

Biological Mechanisms: Organized to Maintain Autonomy¹

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1. Introduction

The reference to systems in the name *systems biology* points to a holistic emphasis that opposes an extreme reductionistic, mechanistic approach to biology that champions decomposition of biological systems into their molecular constituents and emphasis on such constituents in explanations of biological phenomenon. For some theorists who adopt the name *systems biology* (see, for example, van Regenmortel, 2004; Kellenberger, 2004) this entails repudiating the whole tradition of mechanistic biology. On this view, only by maintaining a focus on the whole system in which biological phenomena occur can one hope to understand such phenomena. Many other advocates of systems biology, including the editors of this volume (Boogerd et al., 2002; Boogerd, Bruggeman, Richardson, Stephan, & Westerhoff, 2005; Bruggeman, Westerhoff, & Boogerd, 2002; Bruggeman, 2005), view the focus on systems as providing an important corrective to overly reductionistic mechanism, but construe the resulting understanding to be compatible with a mechanistic perspective. To evaluate the fate of mechanism within systems biology requires us to examine carefully the commitments of mechanism. Mechanism, I will argue, has the conceptual resources to provide an adequate philosophical account of the explanatory project of systems biology, but it can do so only by placing as much emphasis on understanding the particular ways in which biological mechanisms are organized as it has on discovering the component parts of the mechanisms and their operations.

For philosophy of science, the emergence of anti-mechanistic voices in biology is ironical since philosophers of science have only recently recognized and appreciated the ubiquity of appeals to mechanism in biological explanations and offered models of explanation in terms of mechanisms (Bechtel & Richardson, 1993; Glennan, 1996; 2002; Machamer, Darden, & Craver, 2000; Bechtel & Abrahamsen, 2005).² These accounts of mechanistic explanation (which I discuss in section 2) attempt to capture what biologists themselves provide when they offer explanations of such phenomena as digestion, cell division, and protein synthesis. Like the biological accounts on which they are modeled, the philosophical accounts of mechanisms have tended to focus more on the component parts and operations in mechanisms than on how they are organized. Thus, while these accounts have identified organization as an important aspect of any account of a mechanism, they have not focused on the particular modes of organization that are required in biological systems. As a result, they fail to answer the objections of the holist critics (discussed in section 3) who claim that mechanisms, and mechanistic science, are inadequate to the phenomena of life.

¹ I thank Fred Boogerd, Frank Bruggeman, Andrew Hamilton, Alvaro Moreno, Adam Streed, and Cory Wright for very useful discussions and helpful comments on earlier drafts of this paper.

² Until the recent rise of mechanist accounts, most philosophical accounts of explanation viewed universal laws as the key element in an explanation (see, for example, Hempel, 1965, for the canonical presentation of the deductive-nomological model). This has seemed particularly problematic in the context of biology, since biologists infrequently offer laws, and when offered, they seem more to describe the phenomena than to provide explanations of it.

Part of the challenge of developing an adequate account of mechanism stems from the fact that when thinking about how mechanisms are organized, humans tend to think in terms of linear pathways: the product of the operation of one part of a mechanism is passed to another part of a mechanism, which then performs its operation.³ But natural systems (and increasingly engineered systems) rely on far more complex, non-linear modes of organization. Understanding the significance of modes of non-linear modes of organization is daunting, as the history of the development of the concept of negative feedback exemplifies. Many centuries passed between its first known application by Ktesibios in approximately 270 BCE to insure a constant flow of water into a water clock, until it was recognized as a principle of organization that enabled controlled behavior by complex systems. In the subsequent two millennia it had to be repeatedly rediscovered in different contexts in which control was needed (Mayr, 1970). For example, windmills need to be pointed into the wind, and a British blacksmith E. Lee developed the fantail as a feedback system to keep the windmill properly oriented. When furnaces were developed, temperature regulation became important and Cornelis Drebbel designed such a regulator around 1624. A major turning in the recognition of negative feedback as a common design principle followed James Watt's introduction in 1788 of a governor for his steam engine (Figure 1). This

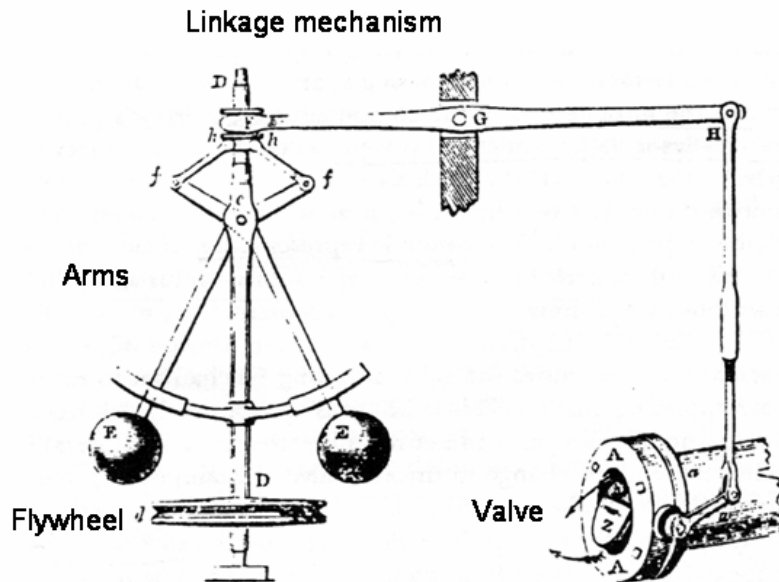


Figure 1: A schematic representation of the governor James Watt designed for his steam engine. The speed of the flywheel determines how far out the angle arms move by centripetal force. They are in turn linked to the valve in such a way that when the flywheel is turning too quickly, the steam supply is reduced, and when it is turning too slowly, the steam supply is increased. Drawing reproduced from J. Farley (1827), *A treatise on the steam engine: Historical, practical, and descriptive*, London: Longman, Rees, Orme, Brown, and Green.

³ This linear focus is highlighted in Machamer, Darden, and Craver's characterization of mechanisms as providing continuous accounts from start up to termination conditions. This emphasizes the role of mechanisms in producing things, but at the cost of downplaying the often cyclic nature of their internal operation. This tendency is exhibited in biochemists portrayal of chemical pathways such as fermentation as linear streams from starting substances (glucose) to products (alcohol). Various reactions such as the reduction of NAD^+ are shown to the side of the main linear pathway, but following these reactions often reveals cyclic relations which link different reactions in the main pathway (see Bechtel & Richardson, 1993, chapter 7).

became the focus of mathematical analysis by James Clerk Maxwell (1868). The idea of feedback control was further developed and utilized in a variety of fields in the late 19th and early 20th centuries. For example, it was employed for automated ship and airplane navigation; Elmer Ambrose Sperry developed a version of the gyroscope adequate for such functions in 1908 and in 1910 founded the Sperry Gyroscope Company. During World War I he became involved in the design of devices to guide anti-aircraft fire and continued to provide guidance to the U.S. military in the interwar period.

Although the system Sperry developed, the T-6 anti-aircraft gun director, used negative feedback in its internal analog computations, it did not use feedback from the target (Mindell, 1995). In the 1930s Norbert Wiener and Julian Bigelow at MIT tried to apply feedback from the target to control anti-aircraft fire. They soon encountered an obstacle: if the feedback signal was at all noisy and the system responded too quickly, feedback caused it to go into uncontrollable oscillations. Through consulting Mexican physiologist Arturo Rosenblueth, they learned of similar behavior in human patients with damage to the cerebellum and came to recognize the importance of dampening the feedback signal to achieve reliable control. The limitations they found in negative feedback did not dissuade them of its importance; to the contrary, it suggested to them that it was a fundamental principle of design in biological systems and, they proposed, social and engineered systems as well. In a paper published in *Philosophy of Science*, they argued that negative feedback provided a means of resuscitating notions such as purpose and teleology, enabling these concepts to be applied to both biological and engineered systems without invoking vitalism (Rosenblueth, Wiener, & Bigelow, 1943). Their idea was straightforward and powerful—if feedback enabled the system to maintain a given temperature, then maintaining that temperature was that system's goal or telos. Wiener and his collaborators championed the notion of negative feedback as a fundamental principle of design, and with support from the Macy Foundation, they established a series of twice-yearly conferences known as the Conference for Circular Causal and Feedback Mechanisms in Biological and Social Systems. Wiener later coined the term *cybernetics* from the Greek word for *steersman* (Wiener, 1948) for feedback control. Thereafter, the conference he and his collaborators had begun was called the *Conference on Cybernetics* and the term *cybernetics* was applied generally to the movement that attempted to understand control in biological and artificial systems in terms of negative feedback. In section 4 I will show how negative feedback, along with such notions as maintaining a constant internal environment, provided an important step in biologists' attempt to address the concerns of vitalists.

