisdiction.

In the 1980's, anticipating the questions about biological systems that would soon have to be addressed scientifically, Mayr articulated a demand for an expanded concept of science that would include principles, con-

cepts, and strategies of both the physical and the biological sciences. Before the emergence of SB, he argued in favor of a pluralistic effort that would promote the understanding of biological complexity. Instead of seeking to reduce biology to physics, the key to this effort would be to construct a “broad-based, unified science” (Mayr, 1988, 21) that acknowledges and incorporates the contributions of biology, physics, and philosophy. Although it may seem paradoxical, Mayr concludes, the first step toward the attainment of this goal is the recognition of the autonomy of biology (1988, 21). Whether SB represents a movement in the direction of scientific unification, or it illustrates instead the plausibility of the alternative, i.e., of continued scientific disunity, remains an open question whose answer depends largely on agreeing on the conditions for attaining the intended unity. For those who regard reduction as a prerequisite, Mayr’s vision of scientific unity could be easily confounded with their understanding of scientific disunity. In my view, however, the present analysis of contemporary systems approaches in biology suggests that SB generally fits the profile of the expanded science that could meet Mayr’s call for unity without reduction, which was also an endorsement of methodological pluralism: SB encompasses and seeks to integrate the various branches of modern biology but it also incorporates theoretical knowledge, techniques, and explanatory methods, originating from a wide array of non-biological sciences <sup>11</sup>. As Mayr had envisioned, a legitimate biological science maintains its autonomy within the multidisciplinary framework of SB, retaining its classical concepts and its explanatory strategies alongside the formal mathematical models and the explanatory methods of physics and chemistry. By providing the required conceptual basis, it complements explanations at different levels of organization, rendering them meaningful and thus useful for beginning to understand aspects of the behavior of complex biological systems that could not have been accounted for without this synthesis taking place.

## 6. CONCLUSION

According to the line of argument advanced in the course of this essay, the evidence from the cases examined supports a relatively straightforward conclusion. It suggests that although SB capitalizes on a variety of non-biological methods of analysis, in the way that it is currently implemented—either as a top-down or as a bottom-up strategy—it still relies on traditional biological concepts and methods for providing meaningful accounts of the phenomena observed and of the models constructed. Therefore, biology as an autonomous science retains an important, even if not always central, position in SB’s multidisciplinary framework. This is a claim about the present state of affairs in SB, a rapidly developing and diverse research



program with an integrative orientation. It does not entail that it would be in principle impossible for SB to eventually substitute biological concepts with formal network concepts, nor does it establish that this explanatory alternative would fail to render biological systems intelligible. Consequently, the conclusion reached about the current position of biology in SB does not settle the normative question about whether biology's autonomy ought to be maintained in order for SB to fulfill its explanatory objectives. It does, however, raise questions about the limitations, and therefore about the fruitfulness, of a biology-free systems approach and advances the argument of advocates for a pluralistic SB; namely, that biology can continue to play the essential explanatory role that, as demonstrated, it is now playing in SB, as long as it participates in the future stages of a pluralistic integrative research program that guarantees the preservation of its autonomy.

- 1 An analytic discussion of concepts and methods which are identified as biological in Mayr's account is included in section 4 of this essay.
- 2 As noted earlier, methods from sciences like physics and chemistry have long been incorporated into molecular biology (Morange 2011). Similarly, mathematical tools have facilitated the development of biological fields such as population genetics and evolutionary biology. But despite the significance of their contributions, "non-biological" disciplines have generally participated in the framework of classical biology without seriously challenging the primacy of those explanations that biologists have traditionally regarded as "biological."
- 3 In fact, the impact of network thinking extends to many other areas of contemporary biology besides SB. Indicatively, references to genetic and metabolic networks are routinely included in experimental design and explanatory accounts in molecular biology, while in ecology system-theoretic approaches, including network theory, have long been influencing the discipline.
- 4 The computer application used for processing the data in this case, GeneCluster, was developed to produce and display self-organizing maps (SOM) of gene expression patterns (Tamayo, et al., 1999).
- 5 Many explanations that are now "felt by biologists to be 'biological'" (Morange, 2011, 140) may not have qualified as such just a short time ago.
- 6 Hamilton (2007) uses the term "nomic inhibitors" to describe those features of the biological systems that rule out the applicability of laws in biological explanation.
- 7 Given that not only design principles, but also organizing principles, produce non-causal explanations which challenge the idea that biological systems are fundamentally contingent, I consider the search for either of these two categories of generalizations to have similar implications for my analysis and I discuss them together.
- 8 As early as 1972, William Wimsatt wrote that, "[a]t least in biology, most scientists see their work as explaining types of phenomena by discovering mechanisms" (Wimsatt, 1972, 67).
- 9 Recognizing that in the absence of basic concepts, like those that biology could supply, the extraction of meaning from the models used in SB would be problematic, Hyman (2011) writes: "A key problem with modeling is that one requires a conceptual basis and a systematic strategy to be able to construct useful and insightful models. Without a systematic approach models are often meaningless" (Hyman, 2011, 3636).
- 10 MacLeod and Nersessian (2013), for instance, describe a bimodal strategy for practicing SB, which consists in the combination of wet-lab experimentation and mathematical simulation.
- 11 Grantham (2004), Love (2008), and Brigandt (2010) provide detailed arguments to make the case that explanatory unification in biology does not require reduction.

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