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Organization needs organization: Understanding integrated control in living organisms



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ABSTRACT

Organization figures centrally in the understanding of biological systems advanced by both new mechanists and proponents of the autonomy framework. The new mechanists focus on how components of mechanisms are organized to produce a phenomenon and emphasize productive continuity between these components. The autonomy framework focuses on how the components of a biological system are organized in such a way that they contribute to the maintenance of the organisms that produce them. In this paper we analyze and compare these two accounts of organization and argue that understanding biological organisms as cohesively integrated systems benefits from insights from both. To bring together the two accounts, we focus on the notions of control and regulation as bridge concepts. We start from a characterization of biological mechanisms in terms of constraints and focus on a specific type of mechanism, control mechanisms, that operate on other mechanisms on the basis of measurements of variables in the system and its environment. Control mechanisms are characterized by their own set of constraints that enable them to sense conditions, convey signals, and effect changes on constraints in the controlled mechanism. They thereby allow living organisms to adapt to internal and external variations and to coordinate their parts in such a manner as to maintain viability. Because living organisms contain a vast number of control mechanisms, a central challenge is to understand how they are themselves organized. With the support of examples from both unicellular and multicellular systems we argue that control mechanisms are organized heterarchically, and we discuss how this type of control architecture can, without invoking top-down and centralized forms of organizations, succeed in coordinating internal activities of organisms.

1. Introduction

Both new mechanists and proponents of viewing organisms as autonomous systems emphasize organization as a central theme. The new mechanists emphasize explanations of specific phenomena, while the autonomy framework advances a theory of what makes a system living. As a result, the locus at which each identifies organization is different. In characterizing mechanisms, the new mechanists look inside mechanisms and emphasize how the components of mechanisms are organized. Different parts carry out different activities or perform different operations, and the results of their individual operations need to be routed to other components of the mechanism that perform additional activities. Only when they are organized to maintain productive continuity do the

operations combine to produce the overall phenomenon associated with the mechanism. The organization identified by proponents of viewing organisms as autonomous systems is not productive continuity within a mechanism but the organization of components (parts, subsystems or mechanisms) and processes within an organism that is required for the organism to construct, repair, and reproduce itself as a far from equilibrium system. This often requires adaptive behavior in which individual components operate as needed by the whole organism. The possible links between the notions of organization adopted by these two traditions have not been given sufficient attention. This may be due at least in part to the historical baggage of the opposition between seventeenth century mechanism and different vitalist, holist or organicist approaches which reacted to the introduction of the Cartesian or LaMettrian concepts of

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bêtes machines or homes-machines (Wolfe, 2011; 2014a; 2014b).¹ In this paper we aim to fill this gap and investigate the relationship between these notions of organization. Our contention is that organization within mechanisms and organization within organisms are complementary and that both are needed for an adequate account of biological phenomena.

We articulate these conceptions of organization as they have been developed in the new mechanist and autonomy traditions respectively in sections 2 and 3. Components of organisms are organized into mechanisms, but they are also organized into organisms. There is an important difference between the two perspectives. Building larger mechanisms by ensuring productive continuity allows for generating new phenomena but does not result in an autonomous organism that is able to maintain itself. That requires the perspective on organization advanced in the autonomy tradition. The two perspectives each identify a form of organization that is employed in living organisms. Accordingly, we argue that although these two conceptions of organization are different, it is useful to consider them not as competitors but as complementary.

Recognizing that the two traditions are complementary is only a first step. In both traditions, there is a tendency to emphasize stability: stable mechanisms or stable organisms. But living systems need to be able to respond to perturbations and coordinate the activities of their parts in effecting a response. To do this, organisms must be able to modulate their own internal dynamics. Recent work in each tradition has addressed this issue by developing accounts of regulatory constraints and control mechanisms. In section 4 we show how bringing these together can provide an important bridge between the two traditions and advance the investigation of this dimension of living systems.

Biological organisms contain a vast number of regulatory or control processes, each allowing one or more other processes to be controlled in light of specific information. In many cases, multiple control processes operate on the same mechanism. This raises the question of how control processes are themselves organized so that the organism can function as an integrated system. Potential conflicts may arise in which individual control processes result in responses that address one challenge to the maintenance of the organism while potentially exacerbating other challenges. In section 5 we discuss how multiple control processes can be coordinated and their effects functionally integrated so as to maintain the organism that harbors them. One strategy for ensuring that different responses are coordinated would be to organize them hierarchically, with top-level or centralized control processes making sure that all challenges to autonomy are met. However, we argue, biological control processes are not organized hierarchically, but heterarchically. Heterarchy is a complex relationship which can be situated between flat distribution and full-fledged hierarchy. It consists in a tangled network of causal relationships according to which there is no overall defined order relationship between elements (McCulloch, 1945) and elements potentially can be ranked in a number of different ways, depending on systemic requirements (Crumley, 2015). Pattee (1991) characterized what he terms “measurement-control” networks in living organisms as organized heterarchically. A heterarchy may include local hierarchical relationships (or orders of control) such as between a control and a controlled process, without these control processes being themselves subsumed under a higher-level or central controller.

2. Organization within mechanisms

What is distinctive of mechanistic explanations, in contrast to nomological explanations or purely causal explanations, is that they

¹ This opposition has survived in some contemporary accounts of organisms as autonomous systems, such as for example Robert Rosen's (1991). This has discouraged reconciliation between advocates of autonomy and new mechanists. However, it is important to point out that the main target of Rosen's criticism is not the same notion of mechanism as adopted by new mechanists, but one based on Newtonian mechanics.

appeal to the constituents of a mechanism to explain how the mechanism responds to causal factors impinging on it. The basic idea is that a mechanism contains multiple parts/entities which perform different operations/activities that together suffice for producing the phenomenon in response to causal inputs (Bechtel & Abrahamsen, 2005; Glennan, 2017; Glennan & Illari, 2018; Machamer, Darden, & Craver, 2000). The search for mechanisms does not begin with the parts, but with a phenomenon for which the mechanism is responsible, where phenomena are understood, in the manner of Bogen and Woodward (1988) as regularities identified in the course of research (see also Woodward, 2010). Some examples of biological phenomena include alcoholic fermentation, the generation of action potentials, and the synthesis of proteins. Phenomena are often closely associated with experimental protocols in which researchers can themselves elicit a given phenomenon and characterize it in detail. The characterization of the phenomena directs the search for mechanisms—only those entities that contribute to the production of a phenomenon count as parts of a mechanism. In this sense, mechanism proceeds top-down. Developing a mechanistic explanation, as opposed to just describing the phenomena, requires going down: decomposing it into parts and operations, which are often identified through different research techniques, and then localizing operations in the different parts (Bechtel & Richardson, 1993/2010).