As challenging as it was for humans to master the concept of negative feedback, it is the simplest of non-linear modes of organization to understand. Once the idea of control via negative feedback is explained, the principle becomes relatively intuitive. The functionality of other non-linear modes of organization is more difficult to understand intuitively. Organization involving positive feedback systems has often been rejected as leading only to systems that run out of control.⁴ But in the 20th century theorists gradually recognized that in some cases positive

⁴ The concern is, in fact, often well-founded. Basic metabolic pathways such as glycolysis involve a positive feedback system: ATP, which is produced by the pathway, is also used to prime the pathway, being consumed in the initial reactions of the pathway to produce hexosemonophosphate and fructose 1,6-biphosphate. In normal yeast a negative feedback from hexosemonophosphate (through the production of trehalose 6-phosphate, which inhibits hexosekinase, the enzyme responsible for the synthesis of hexosemonophosphate) serves to regulate the priming step so that too much hexosemonophosphate and fructose 1,6-biphosphate do not accumulate. In a mutant in which this negative feedback is removed, however, positive feedback continues unabated as long as ATP is available and the

feedback can enable systems to self-organize. It is interesting to note, though, that when Boris Belousov first proposed the reaction now known as the Belousov-Zhabotinsky or B-Z reaction, his paper was rejected on the grounds that such self-organizing reactions are inherently impossible. In the half century since his pioneering investigations, self-organizing systems of reactions have come to be viewed by many theorists as providing the basis for understanding such things as the origins of living systems (Kauffman, 1993; Nicolis & Prigogine, 1977). Nonetheless, in many circles the potency of self-organizing positive feedback systems to create and maintain organized systems remains under-appreciated.

Cyclic organization came to the focus of biology in the 20th century with the discovery that large numbers of biological systems involve cycles. These include various biochemical metabolic cycles, the cell cycle and cycles of reproduction, and cycles through the biosphere such as the carbon and nitrogen cycle (Smil, 1997). In section 4, I focus on the discovery of cycles in biochemistry and their significance for understanding mechanisms in living organisms. I draw in particular on the work of Tibor Gánti, who, recognizing how cycles differed from ordinary chemical reactions, developed a way to represent stoichiometric relations within cycles so as to trace the flow of matter through such systems. From this starting point Gánti went on to articulate an account of how cyclic organization could be harnessed to provide the core of a minimal chemical machine that would exhibit many of the fundamental properties of a living organism.

Non-linear modes of organization provide the tools for understanding the organization of living systems, but further conceptual analysis is required to understand the significance of such organization for accounting for the features of life. Such a framework can be provided if we focus on living systems and some of their salient features. One of the major claims of the cell theory, as it developed in the 19th century through the endeavors of Schleiden, Schwann, Virchow, and others, is that the cell is the fundamental living unit (Bechtel, 1984; 2006). Two things are salient in this claim. First, the cell is a unit—it is an entity whose identity is maintained over time despite exchanges of matter and energy with its environment. Second, as a living entity, a cell is an active agent. Unlike a rock or a crystal, for example, it initiates operations that affect both itself and its environment. To these basic claims recent theorists have added a third claim—many of these internally initiated operations serve to maintain the existence of the system itself. These operations loop back on the cell itself so as to form and repair its own structure so as to enable it to continue to operate. The term *autonomy* is often used to describe this capacity of cells, as the most fundamental units of life, to initiate operations that maintain themselves. I will develop the idea of organization that maintains and enhances autonomy in section 6.

Many of the theorists who have pursued the sorts of themes about non-linear organization that I discuss in this paper have presented them as undermining mechanistic science. A clear example is Robert Rosen who emphasized the role of non-linear organization in maintaining metabolic repair. As I discuss in section 6, he focused on how repair in organisms originated within the system so that the whole system was “closed to efficient causation.” He presented such organization as a radical departure from the principles of mechanistic Newtonian science and offered them as the basis for a very different, non-mechanistic science (Rosen, 1991; see also Mikulecky, 2000). While I too will be making much of the importance in living systems of cyclic

yeast fail to grow despite plentiful glucose and an otherwise intact glycolytic pathway (see Teusink, Walsh, van Dam, & Westerhoff, 1998; I thank Fred Boogerd for pointing me to this example.).

organization, I do not consider this as requiring a rupture with mechanistic science, but as helping to fill out the picture of what mechanisms are capable of doing when they are organized appropriately.⁵

2. The Basic Conception of Mechanism

I begin with a basic characterization of mechanisms that captures many of the features that have figured in recent philosophical accounts of mechanism. I will then elaborate it into a framework for mechanistic explanation. A mechanism

is a structure performing a function in virtue of its components parts, component operations, and their organization. The orchestrated functioning of the mechanism is responsible for one or more phenomena (Bechtel & Abrahamsen, 2005).

The first thing to note about this characterization of mechanism is that a mechanism is responsible for a phenomenon (Bogen & Woodward, 1988) that is here characterized as the function of the mechanism.⁶ The identity conditions for a mechanism are provided by the phenomenon such that what count as parts, operations, and organization are determined by the phenomenon (Kauffman, 1971). By characterizing a mechanism as a structure I mean to emphasize that it consists of an arrangement of parts and has at least some enduring identity. Sequences of causal operations not organized into an enduring system are not mechanisms on this account.

Just as mechanisms themselves are identified in terms of phenomena, mechanistic explanation starts with a characterization of the phenomenon to be explained and seeks to characterize the responsible mechanism. Researchers do not simply hunt for mechanisms, but seek them to explain an already identified phenomenon. Part of identifying a phenomenon involves empirical research that identifies environmental conditions under which the phenomenon will appear. For example, Pasteur determined that yeast perform fermentation when in an oxygen-free environment. This does not mean that the characterization of the phenomenon remains fixed; on the contrary, investigating the responsible mechanism may lead researchers to revise their conception of the phenomenon (in Bechtel & Richardson, 1993, we characterized this as "reconstituting the phenomenon"). For example, research on metabolic mechanisms in organisms began by construing them as responsible for the generation of heat (Mendelsohn, 1964). Only after Karl Lohmann's (1929) discovery of adenosine triphosphate was it recognized that the point of metabolism was to convert the energy of foodstuffs into a chemical substance which could then provide energy to other vital processes. The phenomenon was then reconstituted in a very different way.

⁵ A similar integration of the basic mechanistic view with a focus on system organization is advocated by Ruiz-Mirazo and Moreno (2004, p. 238) "*system thinking* does not imply forgetting about the material mechanisms that are crucial to trigger off a biological type of phenomenon/behavior; rather, it means putting the emphasis on the interactive processes that make it up, that is, on the dynamic organization in which biomolecules (or, rather, their precursors) actually get integrated."

⁶ There are two important features of this characterization. First, in characterizing the resulting phenomenon as the function of the mechanism, I am not committing myself to an evolutionary analysis of function in the manner of Wright (1972). Indeed, as I note below, the construal of biological systems as autonomous systems provides the basis for a very different characterization of function. Second, while there is a significant amount of flexibility available to the scientist in demarcating the phenomenon and determining whether the researcher is dealing with one or more than one phenomena, if the researcher demarcates multiple phenomena, then the researcher will offer multiple, potentially overlapping, mechanisms to account for them.

The second feature of mechanistic explanation to emphasize is that the component parts and operations of a mechanism are within the mechanism and can only be identified by taking the mechanism apart, either literally or conceptually.⁷ There is a compositional relation between parts of a mechanism and the mechanism itself, and so it is useful to characterize the parts as at a lower level than the mechanism itself.⁸ Appealing to parts and their operations is reductionistic, in a sense familiar to scientists, although not necessarily to philosophers.⁹ But it is important to be clear on what the appeal to parts and their operations is designed to do—it explains what resources a given mechanism has that enable it to behave in a particular way when in the context in which it functions. It does not, in any way, supplant the need to identify the manner in which the mechanism as a whole operates under various conditions in its environment. Moreover, and especially important for the purposes of the current paper, it does not mitigate the importance of considerations of how the parts are organized for explaining what the mechanism does or indeed for understanding how a part of the mechanism is operating. It is an important feature of mechanistic explanation to recognize that parts will operate differently under different conditions,¹⁰ and that the organization in which they are incorporated is often a major factor in determining these conditions and hence the operation performed by the part.

Identifying parts and operations are challenging activities. Not every way of carving up a mechanism yields *working parts*—parts that perform operations that figure in the explanation of the ability of a mechanism to perform its function. Moreover, it is often challenging to figure out what sorts of operations might give rise to the function. Biochemistry only made headway when biochemical groups were identified and biochemical reactions were recognized as operations over such groups (Holmes, 1992). There are many cases in which researchers sought evidence for one sort of operation only to discover later that a very different type of operation was responsible for the phenomenon. A classic example is that biochemists, following the lead of E. C. Slater (1953), assumed that the energetic intermediate in ATP synthesis in oxidative phosphorylation would involve a chemical compound and only gradually recognized, after Mitchell (1961) advanced a very different alternative relying on an ion gradient over a membrane, that they were seeking the wrong kind of operation (Allchin, 1997).

⁷ Although literal decomposition has often been a productive strategy in biological research for identifying the operation associated with a component (e.g., isolating an enzyme through fractionation), it can also disrupt the operation when it is dependent on coordinated interactions with other components. A clear example is that the rate at which an enzyme catalyzes a given reaction is dependent on the concentrations of substrates, products, and effectors. Often the effects of being embedded in a particular organization are only realized after noting the differences in behavior in the original system and the isolated component and determining the role of the organized setting in determining the operation of the component. Hence, in the end decomposition is often conceptual rather than literal—in a model the theorist specifies an operation performed by the part and how that performance relates to other operations occurring within the mechanism.

⁸ Although this conception of levels is compositional in the sense articulated by Wimsatt (1976), the levels that result are only defined locally within the mechanism. Moreover, there is no requirement that the parts that interact with each other are of remotely the same size dimensions—in one mechanism membranes may interact with whole bacterial cells whereas in another they may interact with ions. Accordingly, the conception of reduction that emerges is local since the levels to which a scientist appeals are only identified in the context of the attempt to explain a given phenomenon. Moreover, typically a given investigation goes one or two levels down. There is no goal of reducing all sciences to some most fundamental one (Bechtel, 2006).

⁹ In particular, this sense of reduction does not focus on theories and logical relations between them, as in classical philosophical accounts of theory reduction (Nagel, 1961). For discussion, see Bechtel and Hamilton (in press).

¹⁰ Boogerd et al. (2005) emphasize the fact that parts behave differently under different conditions and invoke it as part of their case for the claim that biological systems exhibit emergent properties. Under their analysis, a property is emergent if it cannot be predicted from what is known by studying the part in isolation or in the context of simpler systems.

A common frustration in biological research is the inability to reproduce the phenomenon once one has assembled what appear to be all the component parts and operations. In many cases the failing is that there remains yet unknown parts or operations. But in other cases the failing involves the third feature in my characterization of mechanisms, organization. Lip service is often given to the fact that components of a mechanism must be organized, but the importance of organization is often underappreciated. Yet, it is organization that causes parts of the mechanism to behave in ways they do not in isolation and enables the mechanism as a whole to accomplish things that none of the components alone can do. What is possible when components are put together in creative ways is often obscured when one focuses just on the components themselves. What is learned about the part in conditions in which a researcher has removed it from the context of the mechanism may not include how it will operate in the organized structure. One can appreciate this point better by turning one's focus from science to engineering. Engineers do not build new devices by creating matter with distinctive properties *ab initio*. Rather, they start with things that already exist and put them together in novel ways. What can be accomplished when the parts are put together is typically far from obvious. Creativity is required, and accordingly engineers can win patents and fame for developing a new design that enables old parts to perform new operations. The only thing the engineer added to what already existed was organization, but this is what is critical in developing mechanisms that perform tasks that initially seemed impossible to perform with existing components.

3. The Vitalist Challenge

Although the search for mechanisms within biology has not been particularly controversial since the beginning of the 20th century, it was heatedly debated in the 19th century. The opponents to explaining biological phenomena in terms of mechanisms were often labeled *vitalists*. Although there was no official vitalist doctrine (just as there was no official doctrine of those advancing mechanism), vitalists tended to insist that ordinary physical objects could not generate the phenomena associated with living organisms and to maintain that explaining such phenomena required appeal to additional factors such as vital forces or vital powers. Some vitalists proposed that there was a non-physical component of living organisms that gave them their distinctive properties. Others downplayed the radical nature of such appeals, arguing that vital forces were not substantially different from the sorts of forces Newton had invoked to explain the behavior of physical objects. The behavior of living organisms could be described in distinctive laws of biology that invoked vital forces, and biologists were no more obliged than Newton to explain them in more fundamental terms.¹¹

The historical importance of the vitalists lies not in their positive doctrine of vital forces or vital powers, but in their critique of mechanism. They drew attention to phenomena exhibited by living organisms that mechanists seemed incapable of explaining. The natural tendency of mechanists was to focus on the phenomena they could explain, and to divert their attention from the phenomena that proved more difficult. Vitalists thus provided an honesty check on mechanists, keeping in focus the phenomena of life that were recalcitrant to existing mechanist explanatory strategies.

An exemplar of the vitalist challenge to mechanism is offered by the French anatomist Xavier Bichat. His project began in the fashion of a mechanist as he proposed a decomposition of living

¹¹ For an account of the positions of various vitalists and mechanists in the history of physiology, see Hall (1969).

systems into twenty-one different types of tissues distinguishable in terms of their sensibility and contractility. He then appealed to these properties to explain the phenomena associated with organs built from these tissues. But with the catalogue of tissues, Bichat contended, this explanatory project reached a limit. He highlighted two reasons for resisting any attempt to explain the phenomena associated with tissues in terms of their material composition. The behavior of living organisms was simply not sufficiently deterministic to be explained mechanistically: “The instability of vital forces marks all vital phenomena with an irregularity which distinguishes them from physical phenomena [which are] remarkable for their uniformity” (Bichat, 1805, p. 81). Moreover, he contended that living organisms operate to resist external factors that threaten their existence, construing life as “the sum of all those forces which resist death.” This last characterization is particularly potent. The notion of resistance points to self-initiated action, where that action is directed at maintaining the living organism as a distinct system. As we will see, the construal of biological systems as autonomous systems provides a means of capturing the key insight in Bichat’s characterization of life.

As I will develop in the next section, already in the 19th century Claude Bernard, by focusing on features of the organization of biological systems, took major steps to answering Bichat. But the spirit of Bichat’s objection lives on in such attempts as those of Robert Rosen (1991; for analysis, see Mikulecky, 2000), noted above, to contrast living systems with mechanisms. Attention to the differences between biological systems and humanly engineered mechanisms is not limited to critics of mechanism. I will develop below some of the fundamental insights into the nature of biological mechanisms advanced by Tibor Gánti, but before developing his positive account, it is worth noting how he contrasts biological systems with extant humanly engineered machines:

First, living beings are soft systems, in contrast with the artificial hard dynamic systems. Furthermore, machines must always be constructed and manufactured, while living beings construct and prepare themselves. Living beings are growing systems, in contrast with technical devices which never grow after their completion; rather, they wear away. Living beings are multiplying systems and automata (at least at present) are not capable of multiplication. Finally, evolution—the adaptive improvement of living organisms—is a spontaneous process occurring of its own accord through innumerable generations, whereas machines, which in some sense may also go through a process of evolution, can only evolve with the aid of active human contribution (Gánti, 2003, pp. 120-1).

Many of these features, such as multiplication and adaptive change through evolution, are salient differences between extant machines and living systems, but I take the most fundamental of the features Gánti lists to be the engagement of living beings in self-construction and growth so that they do not merely to wear away or dissipate in the fashion of ordinary physical objects. These capacities must be exhibited by any system that is to be a candidate for reproduction and evolution and are not found in extant machines. Hence, they are critical phenomena for which any viable mechanistic account must offer an explanation.