Bechtel and Richardson characterize decomposition and localization as heuristics in recognition that they are grounded in assumptions about how biological organisms are organized. These assumptions guide research but are not guaranteed to be true. The crucial assumption, articulated by Simon (1962), is that natural systems are nearly decomposable into components whose operations can be understood independently of the rest of the mechanism. The modifier *nearly* signifies that there may be some effects of other components on the operation of a given component but that these can be ignored in developing a first account of the mechanism. These other effects can then be incorporated in a more elaborated account of the mechanism. Simon offers arguments that not only would processes like natural selection result in biological systems being nearly decomposable, but that we would not be able to understand systems that were not decomposable. That near decomposability is an assumption is made clear by holists who reject it and maintain instead that living systems are so highly integrated that one cannot understand their constituents when detached from the whole.

Decomposition, however, is only the first step in developing a mechanistic explanation—researchers must also recompose it and resituate it in the context in which it operates (Bechtel, 2009). This may involve actually putting the parts back together, but it may also involve doing so conceptually (e.g., developing a diagram showing how the parts relate to one another) or computationally (creating a simulation of the whole mechanism from equations characterizing the activities of the components). One reason researchers need to recompose and resituate the mechanism is to establish that the operations of the parts together suffice for generating the phenomenon. Research on mechanisms thus proceeds both top-down from the phenomenon to the constitution of the mechanism and bottom-up to reconstruct the phenomenon for which the mechanism is responsible.

Organization, for mechanists, concerns how components and activities are arranged so as to realize what Machamer et al. (2000) refer to as *productive continuity* whereby the output of each component but the last is taken up by at least one other. Much of the discussion of organization among mechanists has focused on ways components are put together into mechanisms. Machamer, Darden, and Craver emphasize progression from start to termination conditions, but they acknowledge that there can be forks and cycles in the pathway between start and termination conditions. Bechtel and Abrahamsen (2009) draw attention to how often biological mechanisms exhibit non-sequential organization. For example, in the citric acid cycle, the product of a sequence of reactions is fed back as an input to a reaction at the beginning of the sequence. Since it is hard to keep track of such non-sequential interactions mentally so as to determine the phenomenon they will produce, Brigandt (2013) and

Bechtel and Abrahamsen (2013) discuss how researchers often rely on computational modeling in their reconstructions of mechanisms. Such modeling often reveals how the mechanisms generate complex dynamical behavior. Although instances of such non-sequential organization present challenges for researchers seeking to understand mechanisms, they do not fundamentally alter the conception of a mechanism as being nearly decomposable. The mechanism is still viewed as consisting of distinguishable parts that perform different operations, with productive continuity connecting the parts into a whole.

A feature of mechanisms emphasized by the new mechanists is that the process of decomposition can be iterated. The parts of mechanisms can often be treated as mechanisms in their own right, each responsible for its own phenomenon—the operation/activity it performs in the larger mechanism. To explain how the part is responsible for that operation, researchers can decompose it into its parts and the activities or operations they perform. The concern about organization arises again at this level—for the part to perform its operation, its constituents need to be organized so as to obtain productive continuity.² For example, muscle tissues which are involved in movement of a limb consist of muscle cells, which individually contract when stimulated by neurons. This ability in turn is explained in terms of myosin proteins within them creating crossbridges with actin filaments and exerting force, pulling the actin along the myosin. Myosin can itself be further decomposed, identifying structures within the molecule that bind and hydrolyze ATP, resulting in conformational change that modify the ability of other parts of the molecule to bind actin and exert force to pull actin along the myosin fibril (Bechtel & Bollhagen, 2021).

Just as one can go down levels within a mechanism, one can ascend to higher levels. The phenomenon associated with one mechanism may figure in a larger-scale mechanism in which its output is input to another mechanism that further transforms it. For example, one can connect the mechanism of generating the polypeptide chain in the ribosome with those involved in the subsequent folding of the protein and its transport to the Golgi apparatus, which prepares it for export from the cell. However, it is important to point out that in ascending from lower to higher levels at which one can identify larger and more comprehensive mechanisms that carry out higher-level activities, one will not arrive at an account of the organism as an autonomous system. At best, one will arrive at a phenomenon exhibited by autonomous organisms, such as procurement of energy or reproduction. Rather, mechanistic accounts top out where they began—with a phenomenon that a researcher has singled out for study.

Even as researchers are developing accounts of what goes on inside mechanisms, it is important to keep in focus that the phenomenon produced depends not just on what happens within the mechanism but on activity outside the mechanism that causally affects it. Although recognizing that this activity is often the result of other mechanisms in the environment of the target mechanism, philosophers characterizing mechanistic explanations have tended not to focus on the organization of that activity, treating it as just providing inputs to the mechanism. As we develop below, the mechanist account of how individual mechanisms are organized needs to be complemented by an account of the other mechanisms that operate on the target mechanism and how they are organized if we are to understand how and when the target mechanism produces its phenomenon. Below we will focus on some of the mechanisms that operate on other mechanisms and determine their activity. We will show that these mechanisms should not be conceptualized as part of the compositional hierarchy of mechanisms but as operating outside that hierarchy.

² The concept of level is often invoked in discussions of mechanisms—the parts and operations that constitute the mechanism are characterized as at a lower level than the mechanism. As Craver and Bechtel (2007) have argued, however, the mechanistic conception of levels only applies within the context of particular mechanisms and does not give rise to a stratification of levels extending across nature. See Eronen and Brooks (2018) for discussion.

3. Organization in organisms

The autonomy framework starts with an organism regarded as autonomous because it is capable of producing its own components and maintaining itself far from equilibrium with its environment. To explain this capacity, the autonomy tradition appeals to the internal organization of the organism. Organization here refers to the way production and transformation processes are connected so that they are able to synthesize the components that realize them using energy and matter from the environment.

The autonomy framework was built upon pioneering work by Jean Piaget (1967), Robert Rosen (1972), Humberto Maturana & Francisco Varela (Varela, Maturana, & Uribe, 1974), among others. Recently it was further developed by Stuart Kauffman (2000), Cliff Hooker and collaborators (Christensen & Hooker, 1998; Collier & Hooker, 1999; Bickhard, 2000), and Alvaro Moreno and collaborators (Ruiz-Mirazo & Moreno, 2004; Moreno & Mossio, 2015).³ The core feature of the account, also known as the ‘organizational account’ (Mossio, Saborido, & Moreno, 2009), is the identification of topological relations between the operations of components and between processes of transformation within a system. It is important to point out that this account of organization differs from mechanistic accounts in that it emphasizes the relations between activities that contribute to the maintenance on the system, rather than between the component activities that mechanists treat as giving rise to phenomena. Moreover, it treats the organism as a whole as the starting point and the main focus when addressing what is distinctive about living organisms. In doing so, the early work on autonomy did not engage in decomposition as described by the mechanists. In particular, the autonomy tradition privileged approaches that focused on functional relations of the whole organism. When it did reference parts of organisms, it did so functionally in terms of their contribution to the organization of system that they together realize, rather than in terms of material properties (Bich, 2012). As a consequence, the autonomy tradition has been characterized by a high degree of generality and abstraction from materiality.