4. First steps: Bernard, Cannon, and Cybernetics

As I noted above, Bernard (1865) took major pioneering steps toward answering the objections to the mechanistic approach to explaining life advanced by Bichat. Fundamental to Bernard’s view of science was that causal processes are deterministic; accordingly, it was critical for him to explain away the apparent indeterminism in the activities of living organisms that Bichat had highlighted. The key to Bernard’s response was to focus on the internal organization of living

systems and to argue that the internal parts of a living mechanism resided in an *internal environment* that is distinct from the external environment in which the organism as a whole dwells. This provided a ready account of the indeterminacy exhibited by living mechanisms. Whereas there might not be strict determinism in the response of a part of an organism to changes in the external environment, he maintained that strict determinism could be found in its response to conditions of the internal environment. For example, whereas fluctuations in the sugar available in food might not lead to changed metabolic activity in somatic tissue, decreased glucose levels in the blood would result in lowered metabolic activity in somatic tissue. The focus on the internal environment also provided Bernard the beginnings of a response to Bichat's contention that organisms are not mechanistic insofar as they operate to resist physical processes in their environment. The internal environment provides a buffer between conditions in the external environment and the reactive components of the mechanism, insulating component parts of the mechanism from conditions in the external environment. Bernard proposed that this buffering is achieved by individual components of the organism each performing specific operations that served to *maintain the constancy of the internal environment*.¹² Insofar as some of its mechanisms are designed to maintain a constant internal environment despite changes in the external environment, a living system can appear as an active system doing things that resist its own demolition.¹³

Although emphasizing the role of organs in the body in maintaining the constancy of the internal environment, Bernard did not provide a detailed account of how organs might operate in this way. Walter Cannon (1929) introduced the term *homeostasis* (from the Greek words for *same* and *state*) for the capacity of living systems to maintain a relatively constant internal environment. He also sketched a taxonomy of strategies through which animals are capable of maintaining homeostasis. The simplest involve storing surplus supplies in time of plenty, either by simple accumulation in selected tissues (e.g., water in muscle or skin), or by conversion to a different form (e.g., glucose into glycogen) from which reconversion in time of need is possible. A second kind of homeostasis involves altering the rate of continuous processes (e.g., changing the rate of blood flow by modifying the size of capillaries to maintain uniform temperature). Cannon noted such control mechanisms are regulated by the autonomic nervous system.

The crucial idea required to flesh out Bernard's and Cannon's insights into how biological systems are organized to maintain themselves in the face of external challenges is that of negative feedback. As I noted above, the notion of negative feedback was repeatedly rediscovered in different engineering contexts in which it was important to regulate or control a process so as to insure a regular output over 2,000 years. With the development of the cybernetics movement and control theory in engineering in the 20th century, it came to be viewed as a general design principle. Although enriched by a variety of tools, such as the use of off-line emulators and filtering techniques (Grush, 2004), negative feedback remains at the center of the modern field of control theory. It also plays a critical role in the understanding of biological systems. Feedback loops provide a way of insuring that critical processes, such as the consumption of nutrients to generate ATP, only occur when they are required. Figure 2 illustrates

¹² Bernard, for example, says "all the vital mechanisms, however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment" (Bernard, 1878, p. 121, translated in Cannon, 199, p. 400).

¹³ Bernard's focus seems to have been more on the constancy of the internal environment than on just what the conditions in the internal environment were. A key feature of living systems is that via control of flow of materials across membranes they create environments different from those found outside them and in these internal environments component parts operate differently than they do in the external world.

an instance of negative feedback at the junction between glycolysis and the Krebs cycle which halts the generation of pyruvate from phosphoenolpyruvate (coupled with the synthesis of ATP) when there is already a plentiful supply of acetyl-CoA waiting to enter the citric acid cycle.

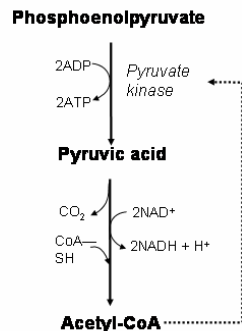


Figure 2: Feedback loop in the linkage between glycolysis and the citric acid cycle. In the final reaction of glycolysis, phosphoenolpyruvate produces pyruvic acid. Pyruvic acid then produces acetyl-CoA, some amount of which is needed to continuously replenish the citric acid cycle (not shown). If more acetyl-CoA is produced than can be used in the citric acid cycle, it accumulates and feeds back (dotted arrow) to inhibit pyruvate kinase, the enzyme responsible for the first step in the reaction. This in turn will stop glucose from entering the glycolytic pathway.

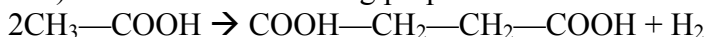
5. Cyclic organization and Gánti's chemoton

As important as negative feedback is in providing control mechanisms in living organisms that enable them to maintain homeostasis, it is not sufficient to explain the tendency of organisms to resist death. A major additional form of organization involves cycles. Cycles appear in biological accounts at various levels of organization (many of the best known involve relations between organisms and their environment, such as the nitrogen cycle), but I will focus on cycles at the level of basic metabolic processes. The pioneers in biochemistry at the turn of the 20th century generally assumed that the chemical reactions in living organisms occurred serially and hence the pathways of reactions would be linear. They sought to identify the intermediates in, for example, the oxidation of fatty acids or the oxidation of glucose to alcohol that could be generated through known chemical reactions (oxidations or reductions of substrates, additions or removals of carboxyl groups, etc.). Often, however, they could go only so far in arranging intermediates in linear sequences; proposed reaction sequences would yield a substance which could not be processed in the same manner. The discovery of perhaps the most famous biochemical cycle, the citric acid cycle, resulted from such a circumstance. After adopting Wieland's (1913) account of oxidation as involving the removal of a pair of hydrogen atoms from a substrate (dehydrogenation), Thorsten Thunberg established that a number of organic acids (lactic acid, succinic acid, fumaric acid, malic acid, citric acid, etc.) could all be oxidized in cellular extracts in such a manner (Thunberg, 1920). He then tried to fit the reactions together in a coherent pathway involving a chain of reactions.¹⁴ Relatively easily he was able to fit the various compounds together into the sequence:

¹⁴ Thunberg actually had the idea of a sequences of reactions as early as 1913, before he encountered Wieland's conception of dehydrogenation: "The oxidative processes in living cells must be thought of as forming chain reactions, a series of reactions connected to one another in such a way that, by and large, none of the links in the reaction chain can proceed more rapidly than the others" (Thunberg, 1913, translated in Holmes, 1986, p. 68)

Succinic acid \rightarrow fumaric acid \rightarrow malic acid \rightarrow oxaloacetic acid \rightarrow pyruvic acid
 \rightarrow acetic acid

He then faced a problem in specifying what happened next—it was not possible to remove two hydrogen atoms from acetic acid. In response to this problem, Thunberg offered a bold proposal—he proposed “a reaction in which two acetate molecules are simultaneously each deprived of one hydrogen atom, with the joining of their carbon chains into one. The substance which must therefore form is succinic acid” (Thunberg, 1920, passage translated by Holmes, 1986, p. 69). The reaction Thunberg proposed was the following:



This resulted in the pathway becoming a cycle, as shown in Figure 3a.

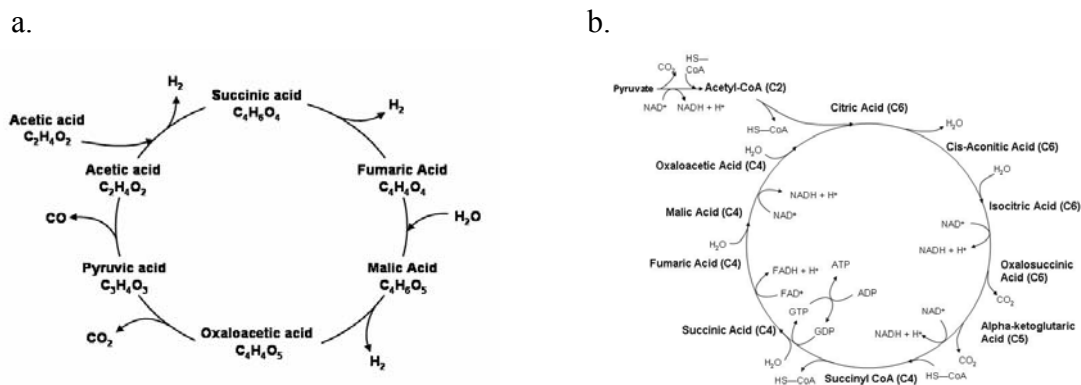


Figure 3. (a) Cycle proposed by Thunberg in 1920 to link various three carbon sugars that figure in oxidative metabolism. (b) the citric acid cycle as understood today.