The abstraction from materiality reflects the origins of the autonomy framework in the 1960s and 1970s when it developed in opposition to mainstream molecular biology (Jacob, 1970; Monod, 1970). Molecular biology focused on the intrinsic properties of the material components of living systems, especially DNA, which was singled out as responsible for the activity and reproduction of the organism. As Maturana and Varela (1980) emphasized, molecular biology ignored all the other processes that make the organism an integrated unity. As molecular biology and related fields were among those which exemplified the pursuit of mechanistic explanations in biology characterized by the new mechanists, there is a core sense in which the autonomy tradition contrasts with that of the new mechanists: mechanist research is invested in unpacking the details of a mechanism whereas the autonomy tradition abstracts from these to focus on the system as a whole.

The main objective of the autonomy research tradition is to identify and characterize aspects common to all actual and possible manifestations of life, thereby revealing the features of living systems that distinguish them from other classes of natural and artificial systems. According to the autonomy framework, these features cannot be found in the basic components of living systems but in the ways they are related. The reasons are two: (1) the same components can participate in other kinds of systems and (2) biological systems are characterized by the fact that components are constantly produced, transformed, and degraded while the system as a whole persists. Therefore, rather than delving into the details of how any particular organism maintains itself, the autonomy framework has characterized the required biological organization in general terms. It recognizes the differentiation of functional roles among the parts of a system and emphasizes how they must be integrated and

³ In this paper we will focus mainly on the account of biological autonomy developed by Moreno and collaborators, unless specified otherwise.

coordinated if they are to contribute to the production and maintenance of the system that harbors and synthesizes them. The autonomy tradition thus emphasizes a generative framework in which there is a mutual dependence between components of the organism, such that the very existence of each component depends on its relationship with the others and with the system as a whole. Accordingly, Piaget (1967) first, and then Rosen (1972) and Maturana and Varela (Varela et al., 1974), have emphasized the circular relation between processes of production and components (*Organizational closure*) even as the system is open to and exchanges matter and energy with the environment (*Thermodynamic openness*). In Maturana's words "The living organization is a circular organization which secures the production and maintenance of the components that specify it in such a manner that the product of their functioning is the very same organization that produces them" (Maturana, 1980, p. 48). Note, insofar as this concept of circular organization underlies autonomy—the maintenance, repair, and replication of the organized system itself—it is different from cyclic organization found in mechanisms such as the Krebs cycle.

Varela and Maturana (1972) motivate focusing on the abstract level in a paper in which they discuss mechanistic explanation in biology. Following the cybernetic tradition, they argue that both in the case of human-made machines and biological mechanisms,⁴ what is critical are the relations between the components of the machine or mechanism, not the identity and intrinsic properties of the components. These relations establish the requirements on the components and allow that any component that meets them will suffice: "the components might be any components at all as long as their possible interrelations satisfy a given set of desired conditions. Alternatively, one can say that what specifies a machine is the set of component's interrelations, regardless of the components themselves" (1972: 378). In focusing on these abstract relations (which they termed the *structure* of the machine in this paper and *organization* in subsequent work), Varela and Maturana are not denying the materiality of the machine. What they are denying is that materiality is the distinguishing feature of a machine or a biological mechanism such as a living system. In their view, what defines a specific type of system is its organization. Materiality does not enter *per se* into "the interactions and transformations" which constitute the system, although some organizations such as the biological one might be not be realized in any material domain but only in those, such as the molecular one, that can afford certain types of generative relationships (Bich & Arnellos, 2012).

In addition to its abstract focus on topological relations, the autonomy account emphasizes dynamics: it focuses mainly on activities and transformations rather than on the properties of the components that perform or undergo them. The relations that the components establish among themselves serve to produce, repair and transform the components while maintaining the whole system. As a result, the organism is not static, but dynamic. The focus on dynamics is made especially clear in recent work on autonomy, which goes beyond emphasizing the circularity of construction to consider the thermodynamic requirements of maintaining an organized system far from equilibrium (Ruiz-Mirazo & Moreno, 2004). This work has borrowed from Pattee's (1973) account of constraints, Kauffman's (2000) idea of work as the constrained release of energy, and Rosen's (1972) account of closure in which functional components act on transformation processes.

Constraints, as understood in the autonomy tradition, are components that figure causally in the generation of processes: a component *C* acts as a constraint on process *P* iff: (1) at a time scale characteristic of *P*, *C* is locally unaffected by *P* and (2) exerts a causal effect on *P*. As a result of

this causal influence of *C*, there is a difference between free *P*, and *P* under the influence of *C*. *P* may be responsible for the production and maintenance of other constraints. For any activity to occur as a result of constraints, there must be a source of free energy. Accordingly, Moreno, Mossio and Montevil (Montevil & Mossio, 2015; Moreno & Mossio, 2015) foreground both constraints and energy in their account of closure: the constrained release of energy in organisms accounts for the production and maintenance of the very constraints that make the performance of work possible. In this view, for the set of constraints operative in an organism to realize *closure*, the existence and activity of each of these constraints acting on processes must depend on the action of other constraints in the system. A system realizing *closure* of constraints is able to maintain its dynamical organization despite the constant transformations and turnover at the level of components.

Since constraints contribute to the maintenance of the biological system, they are viewed by the autonomy tradition as serving biological functions: a function is identified as the contribution a constraint makes to the realization and maintenance of the organization that produces it (Mossio et al., 2009). This functionalist focus of the recent autonomy approach means that functions are ascribed to the components of a system (in terms of their contribution to the maintenance of the system) and therefore components need to be identified (as constraints). Moreover, in a strong sense, constraints depend on the whole organism while the whole organism is dependent on the contributions of each of its constraints. This does impose further requirements on the types of material components that can perform the needed functions (membranes, catalysts, etc.), but these requirements are generated top-down in terms of the functional activity they must perform, not derived from the material constitution of a given organism.

4. Creating a bridge between the two conceptions of organization: control mechanisms

In the previous two sections we have presented the mechanist and autonomy traditions separately and drawn out some important differences between them, focusing especially on the understanding of organization each employs: productive continuity of mechanisms on the one hand and generation and maintenance of the whole organism on the other. But these senses of organization are not incompatible. Rather, they are directed at accounting for different features of biological organisms. The mechanist tradition has been concerned with explaining how components of a mechanism give rise to the phenomena exhibited by the mechanism, but not how the mechanism comes to be or is maintained in the organism or is invoked on a given occasion. Accordingly, most new mechanists have not addressed the autonomy tradition.

The two traditions both adopt top-down approaches to investigating causal components of organisms but with different starting points and aims. New mechanists start from a specific phenomenon and aim to explain how it is materially realized. Components are identified in terms of the contribution to the phenomenon they produce. Autonomy focuses on the organism and aims to identify what functions are necessary to produce and maintain it and how they depend on one another. Not only are components identified in terms of their contributions to the maintenance of an autonomous organization, but their very existence is dependent on such contribution: they exist because of what they do in the system that harbors them. Thus, the autonomy tradition has emphasized wholeness of living organisms by characterizing biological causal processes in more abstract functional terms and maintaining a focus on their contribution to the system as a whole.