Thunberg's proposed cycle was speculative, and a good deal of research went into trying to determine the actual intermediates in the oxidation of three carbon sugars until Hans Krebs and William Johnson (1937) published their account of the citric acid cycle (also known as the *tricarboxylic acid cycle* and later as the *Krebs cycle*). As shown in Figure 3b, instead of two molecules of acetic acid combining to form succinic acid, Krebs proposed that oxaloacetic acid combined with a three-carbon substance, which Krebs designated simply as *triose*, to generate citric acid. He then proposed that citric acid underwent a sequence of reactions resulting in succinic acid. After the discovery of co-enzyme A in the 1940s, biochemists recognized that it was acetyl-CoA that entered the cycle by combining with oxaloacetic acid to form citric acid.

What is noteworthy about Thunberg's and Krebs' research, as well as that of many other biochemists who proposed cycles in the early decades of the 20th century, is that they were guided purely by the desire to articulate plausible pathways of chemical reactions that would provide complete accounts from known starting points to appropriate endpoints. Cyclic organization was not construed as theoretically significant. Subsequently, as the ubiquity of cycles became apparent, some theorists did take up the question of why cycles were so common. One advantage of cyclically organized processes is that they provide a means of effective negative-feedback regulation—only when the products of the cycle are generated will new substances be able to enter the cycle. But they play an even more significant role in organizing chemical operations into biological systems.

An illuminating perspective on the function of cycles in biochemistry is offered by Tibor Gánti (see his 2003 for a synthetic statement of an account which he initially advanced in the 1970s).

Gánti's project has been to identify the simplest chemical system that exhibits the distinctive features of life, a system he calls the *chemoton*.¹⁵ In pursuing this project, Gánti takes his lead from the minimal biological system exhibiting the properties of life, the cell. He identifies three subsystems as common to all cells—"the cytoplasm, the membrane, and the genetic substance." His analysis plays particular attention to the cytoplasm, which he characterizes as "the chemical motor."¹⁶ He then notes a general feature of motors designed to produce work—they are not one-time causal agents but must be continually able to produce work:

Continuous work performance can only be achieved by means of suitable work-performing systems characterized by changes occurring through a series of constrained motions, such that the inner organizational characteristics of the system remain unchanged (p. 68).

In order to maintain the system unchanged while yet performing work, cyclic organization is required, and this he contends is true of both humanly designed mechanical systems and biological systems:

In an internal combustion engine the explosion moves the piston from its original location, but the engine is so constructed that the displacement occurs on a constrained path and after performing work the piston returns to its starting position. . . . The ability of non-mechanical systems to perform continuous work also depends on cyclic processes or, as they are often call for simplicity, cycles. (p. 72).

In the case of the internal combustion engine, the component parts are (relatively) permanently fixed. As Gánti puts it, they exhibit a "geometrical structure of fixed materials." While there is some material fixity in living systems, for the most part organization involves what he terms a "soft geometrical structure" (pp. 64-5).¹⁷

Gánti uses several biochemical cycles to illustrate the ideas in the chemoton. He begins with the citric acid cycle introduced above and initially deemphasizes the importance of new inputs of

¹⁵ It is important to note that Gánti is not trying to provide a detailed account of first organisms or the origins of life but, as Griesemer & Szathmáry (forthcoming) emphasize, a heuristic model to help probe the organization required in living systems: "the chemoton model is not intended as an accurate representation which, if implemented exactly, could live. It is instead a heuristic guide to the organizational properties of chemical systems that would minimally fulfill the living state." Although the account is not presented as accurate in detail, in another sense Gánti is seeking to be true to the systems modeled—the general architecture of the model is intended to correspond to the architecture of the actual system. This is a feature of many similar modeling efforts that attempt to demonstrate how, possibly, a given phenomenon might be produced.

¹⁶ Although emphasizing all three sub-systems, Gánti explicitly comments on how cytoplasm is the most complicated and in many respects the most critical:

Firstly, it is the chemical motor. The cytoplasm contains the system transforming the chemical energy of nutrients into useful work. Secondly, it is the homeostatic subsystem compensating the influences of the external world by dynamically responding to them. Therefore, the cytoplasm is responsible for the dynamic and organizational responsibility of the cell. However, it is also responsible for sensibility and excitability, since the accomplishment of homeostasis is nothing more than excitability. To achieve all of these it is necessary that processes in the cytoplasm should occur in a regulated order and thus that the cytoplasm carries the property of regulation and is considered a soft system. Finally, the raw materials necessary for the growth and reproduction of all three subsystems (cytoplasm, cytomembrane, and genetic substance) are also delivered by the cytoplasm; thus it is a self-reproducing soft system (pp. 83-4).

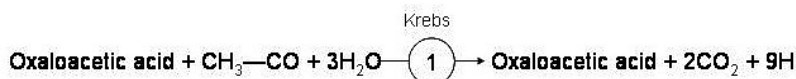
In locating the motor in the cytoplasm, Gánti is reflecting a pre-Mitchell conception of the critical chemical reactions. According to Mitchell's chemiosmotic account, a central part of the mechanism transforming chemical energy into ATP is the inner mitochondrial membrane, across which a proton gradient is established that then provides the energy for ATP synthesis.

¹⁷ Soft-organization is central, for Gánti, for cell life: "Now what makes the cell living? The soft organization of its inner events and occurrences. Thus, if we are looking for the fundamental laws, for the principle of life, we have to establish the connections of this soft organization" (p. 66).

acetyl-CoA and instead emphasizes that oxaloacetic acid, and all other intermediates, are regenerated by the cycle. He represents this by the following formalism¹⁸:



To show that nutrient material is entering the cycle and waste products are leaving, he expands the formalism:



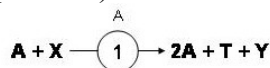
More abstractly, Gánti uses **A** for the components of the cycle, **X** for the reactants entering the cycle, and **Y** for the reaction products:



For Gánti the citric acid cycle is only the starting point. He views living systems as fundamentally growing systems and so turns to autocatalytic cycles which create more of the cycle intermediates on each iteration (Gánti presents the malate cycle as an example of such a cycle):



To appreciate the significance Gánti attaches to such autocatalytic cycles, we need to bring in the second subsystem of a chemoton, the membrane.¹⁹ For Gánti, the membrane both isolates the autocatalytic system (insuring, for example, that the concentration of intermediates is sufficient that ordinary diffusion will bring reactants together) but also allows for the control of admission and expulsion of materials from the system. (Insofar as it is a selective semi-permeable barrier, the membrane itself is a sophisticated and complex mechanism—a nontrivial component for the system to build and maintain.) It is critical for Gánti's account that the chemoton creates its own membrane, and to explain how it might do this, Gánti further amends his account of the metabolic cycle so that it not only generates more intermediates of the cycle but components of the membrane, which Gánti represents as **T** (as Gánti has now moved into the realm of a purely theoretical cycle, he designates it simple as **A**):



Assuming that the membrane bound system naturally takes the shape of a sphere, Gánti notes that such a stoichiometric relation would lead to the membrane increasing more rapidly than the

¹⁸ This formalism, as Griesemer & Szathmáry (forthcoming) discuss, was introduced by Gánti so as to draw attention to the stoichiometric requirements of catalyzed reactions. This attention to the flow of matter through the system by balancing each reaction, is an important feature of Gánti's approach.