One feature that characterizes both the mechanistic and autonomy accounts of organization is a focus on the stability and the regularity of the functioning of an organization. Mechanists often assume mechanisms operate in a regular manner—any time the start-up conditions are realized, they produce the phenomena for which they are responsible (Machamer et al., 2000). The autonomy tradition has tended to assume that the constitutive regime of self-production is dynamically stable. The

⁴ In this paper we are not addressing the relationship between autonomous biological systems and machines, which has already been extensively debated within the autonomy tradition (Bich & Damiano, 2008; Gánti, 2003; Letelier, Cardenas, & Cornish-Bowden, 2011; Militello & Moreno, 2018; Rosen, 1991). See also Nicholson (2012, 2019) and Skillings (2015) for arguments against considering organisms as machines from without the autonomy perspective.

focus on repair, for example, emphasizes restoring the organism to its stable condition. Both have thereby viewed biological systems (mechanisms or organisms) as stable. Neither mechanists nor autonomy theorists deny that there is variability in how even individual living organisms behave over time, but neither addresses it in their accounts. Some proponents of autonomy argue that organization and variation should be considered as two distinct theoretical principles (Montévil, Mossio, Pocheville, & Longo, 2016; Mossio, Montévil, & Longo, 2016). On this view, the biological organization that realizes closure is stable while variation is something that happens to this organization during ontogeny and evolution (through perturbations, mutations etc.). Variation is regarded like a source of noise: external to a biological organization and not required for it to function.⁵

Yet, in living organisms, regular behavior, stability, and continuity might be the exception rather than the rule. Cells, for example, engage in division, but they are not constantly dividing (when they do, the result is a pathology such as cancer). Cells metabolize glucose to produce ATP, but they only do so when ATP levels drop and energy is needed. Otherwise, they convert glucose to glycogen. Protein synthesis is another process that is inhibited or activated on the basis of the needs of the cell. Neurons generate action potentials, but either do so only when they receive an appropriate stimulus or change the rate at which they generate action potentials in response to stimuli. Recognizing this, recent theorists in both traditions have focused on the importance of regulation and control (Bich, Mossio, Ruiz-Mirazo, & Moreno, 2016; Winning & Bechtel, 2018). This common recognition provides the foundation for a constructive bridge between the two traditions, a bridge that on one end connects to the dynamic autonomy of organisms and on the other end to the mechanisms employed by the organism. We will begin to construct the bridge from the autonomy side by focusing on the critical importance of regulation for achieving autonomy and then link it to mechanism by introducing a special type of mechanism, a control mechanism, that is external to but operates on and alters the behavior of other mechanisms.

Recognizing that organisms must cope with variability in order to maintain their autonomy, Bich et al. (2016) develop an account of regulation, defined as the capability to selectively switch between different basic regimes of self-maintenance due to the action of dedicated subsystems or mechanisms that are specifically sensitive to these variations. Regulation entails an architecture of constraints that satisfies three main requirements: (1) Some constraints are higher order in that they modulate the activity of other constraints instead of directly channeling metabolic processes, as first-order constraints do; (2) These constraints must be sensitive to variations and capable of performing different activities; (3) These constraints must contribute to the maintenance of the system (i.e., they are functional).

The need for regulation arises not just as a response to environmental perturbations, but also as a result of the fact that autonomous organisms possess multiple capacities resulting from the constraints they construct within themselves. These cannot all be realized simultaneously due to spatial and energetic limitations and hence those needed in the current situation need to be selected. Such regulation is critical if the autonomous system is to carry out the activities required to maintain itself and avoid internal conflicts (Bich, 2018). In order for autonomous systems to succeed in building, repairing, and replicating themselves they need to regulate their activities so that they are performed when and how they are required to accomplish these ends.

Whereas the autonomy tradition arrives at the need for regulation in organisms from the perspective of the need to shift between different

⁵ These ideas are common to much of the tradition of biological autonomy, which has emphasized self-production and self-maintenance, with the exception of Piaget (1967), who addressed intrinsic change and adaptivity as he integrated the notion of organizational closure with those of assimilation and accommodation.

possible regimes in order to achieve self-maintenance, the mechanist tradition starts from individual mechanisms and the observation they are subject to control by other mechanisms that are external to them and operate on them. Winning and Bechtel (2018) characterize these other mechanisms as control mechanisms and offer an account of how they operate according to different principles while acting on the mechanisms that are responsible for the productive phenomena that have been the prime focus of the new mechanists. (To distinguish them from control mechanisms, we term the mechanisms that carry out the basic metabolic and motoric activities of organisms *production mechanisms*.) Winning and Bechtel begin with a revisionist characterization of mechanisms: rather than invoking parts performing activities, they employ the same notions of constraints and free energy that have figured in recent accounts of autonomy.⁶ Following Pattee (1972, 1973) and Hooker (2013), they borrow the conception of constraints from classical mechanics in which constraints impose limits on what are otherwise degrees of freedom through which the states of a physical system can change in time. As a result of constraints foreclosing degrees of freedom, scientists can develop accounts in terms of macroscale objects. While limiting, constraints are also enabling—by limiting how the components of the system can change, constraints enable the system itself to change in ways that it would not otherwise. A pipe, for example, constrains the flow of water, but enables it to direct water to locations it would not otherwise reach. The parts of a mechanism constitute constraints—they limit the flow of free energy within the mechanism but enable it to perform particular activities. For example, the mechanism of protein synthesis limits how amino acids are assembled into polypeptide chains but enables the regular construction of particular proteins. Activities, on this account, are not primitives, but result from free energy acting in a constrained system.

To understand how one mechanism can be controlled by another, Winning and Bechtel distinguish stable and flexible constraints within the controlled mechanism. Many constraints are highly stable—they operate in the same manner through the life of the mechanism. This undergirds the fact that even metastable mechanisms endure for periods of time and can be identified during these periods in terms of their physical constitution (Levy & Bechtel, 2020). But other constraints are flexible—they can change, and as they do, they change how the mechanism operates or even whether it operates at all. In human-made machines switches are included to enable operators to turn the machine on or off. Switches represent flexible constraints—they can assume two (or more) positions, and the activities of the related production mechanism proceed differently depending on the position of the switch. Proteins, key elements in many biological mechanisms, can often adopt two or more conformations and, depending on which one they are in, catalyze different reactions. Specific catalytic activities can be activated and inhibited by altering the conformation of the protein (e.g., through the binding of a phosphate at a particular locus).