¹⁹ The membrane was not part of Gánti's initial account (see Griesemer & Szathmáry, forthcoming) and was introduced only as he recognized a need, when dealing with reactions occurring in a fluid milieu, to keep reaction components together in sufficiently high concentrations. Moreover, Gánti's account underplays the role membranes play in actual living cells—the not only provide a way to create distinct environments, but a potent tool for energy storage. In oxidative metabolism, for example, a differential concentration of protons across a membrane, as a result of the oxidations along the electron-transport system, results in a proton-motive force that then drives the synthesis of ATP.

volume of metabolites enclosed. The solution he proposes is that the system will divide into new spheres when the membrane grows sufficiently to close in on itself and bud.²⁰

The metabolic and membrane (including membrane generation) systems together give rise to what Gánti characterizes as a *supersystem* which exhibits biological features:

We have combined two systems of a strictly chemical character into a ‘super-system’ (or, to put it another way, we have combined two chemical subsystems), and we have obtained a system with a surprising new property of expressly biological character. What can this system do? It is separable from the external world and its internal composition differs from that of the environment. It continuously consumes substances that it needs from the environment which are transformed in a regulated chemical manner into its own body constituents. This process leads to the growth of spherule; as a result of this growth, at a critical size the spherule divides into two equal spherules, both of which continue the process. (p. 105)

But, according to Gánti, this system is still not living because it lacks an information-storing or control subsystem.²¹ Gánti proposes to provide an information-storing subsystem by having the metabolic system also add a monomer to a polymer that is built along an existing polymer template. The length of the polymer is thereby able to carry information about the number of cycles completed.²² (See Figure 4 for Gánti’s portrayal of the complete chemoton.)

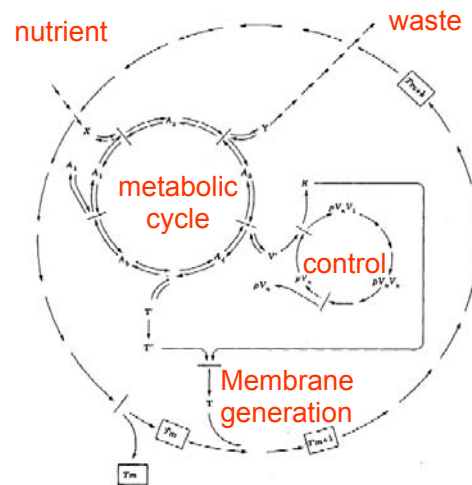


Figure 4: Gánti’s chemoton with the three subsystems labeled.

Gánti seems to have been led to insist on this third subsystem only because such an information storage system, in the form of DNA, has been found in extant organisms: “This property is not

²⁰ Gánti’s account of the membrane is overly simplistic. In order to deal with the osmotic crisis that results from concentration differences inside and outside the enclosure and the tendency of water to spontaneously enter the enclosure, resulting in its swelling bursting, the membrane must from the outset be active in pumping materials in and out (Kepa Ruiz-Mirazo & Moreno, 2004, p. 244).

²¹ James Griesemer and Eörs Szathmáry include marginal notes accompanying Gánti’s text, and Griesemer notes at this point that had Gánti not been focused on a template-based information system, he could have included an information encoding structure within the membrane system by allowing, for example, the incorporation of a variant molecule into the membrane that will be replicated as the membrane is replicated, resulting in what Jablonka and Lamb (1995) describe as a “structural inheritance system.”

²² Griesemer provides some suggestions as to how polymer length carries information. For example, if one molecule is added to the polymer at each turn of the metabolic cycle, it can provide a more reliable indicator of the growth that has already occurred and when the next division should occur.

one of the classical life criteria, but on the basis of knowledge gained from molecular biology, it has been selected as an absolute life criterion” (p. 106). Gánti in fact says little about what the information system is to be employed for and one might ask why such an information system is required in a living system. An appreciation of its significance is provided by Gánti’s own coupling of the notions of *information* and *control*. In the two-component supersystem, the metabolic and membrane systems were strictly linked with each other such that as the metabolic system produced metabolites it also produced membrane. This will work as long as the environment of the system continues to provide the system exactly what it needs, regularly removes its waste, and does nothing to interfere selectively with either the membrane or the metabolic process.

Even slight variations in the environment may disrupt such a system. Imagine the environment changed so that a new substance entered the system which would react with existing metabolites, either breaking down structure or building new additional structure. This would disrupt the delicate balance between metabolism and membrane generation that Gánti relies on to enable chemotons to reproduce. What this points to is the desirability of some procedures for controlling operations within the system that is not directly tied to the stoichiometry of the metabolic reactions themselves. Although stoichiometric linkages between reactions are effective for insuring linkages between operations, they do not provide a means for varying the reactions independently. Such independent control can only be achieved by a property not directly linked into the critical stoichiometry of the system.

Griesemer and Szathmáry (forthcoming) provide an account of the stoichiometric freedom that is made possible with the information subsystem Gánti proposes. If, instead of just one type of molecule being combined into the polymer, two or more constitute the building block, then the polymer will exhibit both a composition of monomers in specific concentrations and a sequence. The concentrations, like other features of the chemoton, will depend on specific stoichiometric relations. The sequential order, however, will not—it is a “free” property which can then be linked to component operations in the chemoton in other ways so as to control them. Moreover, it can also undergo selection. This points to a general point about control systems—if control is to involve more than strict linkage between components, what is required is a property in the system that varies independently of the basic operations. Particular values of this variable property can then be coordinated with responses by other components so that the property can exert control over the operation of the other component.

What is required for an information-based control system that goes beyond direct negative feedback loops, then, is a property that is sufficiently independent of the processes of material and energy flow that it can be varied without disrupting these basic processes (which may themselves be maintained by negative feedback), but still able to be linked to parts of the mechanism so as to be able to modulate their operations. Such properties need not involve a template matching system but there are reasons to employ such a system. We can appreciate this by considering the role of enzymes in catabolism. On some occasions²³ Gánti tries to characterize the chemoton without invoking catalysts or enzymes to promote the reactions, but it

²³ When he appeals to examples such as the Krebs’ cycle, however, Gánti is already invoking an enzyme catalyzed metabolic cycle. Enzyme catalyzed systems pose an additional challenge for Gánti’s account since they must themselves be made by the system. One way to view this is to differentiate the function of procuring raw materials and energy from that of synthesizing new products, and distinguishing both of these from the functions of differentiating the system from its environment and of storing information in a template.

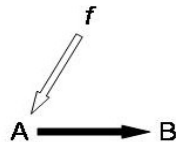
is ultimately unlikely that a system of uncatalyzed reactions could maintain the flow of matter and energy needed in the chemoton. If enzymes are to play a role, however, they must be synthesized by the system. The method for synthesizing proteins, including enzymes, in actual living cells utilizes a common mechanism (a ribosome) that adds amino acids to a developing string. If this mechanism is to make different enzymes on different occasions (as it must if the result is the set of proteins needed to catalyze a given reaction), a stable information source for specifying the sequence in each protein is required (plus a component for insuring that the right instructions are followed at a given time). In living cells, mRNA plays this role. Here we see a compelling reason for an informational system—it insures that the system is able to make the needed components so that it is able to function. The fact that it also provides the retention component for a process involving variation and selective retention, that is, natural selection (Lewontin, 1970), is an added plus but not an essential feature of the information-based control system.

Gánti's chemoton proposal is highly speculative, but it offers an intriguing perspective on the centrality of cyclic organization in biological systems. Cycles provide a vehicle through which a set of operations that depend on each other can be maintained even as the overall mechanism performs work. When part of the work done involves building a semi-permeable membrane, the cycle provides the central resource for a mechanism that can obtain a critical autonomy from its environment. Moreover, when cycles are autocatalytic and produce multiple copies of themselves, cycles provide a way to account for growth and reproduction. These features, as we will see, are all critical to providing an adequate answer to vitalists such as Bichat, but to see how they fit into such an account, it will be useful to consider a different theoretical perspective.

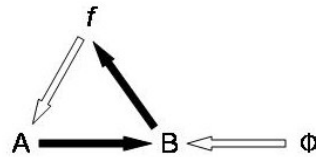
6. From Gánti's Chemoton to Autonomous Systems

During the same period in which Gánti was developing his ideas of a chemoton other theorists were focusing on efficient causation and ways of closing chains of efficient causation. As Rosen characterized a mechanism, which he contrasted with an organism, there was always some component operation in it that was not caused by other components within the mechanism. It would always be possible to incorporate the efficient cause of that operation within the description of the mechanism, but then one described a new mechanism that had a new uncaused operation. For Rosen the key contrast between mechanisms and organisms was that organisms had no uncaused operations—they are “closed to efficient causation.”