Flexible constraints in a production mechanism make it possible for other mechanisms, control mechanisms, to control them by acting on and changing those constraints. Control mechanisms are themselves mechanisms—their behavior results from constraining flows of free energy. But what they do—alter constraints in a production mechanism—does not contribute to the product of the production mechanism, but determines whether (or how) it operates to produce its product. Their relationship to

⁶ Winning and Bechtel invoke the autonomy tradition in discussing control, embracing the claim that the need for control stems from the requirements of an autonomous system. Their main focus, however, is on addressing an issue internal to the mechanist tradition—how to explain causal processes in living organisms without treating activities as primitives, as Machamer et al. (2000) do. From the autonomy perspective, Militello and Moreno (2018) invoke the mechanist tradition to provide a characterization of how molecular machines constrain energy to produce work within the cell. The main focus, in this case, is on how the functional organization of molecular machines depends on constraints exerted by other structures in the cell.

other mechanisms it is not based on composition but on the exercise of control. Accordingly, they do not appear in the compositional hierarchy of production mechanisms but exist outside it (Bechtel, 2022).⁷

A second important feature of control mechanisms involves the constraints that determine their behavior. The flexible constraints of control mechanisms are set by carrying out measurements of one or more relevant variables. Control mechanisms make measurements by allowing flexible constraints within them to change as a result of the interaction of the control mechanism with the measured quantity. These can be regarded as sensory constraints. As sensory constraints change, they alter effector constraints in the control mechanism which direct work on the constraints in the controlled mechanism. A simple thermostat illustrates this. The temperature measurement changes sensory constraints in the thermostat. These changes propagate to the effector constraints that enable the thermostat to change constraints in the furnace it controls.⁸ The point is general: As a result of these changed constraints, the control mechanism operates differently on the controlled mechanism, setting its constraints to perform one activity rather than another.

As an extension of the mechanist framework, the account of control mechanisms provides an account of how control processes can result in altered productive activity in organisms as a result of the values assumed by different variables. By adopting this framework, the autonomy tradition can fill in its account of how control is achieved. On its own, however, the mechanist's account of a control mechanisms does not itself provide the functional perspective on control as serving the construction, repair, and reproduction of the organism. This requires that, as described by the autonomy tradition, the measurements and actions of the control mechanism generate changes in the controlled mechanisms that actually serve the maintenance of the autonomy of the organism (Bich et al., 2016). The account of control mechanism bridges the mechanist and autonomy accounts by connecting on one end to the operation of production mechanisms and on the other to the organism as an autonomous system that acts to maintain itself.

To flesh out the account of how control mechanisms operate so as to support the autonomy of the organism, consider a classic example, the *lac operon*.⁹ Ironically, this was first characterized by Jacob and Monod (1961), two of the pioneers of molecular biology that was criticized by the early pioneers of the autonomy tradition. Their project was to explain how *E. coli* adapts its metabolism depending on the food source available. When lactose but not glucose is available, the bacterium needs to transcribe and translate three genes for the enzymes required to oxidize lactose, that is, to produce the right functional constraints to cope with the availability of food sources in the environment. It is wasteful to synthesize these enzymes when glucose, a more useful energy source, is available or when lactose is absent. To avoid such wastefulness and yet

⁷ The difference can be appreciated by focusing on what work is being performed by the constrained release of free energy. Control mechanisms do not directly contribute to the work performed by the production mechanism any more than flipping the switch on an appliance contributes to the work it performs. Since they are not contributing to the work the production mechanism is performing, they often require much less energy to carry out their activities than do than the production mechanisms they control.

⁸ As argued by Bich and Bechtel (2021) the basic abstract conceptualizations provided by each tradition (Bich et al., 2016; Winning & Bechtel, 2018) of how specific control and regulatory mechanisms/subsystems work, are compatible as they employ similar concepts and assumptions, such as sensitive or sensory constraints, modulable or flexible constraints, etc.

⁹ For a more detailed discussion of the *lac operon* example in terms of regulatory constraints, see Bich et al. (2016).

¹⁰ Depending on the level of description one can either consider CAP and the lac-repressors as individual sensory-effector constraints or as control mechanisms constituted by different constraints including sensors and effectors. In this case the first option might be more parsimonious, while in more complex cases (for example including several proteins, vesicles and membranes) the second might be more informative.

produce the enzymes when they are needed to maintain the organism, the operon (the production mechanism) is controlled on the basis of two measurements performed by regulatory constraints or control mechanisms (requirement 2 for regulation): the catabolite activator protein (CAP) and the lac repressor.¹⁰ First, CAP measures whether glucose is absent. It does this by binding with cAMP, which is synthesized in cells when glucose is absent. Second, the lac-repressor protein measures whether lactose is present by binding with allolactose, a protein whose presence is typically correlated with that of lactose. When both of these happen, the two regulatory proteins constrain the operon (requirement 1) by configuring it to allow the DNA polymerase to start transcribing the three genes crucial to metabolizing lactose. Thus, the sensory components make measurements which set the constraint structure of their effector components which in turn activate the operon and bring forth a shift between different metabolic regimes. The new regime is able to cope with the change of food sources in the environment and therefore it is functional (requirement 3) in that it contributes to the maintenance of the organization that harbors it.

As this example illustrates, it is possible to cross over from a purely mechanistic understanding of a control mechanism such as proposed by Jacob and Monod (1961) to one framed in terms of supporting autonomy. But the ease of doing so should not conceal that a transition is occurring between the two theoretical frameworks. In developing the notion of constraint, Pattee (1972) argues that physicists end up speaking two different languages, one describing particles themselves and the other particles as constrained. This problem is especially severe when constraints are flexible. As Hooker (2013) argues, there is no way *in general* to incorporate flexible constraints into the basic force laws as presented in either Hamiltonian or Lagrangian formalisms. This idea of having to operate with two different languages applies as well to the different features of control mechanisms emphasized by mechanists (transforming measurements into altered constraints) and those foregrounded in accounts of autonomy (acting in the service of the maintenance of the organisms). And yet, as in the case of constraints themselves, both languages are applicable—control mechanisms act on controlled mechanisms in virtue of measurements they make, and what they measure is appropriate for maintaining the autonomy of the organism. The process of control provides a bridge at which the two perspectives can be brought together without translating or reducing one to the other.

5. Expanding the bridge between mechanism and autonomy: the organization of control mechanisms

In the previous section we showed how regulatory constraints and control mechanisms provide the basis for bridging from the mechanist perspective to the autonomy perspective.¹¹ Like other mechanisms, the activities of control mechanisms are determined by their parts and operations. But what they do is enable other mechanisms to adapt their operation to needs that the organism must address to maintain itself as an autonomous system. Control mechanisms allow a host of production mechanisms, such as those that synthesize proteins, repair components, and duplicate genes, to operate as needed so that the whole organism maintains and reproduces itself.

A single control mechanism does not yet make a system autonomous. By adding a governor to the steam engine, Watt enabled adaptive control of the steam engine—as a result of the governor, the steam engine increased or decreased its steam release as needed to maintain a constant speed despite varying loads. But even with the governor, the steam engine is not autonomous—it does not carry out the range of activities required to construct, repair, and replicate itself. This requires, from the

¹¹ We will not try to adjudicate between the vocabulary of “regulatory constraints” and “control mechanisms,” as the aim of this paper is to bring them together and explore their insights into the organization of living systems. For clarity, from now on we will adopt the terminology from mechanism.

mechanist perspective, mechanisms that perform each of these activities. From the autonomy perspective, all of these need to be controlled so that they act when needed to maintain the system. Minimally, this will require a large number of control mechanisms. The number may exceed the number of production mechanisms if one considers that production mechanisms can be and often are controlled by several control mechanisms at a time (such as in the case of the control of the *lac-operon* by the CAP and lac-repressor proteins) and that, in turn, control mechanisms can and often are controlled by one or more other control mechanisms (such as a control enzyme, inhibited or activated by other enzymes through phosphorylation).¹²

One might think of these control mechanisms as each operating independently and making its own contribution to the maintenance of the organization of the system. This will not suffice. To maintain itself, an autonomous system needs to evaluate measurements of different types of quantities and integrate them in the control of its components. Not only do individual production mechanisms need to be controlled, but their operations need to be coordinated for a variety of reasons. Some mechanisms simply cannot act at the same time—for example, they require different use of the same spatially localized structure. Timing of different operations is often important—digestive operations need to occur after eating, not during fasting, but they require anticipation so as to start the activation of some digestive functions in advance of food intake so that they are ready when needed. In addition, the operation of each mechanism makes energy demands on the organism, and only so much energy is available. For the organism to maintain its autonomy it is not enough that different mechanisms be controlled but that control be integrated. In this section we explore integration of control mechanisms. Doing so will reveal not a single bridge from mechanism to autonomy but a complex network of control mechanisms linking production mechanisms to the demands of autonomy.

As we have noted, discussions of autonomy are often abstract, referencing closure of constraints but without providing detailed accounts of how, in any given organism, such closure is obtained. This is not surprising—without details about the mechanisms that are deployed in

¹² The importance of taking into consideration the complexity of control has been emphasized for example by Keller (2005). She discusses how properties attributed to the DNA are relational, not dependent on sequence alone, and how patterns of gene expression are “under the control of a vastly complex regulatory apparatus” (Keller, 2005, p. 4). She points out the importance of focusing not only on the structure of DNA and protein products but on the communication networks of which the DNA and proteins are part. Her approach is different from ours, as she advocates for a framework based on a relational dynamic epistemology that takes into consideration the dynamics of these networks in time. Although we consider time and change as fundamental features of control, we focus here on more the relational side, conceptualizing production and control mechanisms in the contest of a biological autonomous system. As discussed by Moreno and Suárez (2020), mechanistic approaches provide causal explanations while dynamic network approaches provide information on global dynamical properties of large sets of interacting entities. Some work on network models (discussed in Bich & Bechtel, 2021) has simulated dynamical properties based on abstract theoretical models of biological systems such as Rosen’s M/R-Systems (Piedrafita, Montero, Morán, Cárdenas, & Cornish-Bowden, 2010) and Kauffman’s autocatalytic sets (Hordijk, Steel, & Kauffman, 2019). Other theorists (Huneman, 2010; Jones, 2014; Kostić, 2018; Suárez & Deulofeu, 2019) go further, advocating for the distinctive explanatory potential of abstract network analysis not grounded in knowledge of underlying mechanisms. Green et al. (2018) analyze the diversity of network analysis in systems biology, considering both those that are grounded in traditional mechanistic strategies and those that are not so grounded and seek to advance novel strategies for dealing with biological complexity. We contend that conceptualizing, understanding, and explaining the mechanistic details of the parts, their operations, and their organization, is important if network models are to provide reliable and biologically relevant descriptions of global properties. See Bich and Bechtel (2022) for a discussion of intracellular signaling control networks and how they can be understood by integrating mechanisms, networks and pathways.

generating, repairing, and reproducing the organism, one cannot elaborate on the overall organization through which closure is realized. Accordingly, a reasonable strategy is to build from specific local control mechanisms to the global organization through which autonomy is obtained. Bich, Mossio, and Soto (2020) have adopted this approach of starting locally to explain glucose regulation in mammals. They begin by identifying the relevant processes involving glucose, the timescale at which they proceed, and the constraints responsible for them. The second step identifies the control mechanisms (such as insulin release from pancreatic cells) which are responsible for regulating the production mechanisms so that they act adaptively in the face of internal and external variations. This step can then be iterated by including in the picture additional control mechanisms (such as the nervous system) which in turn may regulate the control mechanisms identified at the second step.

The challenge is to determine how multiple control mechanisms work together to regulate the various production mechanisms so that each operates as needed to maintain the whole system. One way to conceptualize integration and coordination of control is in terms of a pyramid in which, at each level multiple control mechanisms are subsumed under one, with a single control mechanism at the top.¹³ The top-level controller integrates inputs from the parts of the system and determines the operations for the whole organization, while individual lower-level control mechanisms serve only to implement its directives. For such an architecture to be viable, the top controllers must determine all the required operations and ensure that they are mutually satisfiable. Implementing such a scheme requires a high level of sophistication that is hard to realize even in social systems in which the top level of control is a human with great cognitive capacities. It is difficult to envision such an intelligent control mechanism operating in organisms.

There is a further problem with organizing control in this way in biology. Establishing it takes forethought—developing an appropriate organizational plan and providing the means for each control agent to acquire the requisite information and to carry out the appropriate control operations. This is unlikely to develop through a process of evolution. What is more likely is that control mechanisms in living organisms are added incrementally over evolutionary time starting with controllers that measure specific information and use that to control one production mechanism (see, for example, Keller, 2011). When new control mechanisms render whole organisms better able to maintain themselves given the challenges they face, they are likely to be maintained by evolution. A powerful way of building up control mechanisms piecemeal is to construct a new one by modifying the relation between the sensory and effector part of an existing control mechanism by, for example, allowing different effectors to take advantage of the same sensory unit or a given effector to respond to multiple sensory units. In such a manner, even as the control mechanisms become organized in more complex ways, they are the product of incremental additions over the course of evolution, not an intelligent designer.

One motivation for thinking that control mechanisms were added piecemeal in evolution is provided by the observation that the basic production mechanisms required to maintain a living organism appear all to have been acquired early in evolution—organisms required the ability to synthesize their components, procure and utilize energy, restrict flows of matter and energy over their boundaries, and replicate themselves. Changing basic production mechanisms to adapt to environmental variation would require each time a modification of these basic capabilities with the risk of disrupting the whole system. A more likely scenario for phylogenetic change would involve modifying control mechanisms so as to use existing mechanisms in novel ways while retaining their original contributions (Kirschner & Gerhart, 2005).

¹³ The notion of level applied to control mechanisms is distinct from the notion of mechanistic levels. It is not based on composition but on exercise of control. See Bechtel (2022) for discussion.

The result of such an accretion process is that, despite the fact that individual control relationships (between control and controlled mechanism) are locally hierarchical, the collection of control mechanisms ends up being organized heterarchically.¹⁴ We characterize heterarchy in terms of three distinctive features. First, as argued before, at any level, there may be more control mechanisms operative than controlled mechanisms. Second, there are, even at the highest level, such as it usually ascribed to the nucleus of the cell or the nervous system, multiple controllers operating relatively independently. Third, in many cases, control mechanisms form cycles, in which the output of one mechanism exercises control over a component of the second, while the output of the second in turn exercises control over a specific component of the first. This undercuts a single ordering of levels. In addition, control relations, such as those performed in the mammalian lateral hypothalamus (Admantidis & de Lecea, 2008), may link together seemingly independent activities such as digesting food and maintaining alertness. A further complication is that different control processes may act on different timescales. The result may be an imbricated network manifesting complex dynamics.