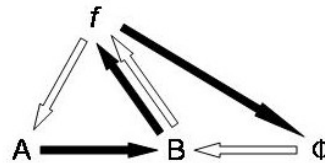
To see more concretely what Rosen was contemplating, consider a metabolic mechanism in which component f is responsible for metabolizing A into B. Using open arrows to represent efficient causes and closed arrows to represent material causation, Rosen represented the relation as below.



But f is uncaused in this account. One possibility is to use material in B to make, or in the case Rosen considers, to repair f . But what is the efficient cause of this change? Rosen introduces a new component Φ , yielding the relations shown below.



But now Φ is uncaused. Perhaps materially it was produced from f . But there would have to be an efficient cause of making Φ from f . Rosen initially considers introducing a component β as the efficient cause, but notes that this is a recipe for an infinite regress. The way out, Rosen proposes, is to let B serve as the efficient cause of making Φ from f . Now each causal transformation (from A to B, from B to f and from f to Φ) has an efficient cause (f , Φ , and B, respectively).



The result is a material system closed to efficient causation (there are no components which undergo a material change without an open arrow coming in to them) thereby satisfying Rosen's characterization of an organism. (Φ does not have an open arrow coming into it, but it is not changed into anything else in the system, so there is no efficient causation to account for.) Importantly, the system is still materially open since A is not produced from anything within the system. (Although Rosen doesn't emphasize it, it is also energetically open.)

A similar emphasis on efficient causation lies at the heart of Francesco Varela's characterization of a living system (although Varela, unlike Rosen, begins with the idea that living organisms are machines and focuses his attention on delineating what sort of machine they are). He begins with the idea that a living system has an identity in terms of an organization which it maintains "through the active compensation of deformations" (Varela, 1979, p. 3). Here Varela invokes Cannon's notion of homeostasis, on which he then relies to develop what he takes to be the key concept of *autopoiesis*. He does this by expanding on homeostasis in two ways: "by making every reference for homeostasis internal to the system itself through mutual interconnections of processes, and secondly, by positing this interdependence as the very source of the system's identity as a concrete unity which we can distinguish" (p. 12-13). In other words, all homeostatic operations in organisms are efficiently caused from within the system and it is the continued existence of the set of causally dependent processes that constitutes the continued existence of the system. Varela then provides his canonical characterization of autopoiesis:

An autopoietic system is organized (defined as a unity) as a network of processes of production (transformation and destruction) of components that produces the components that: (1) through their interactions and transformations continuously regenerate and realize the network of processes (relations) that produce them; and (2) constitute it (the machine) as a concrete unity in the space in which they exist by specifying the topological domain of its realization as such a network. (Varela, 1979, p. 13; see also Maturana & Varela, 1980).

The crucial idea, as it was for Rosen, is that all the pertinent causal processes needed to maintain the network of causal processes have their efficient cause within the system itself.²⁴

²⁴ In his last published paper (Varela & Weber, 2002), Varela traces the roots of the idea of autopoiesis back to Kant.

Autopoiesis is important according to Varela because autopoietic systems can be *autonomous*, where autonomous systems are those that perform the necessary operations to maintain their own identity.²⁵ This notion of autonomy provides a powerful way to conceptualize what is special about living systems. It also provides a perspective from which to view any additions to the initially conceived minimal autonomous system—they are ways of extending the autonomy of the system. I will return to this point in the final section of this paper. But before moving on, it is important to qualify the notion of autonomy. We should not view an autonomous system as completely encapsulated. Minimally, on both Rosen's and Varela's conception, such systems are materially and energetically open to their environments. As a consequence, they are also potentially open to efficient causation, but not in a sense that Rosen was seeking to avoid. With respect to autonomy, what is crucial is what a system does when causal processes impinge on it. If the system responds to such impingements through operations it initiates, then the critical autonomy is preserved. If, on the other hand, external efficient causes simply change the system (e.g., a falling rock smashes a cell or a wind transport it to a new location), the resulting effects are not due to the system's autonomous action.

There are a couple of features of both Rosen's and Varela's account that merit comment. First, both of them dissociate the organizational features that are crucial for living systems from their material realization. Varela, for example, comments:

“We are thus saying that what defines a machine organization is relations, and hence that the organization of a machine has no connection with materiality, that is, with the properties of the components that define them as physical entities. In the organization of a machine, materiality is implied but does not enter *per se*” (p. 9).

In making this dissociation, both Varela and Rosen endorse the sort of multiple realizability argument that has figured so strongly in functionalist theories of mind and has led numerous philosophers of mind to downplay the significance of the brain to the understanding of cognition. The plausibility of multiple realizability claims, however, often results from adopting overly simplistic accounts of functional organization and from focusing on abstract accounts of machines, such as the Turing machine. In real machines, the relations in which a component can stand are significantly limited by the material out of which they are constituted—change the material, and there will be detectable changes in functionality. When one takes very seriously the organizational demands on complex systems, it is far from clear that there are multiple material realizations that could produce the same functionality (Bechtel & Mundale, 1999).²⁶ A second,

²⁵ “Autopoietic machines are autonomous: that is, they subordinate all changes to the maintenance of their own organization, independently of how profoundly they may be otherwise transformed in the process. Other machines, henceforth called *allopoietic* machines, have as the product of their functioning something different from themselves” (p. 15). Varela later generalizes the notion of autonomy so as to apply beyond autopoietic machines: “Autonomous systems are mechanistic (dynamical) systems defined as a unity by their organization. We shall say that autonomous systems are organizationally closed. That is, their organization is characterized by processes such that (1) the processes are related as a network, so that they recursively depend on each other in the generation and realization of the processes themselves, and (2) they constitute the system as a unity recognizable in the space (domain) in which the processes exist” (p. 55).

²⁶ A second consideration that leads other theoreticians to attempt a materially independent characterization of living systems is found in the artificial-life community which seeks to understand life in its full generality and not to be “earth chauvinists.” Seeking universal categories, however, is not the only way of avoiding earth chauvinism. A different strategy is to begin with the concrete case we know—life on earth—and to branch out from it by considering variations that are possible. This fits the common strategy in biology of starting with a model system (e.g., the giant squid axon), develop an account of the mechanisms operative in it, and then investigate the similarities and differences found in other related species. One reason this is likely to succeed often on earth is the

and related point, is that neither focuses on the energy requirements of the systems they consider. In this regard, it is interesting to focus on the fact that the first component that Rosen added to his metabolic operation was a repair operation. Indeed, repair is a crucial feature of living systems, but the reason it is so important is that biological systems, as highly organized systems, exist far from thermodynamic equilibrium. As such, they will dissipate, and in so far as they are chemical, not solid systems, such dissipation will be relatively rapid.²⁷

Thermodynamic considerations apply to all machines, not just biological ones. All must operate within an energy flow between a high-energy source and a low-energy sink and must draw upon the energy available at the source and release its waste-products, now in a lower energy state, into the sink. A waterwheel, in which water at a higher elevation stores more free energy than the water at a lower elevation, often provides a fruitful metaphor for this process. What is critical for any mechanism is that the energy liberated in this flow is employed to perform work and this requires that it be channeled in the appropriate way. This typically means that it is transformed into a different format—the waterwheel converts the energy stored in water at a higher elevation into the rotational energy of the wheel's axle, and linkages appended to the axle in turn convert the motion into the form required.

What is distinctive in the case of living organisms is that the thermodynamics must be regulated so as to enable the organism to maintain itself—to repair itself or to build itself initially. This need is brought into clear focus by considering the autocatalytic networks, to which theorists such as Stuart Kauffman (1995) have turned in their accounts of the origin of life. Such networks, as well as other self-organizing systems such as hurricanes and tornadoes, are extremely fragile and are not able to maintain themselves for long. Part of the reason is that they rely on an energy source which may be quickly expended. But a further part of the reason is that they are not organized so as to channel the energy they do secure to construct themselves so as to extract more energy from the source in the future (Kepa Ruiz-Mirazo & Moreno, 2004; see also Bickhard, 1993; Kauffman, 2000). (This would be pointless if there is no further energy source to tap, but of great importance if there is a continued source of energy, but one that can be utilized only if the system is properly configured.)