Recognizing that the organization of control mechanisms in living organisms is heterarchical makes the initial challenge of accounting for integration even more challenging. Without an agent overseeing others and resolving conflicts, it might be thought likely that conflicts will rise between control mechanisms and, as a result, between the mechanisms they control. Although conflicts between production mechanisms do arise, they are infrequent in organisms existing today. Evolution provides a possible explanation for this. Those organisms in which novel control mechanisms impair the functioning of other mechanisms and thus undercut the autonomy of the organism will tend not to replicate, and their new control mechanisms will disappear. Those that are passed on will tend to harmonize with those already evolved, at least in the environments in which they first arose. In new environments, conflicts may surface. If the population includes variant control mechanisms, some organisms in the population may be able to accommodate the new environment and their control mechanisms will continue to be inherited. Other organisms will die without reproducing, and their control mechanisms will disappear. Successful integration of control mechanisms may, accordingly, be in part the product of a history of incremental addition of new control mechanisms, with selection tending to preserve those that enable the organism to adapt to its challenges. This scenario does not preclude active coordination between control mechanisms (we consider examples of this below) but it does suggest that a higher-level supervisor is not always required for integrated control.

To illustrate the heterarchical organization of biological control mechanisms, below we consider examples from various orders of organisms. But a useful place to start is with research to create protocells. In this endeavor, researchers confront the task of designing systems that exhibit the autonomy manifest in living organisms. To synthesize a living system, multiple production mechanisms must be integrated—those that build the system, those that process energy through the system, those that replicate the system, etc. Gánti's (1975) proposal of a chemoton was a pioneering effort in this direction. At the core of his proposed system was a metabolic mechanism modeled on the Krebs cycle which also served to synthesize a membrane. This provided a semipermeable barrier that kept an appropriate set of component chemicals together and

allowed for export of waste products that would otherwise impair the system. Gánti conceptualized the chemoton as replicating through division when the set became too large. He also, however, recognized the need to regulate division, and incorporated a control mechanism that would track how long the chemoton had been operating and trigger division.¹⁵ Although Gánti's account might be viewed as the product of an intelligent planner, his own thinking seemed to reflect the incremental addition of components as needed to address issues with earlier proposals.

Gánti proposal was theoretical, but subsequently a variety of researchers have tried to construct actual protocells that exhibit autonomy (Rasmussen et al., 2009; Ruiz-Mirazo, Briones, & de la Escosura, 2014). Designs may be inspired by biological cells, but the project is an engineering one of putting molecular components together. The issue of control, especially of membranes, looms large for these investigators. Protocells must be designed with a basic metabolism capable of synthesizing the phospholipids that constitute their membrane and to incorporate phosphoproteins into these membranes so as to provide channels through which specific molecules are admitted or expelled from the cell. However, protocell designers recognize they must build in mechanisms that regulate channels so as to avoid osmotic crises and to ensure that materials enter and are expelled consistently with the needs of metabolism (Ruiz-Mirazo & Mavelli, 2008). This has been an ongoing process in which protocells are designed, evaluated, and redesigned, typically by adding new control processes to regulate the mechanisms already incorporated into the proposed protocell. The manner in which the engineering effort has proceeded is suggestive that control mechanisms have been added incrementally in the course of evolution.

Turning from the engineering of protocells to the study of an actual single-celled organism, in the bacterium *E. coli* we find multiple control mechanisms operating in relative independence. We have already discussed the control mechanisms acting on the *lac operon*, which determines which enzymes are synthesized in response to what sugars are available. A different control challenge is to understand how membrane proteins are regulated. These are controlled based on measurements of concentrations gradients inside or outside the cell itself as well as by signals (phosphorylated proteins) that transmit measurements of specific variables from metabolism or the environment (Karpen, 2004; Kulasekara & Miller, 2007). Signals from the membrane, in turn, serve to regulate gene expression, including of membrane constituents (Stock, Ninfa, & Stock, 1989). Separate from these, the flagellum that enables *E. coli* to navigate its environment is controlled by a sensory system, consisting of a complex of five transmembrane proteins sensitive to different molecules. These measure the change in concentration of nutrients, toxins, and the energetic state of the bacterium itself. A process that integrates these measurements results in setting the phosphorylation state of CheY, which determines which direction the flagellum motor turns and consequently whether the bacterium moves forward and tumbles.

It is notable that the control mechanisms we have identified in *E. coli* are all relatively independent of each other, not under the control of a central control mechanism. While there is little evidence about when and how these control mechanisms appeared in the *E. coli* lineage, it seems plausible that each was introduced independently and was retained if it served to promote the autonomy of the organism. (For discussion of additional control mechanisms in *E. coli* and how they are

¹⁴ See Winning and Bechtel (2018) and Bechtel and Bich (2021) for work on the notion of heterarchical control, inspired by Pattee (1991). Here we further develop this idea in relation to the integration and coordination of control mechanisms. The question of whether control relations depart from hierarchical organization is distinct from that of whether mechanisms are organized hierarchically (Bechtel, 2022). The latter is a question of composition, but as we developed in section 4, control mechanisms do not include the mechanisms they control as parts, but are external mechanisms that act on the mechanisms they control.

¹⁵ Recently, it has been pointed out that even a relatively simple hypothetical prebiotic system such as the Chemoton would require additional mechanisms for the control of membrane permeability (Ruiz-Mirazo & Mavelli, 2008). Otherwise “a chemoton could not take up food (X) or excrete waste (Y) without also possibly losing its core metabolic molecules (Ai), genetic monomer precursors (VO) and polymers (pVn), and membrane precursors (R, Tn) to diffusion and thus its inherent unity, dynamic or inherent stability, regulation, and control” (Griesemer, 2015, p. 26).

heterarchically organized, see Bich & Bechtel, 2022.) Little is known about coordination between different control mechanisms in *E. coli*, but a bacterial example of a global control mechanism that interacts with specific control mechanisms is found in many cyanobacteria. As photosynthetic organisms, cyanobacteria produce molecular oxygen, which is inimical to the enzymes they use to fix nitrogen. Some species of cyanobacteria overcome the problem by having different organisms perform nitrogen fixation and photosynthesis, while others segregate the conflicting activities to different times of day in a single organism. To do this, they evolved a circadian clock that is entrained to the light-dark cycle in the bacterium's environment (by measuring redox state as a proxy for light in the environment). The clock controls gene expression so that different genes are expressed when light first appears and when night starts (Cohen & Golden, 2015). While producing a global effect on gene express, the circadian control mechanism is still just one control mechanism amongst many, with others exercising more specific control over which proteins are expressed and how they are regulated post translation.

We find much the same situation involving multiple control mechanisms, some very specific and some more global, when we turn to eukaryotic cells and multi-cellular organisms. Within single-cell eukaryotic organisms such as yeast there are a multitude of control mechanisms responsible for initiating processes such as cell division, regulating metabolism, beginning protein synthesis, performing DNA repair, and carrying out autophagy. In multi-cellular organisms different control mechanisms are operative in different tissues, resulting in different patterns of gene expression. This not only accounts for different cell types found in different tissues but for their changing patterns of activity as conditions vary.

In multicellular organisms there is often a need for control mechanisms to make measurements of conditions distant from the production mechanisms they control. In plants and animals, this is often accomplished by sensory constraints in cells in one part of the organism releasing chemical signals that are transmitted through the organism (for example through vascularization) and taken up in other parts where effector constraints result in altered behavior. One consequence of releasing a signal that travels long distances is that it opens up new possibilities for other control mechanisms to be added that respond to the same signal and effect action on different production mechanisms.

In animals, neurons play important roles in achieving distal control. However, once again, control is heterarchical. A plausible hypothesis for the first evolutionary role for neurons is to facilitate coordinated contraction of muscle cells (Keijzer, van Duijn, & Lyon, 2013). Once such control mechanisms were in place, other control mechanisms that sense specific information (e.g., presence of food or a predator) could then act on these already functioning control mechanisms to generate contractile behavior in conditions in which the organism needs it (for several examples in jellyfish, see Mackie, 2004). In the nematode worm *C. elegans*, numerous neural circuits exist to coordinate responses (e.g., forward or backward movement) to various stimuli that individual neurons detect (Bargmann & Marder, 2013). In subsequent invertebrates such as the medicinal leech, these circuits are localized in ganglia along the organism's body that each effect control over locomotor and other behaviors. This is accomplished without a central controller, but through different ganglia sending and receiving signals from each other so as to generate coordinated action (Kristan, 2017).

In sum, in heterarchical control organizations at least four different strategies are employed to integrate the operations of control mechanisms and coordinate them to maintain the organism. The simplest way is for the controlled mechanism, rather than a main controller, to integrate the effects of different control mechanisms. Individual control mechanisms operate on different flexible constraints as a result of measuring different variables, and the controlled mechanism determines the response to different combinations of actions on it by multiple control mechanisms. For example, the *lac operon* integrates the measurements about two food sources (by responding to the CAP and lac-repressor

proteins) and either initiates or continues to inhibit the synthesis of genes required to metabolize lactose. The second strategy consists in control mechanisms themselves possessing several sensitive constraints that enable them to measure different variables. The transmembrane receptor complex of *E. coli* involved in chemotaxis is an example of this form of integration. But the transmembrane receptor is, in turn, controlled by other mechanisms sensitive to different internal and external variables. The third strategy is to employ one complex mechanism that controls several production mechanisms. An example is the global control mechanism represented by the circadian clock. As we have seen, even a global controller such as the circadian clock is, in turn, controlled by several other mechanisms at different levels. The fourth strategy is to rely on signaling networks that transmit and integrate the result of multiple measurements and enable multiple control mechanisms to affect different production mechanisms. We illustrate this below with examples of neural control mechanisms.

Over the course of invertebrate evolution, many neural control mechanisms became localized in a brain at the front of the organism (Arendt, Tosches, & Marlow, 2016). This may suggest that hierarchical control replaced heterarchical control with the brain serving as a central executive. But this is misleading. Even in vertebrates, much of the brain consists of distinct nuclei, each of which integrates information from multiple sources and exercises partial control over different activities. The hypothalamus provides an illustrative example. It contains nuclei that are devoted to control of eating and drinking, sleep and alertness, responses to stress, and reproduction. Although there are signals sent between these nuclei, each nucleus for the most part performs its own control activities based on information it collects (Leng, 2018). Interconnections enable individual nuclei to modulate their control activities in light of the control activities performed by other nuclei, but this integration does not give rise to a central executive but rather to more distinct controllers. In addition, the nervous system (both central and peripheral) interacts with the immune system with control processes operating in both directions (Badimon et al., 2020; Schiller, Ben-Shanan, & Rolls, 2020).

Integrating multiple sources of information does not require centralization. One way different nuclei inform each other is through the release of volume transmitters (e.g., serotonin, dopamine). Unlike classical neural transmitters, which are released and reabsorbed at individual synapses, volume transmitters disseminate widely from where they are released. For each volume transmitter there are numerous different receptors that enable different brain regions to respond in different ways to a common signal. Although these volume transmitters enable large-scale coordination across the organism, what they accomplish is integration of activity, not the creation of a central executive (Guidolin, Marcoli, Maura, & Agnati, 2017; Taber & Hurley, 2014).

For an organism to achieve *closure* and maintain itself, it needs to control its various production mechanisms. In the previous section we introduced control mechanisms. In this section we took up the question of how these control processes can be organized (that is, integrated and coordinated) so as to enable the whole organism to maintain itself. We contrasted hierarchical control, in which a central controller receives information and directs activities throughout the whole system, with heterarchical control in which control is distributed among multiple control mechanisms. We also argued that heterarchical control is likely to have evolved in biological organisms through the incremental incorporation of new control mechanisms that measure additional variables or that integrate the measurements performed by other control mechanisms and act on various mechanisms in light of these measurements. Control mechanisms that enhance the ability of the organism to maintain itself are more likely to be inherited. Research on protocells illustrates that the challenge is not so much to incorporate appropriate production mechanisms but to incorporate appropriate control to regulate them.

Today's single-cell organisms are the products of nearly four billion years of such evolution and, as we have observed in the case of *E. coli* and cyanobacteria, contemporary organisms have accumulated numerous

control mechanisms that enable them to maintain themselves. Evolution seems to have succeeded in deploying relatively independent control mechanisms that succeed as a collective. With eukaryotic cells and especially multicellular organisms, however, the demand for coordination between control mechanisms is greater. Accordingly, one finds signals released by individual cells that are responded to by others, where the recipient cell determines the response. Neurons are organized into ganglia that integrate information that controls specific activities. These signal to each other, but nonetheless carry out their own control functions as part of a heterarchical network (Bechtel & Huang, 2020).

6. Conclusion: organizing organized mechanisms in organized autonomous organisms

Both the new mechanists and proponents of the autonomy perspective emphasize organization. Our first goal in this paper was to analyze the two modes of organization invoked by each, discuss their differences, and identify their compatibilities. The new mechanists emphasize how mechanisms can be put together to constitute higher-level mechanisms that are responsible for phenomena that none of their components can produce on their own. This involves providing productive continuity between the component mechanisms. The proponents of autonomy are concerned with how the activities of an organism serve the construction, repair, and reproduction of a system that, to maintain itself far from equilibrium with its environment, must act adaptively.

Both senses of organization are important for understanding biology. Our second goal has been to bridge between these conceptions of organization by demonstrating how both maintaining autonomy and understanding biological mechanisms requires taking into account the problem of regulation and control. Having characterized parts of mechanisms as constraints that direct flows of free energy into the performance of work, we have distinguished control mechanisms as acting on flexible constraints of other mechanisms in response to measurements they make about the state of the organism and its environment. Understanding control mechanisms requires two perspectives, one in which they are integrated into the productive continuity of the organism and another in which they act on and alter the operation of other mechanisms because of the measurements they make. Drawing from both traditions we have developed implications of the notion of control for an understanding of how biological organisms are integrated systems. Specifically, we have discussed how control mechanisms are themselves organized in such a way that they realize a heterarchical architecture within which their activities can be viably coordinated.

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Declaration of competing interest

None.

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