Whereas Varela did not focus on thermodynamics and the management of energy in his account of autonomy, Kepa Ruiz-Mirazo and Alvaro Moreno (2004) have made it central to their account. They begin with the recognition that as organized systems, living systems are far from thermodynamic equilibrium and, in order to maintain that organization, must maintain themselves far from equilibrium (cf. Schrödinger, 1944). Many of the chemical reactions required to maintain such a system are endergonic (require Gibbs free energy) and so must be coupled with those that liberate energy from another source (exergonic reactions). In order to maintain themselves far from equilibrium, Moreno focuses on how the system *manages* the flow of energy so as to provide for its own construction and reconstruction. The membrane presents

conservation of mechanisms that results from natural selection, which of course will not apply to non-earth based life. Nonetheless, the strategy of starting with mechanisms we know to function successfully on earth and then considering variations is far more likely to succeed than a strategy of seeking generality by discounting what we know of earth-based mechanisms. The latter is a strategy that may only result in vacuous generalities.

²⁷ It is perhaps because of the problem of dissipation that humanly engineered machines have historically been made of solid, rigid components. Although such machines do experience “wear and tear” and so need repair, the bonds that render them into solids make them less subject to dissipation than structures in fluid milieus. On the other hand, it is harder to design a self-repair process for a system made of solids, which may explain why the strategy for dealing with breakdown in human engineered systems has been to build in redundancy rather than self-repair.

one point of management, determining what gets in and out of the system. The metabolic pathways that extract energy and raw materials and then synthesize constituents of the organism's own structure are another. Focusing on these management processes, Ruiz-Mirazo and Moreno characterize *basic autonomy* as:

the capacity of a system to *manage* the flow of matter and energy through it so that it can, at the same time, regulate, modify, and control: (i) internal self-constructive processes and (ii) processes of exchange with the environment. Thus, the system must be able to generate and regenerate all the constraints—including part of its boundary conditions—that define it as such, together with its own particular way of interacting with the environment. (Kepa Ruiz-Mirazo & Moreno, 2004, p. 240; see also Kepa Ruiz-Mirazo, Peretó, & Moreno, 2004, p. 330).

Moreno's notion of basic autonomy provides the appropriate complement to Gánti's conception of the chemoton as the simplest chemical system exhibiting the features of life. Construing the chemoton as an autonomous system requires adopting a perspective that is implicit, but not explicit in Gánti in the description of the chemoton.²⁸ The chemoton not only takes in matter, incorporating some of it within itself and expelling other parts as waste, but it takes in energy and utilizes some of it in the various work it performs and expels the rest as waste (generally as heat or in substances with too little free energy to be useful). Biochemists were, it is interesting to note, slow to recognize this aspect of metabolism. Until the 1930s they focused principally on the generation of animal heat (in fact, a waste product) and the incorporation of matter into the organism. It was not until the discovery of phosphocreatine and adenosine triphosphate (ATP) and their linkages to the processes of glycolysis that energetic relations became a central focus of metabolism studies (Bechtel, 2006). Even if a latecomer, however, it is a crucial feature of any metabolic system.

7. Concluding Thoughts: Beyond Basic Autonomy

My focus in this paper has been on how organization is far more critical than often recognized in mechanistic science and philosophical accounts of mechanistic explanation. Only by keeping a keen eye on the organization at play in living systems is it possible to understand the mechanisms that figure in living organisms. Vitalists and holists play an important function when they remind mechanists of the shortfalls of the mechanistic accounts on offer. Ideas such as negative feedback, self-organizing positive feedback, and cyclic organization are critical to explaining the phenomena exhibited by living organisms. Moreover, the importance of these modes of organization can be appreciated when the relevance of notions such as being closed to efficient causation is taken into account and it is appreciated that as organized systems, living systems are far from equilibrium and to maintain themselves require ways of channeling matter and energy extracted from their environment so as to maintain themselves far from equilibrium. These critical features are nicely captured in Moreno's conception of basic autonomy in which we recognize living systems as so organized to metabolize inputs to extract matter and energy and direct these to building and repairing themselves.

²⁸ Prior to introducing the chemoton itself, Gánti makes the point about energy: "The operation of every machine, device, instrument—every continuously operating system—is based on energy flow. Energy enters the system from somewhere and eventually leaves it. While it is within the system it is manipulated so that part of it is forced to make the system operate, whereas the other part leaves the system, mainly in the form of heat" (p. 18).

My contention is that recognizing organization does not require a rupture with the tradition of mechanistic science. Mechanism has the resources to identify and incorporate the forms of organization critical in living systems. Moreover, attempts to focus on organization independently of the matter and energy of actual systems are likely to fail since the organization that is required to maintain autonomy is organization that is suited to the matter and energy available to the system. It is in this context that the notion of basic autonomy reveals its importance: it provides a framework for relating organization tightly to the matter and energy of the system since the organization of interest is one which, given the energy and material to be utilized, is able to be built and maintained by the living system.

I have restricted myself in this paper to Moreno's notion of basic autonomy. As the reference to *basic* suggests, there are additional levels of autonomy.²⁹ These involve functions that can be performed within a system that further enhance the system's ability to maintain itself. Some of these involve ways of interacting with the environment. A basic autonomous system remains highly dependent upon moment to moment conditions of its environment since it must continually extract energy and raw materials from it and excrete waste into it. If energy and material resources are not provided in high enough concentration that the osmotic or pumping mechanisms in the membrane are able to bring them into the system or if waste accumulates to such a degree that they overwhelm the ability of the mechanisms to expel more waste, the viability of the system is undermined. By developing mechanisms to perform operations outside the organism itself and especially by developing mechanisms to navigate the environment, the organism can take proactive measures to insure the needed conditions of its environment and thereby increase its ability to maintain itself as a functioning system. It makes sense to construe these additional functions as enhancing the system's autonomy. Other ways of enhancing autonomy focus on the operations internal to the system. For example, by developing ways to perform operations more efficiently, procedures for storing energy and raw materials (or even recycling raw materials), and ways to regulate the internal environment, the system improves its ability to maintain itself.

In consider mechanisms that enhance autonomy, we must bear in mind that an organism must be able to construct all of these additional mechanisms itself. Each structure specialized to perform an additional operation must be constructed from matter and using free energy the system recruits from its environment and channels into the construction of the structure. Moreover, its operation requires energy that the system has recruited and made available. From the point of view of the autonomous system, each addition only makes sense if the benefit it provides in terms of maintaining the system equals or exceeds the costs of constructing and maintaining the addition. In this way, as Moreno himself emphasizes, the notion of autonomy provides a framework to speak of function not just as something that is done by the system but done for the system: "*Functional* actions in this context are those that ensure the self-maintenance and autonomy of the organization" (p. 241) Since it is the organization of the whole that is being maintained, function cannot be assessed locally but only in the context of the whole system.³⁰

²⁹ Other theorists, such as Collier and Hooker (1999), link the notion of autonomy to more active behavior of a system such as adapting to varied circumstances and anticipating the response of the environment its behavior. They maintain that autonomy, adaptivity, anticipation, and reproducibility are all required before one has a living system. While in fact most real organisms are adaptive and do anticipate responses of the environment to their actions, and these provide an extremely potent source for learning and hence further development, I think it is conceptually important to focus initially on basic autonomy and then consider additions to it.

³⁰ The sense of function provided by focusing on organisms as autonomous systems is different from both the sense of function invoked in purely causal accounts that treat any activity of a system as its function or evolutionary

Evolution via natural selection is a process that over time can develop systems with greater autonomy. Although not denying the traditional accounts of evolution (e.g., that evolution requires mechanisms of variation and selective retention³¹), the focus on autonomous systems provides a rather different perspective. First, it places the organism in the central role and emphasizes that an organism needs to be able to maintain itself as an autonomous system. Otherwise, there is nothing to evolve. This does not mean that individual organisms must be totally self-sufficient. Organisms can evolve to rely on features of the environment that are regularly present to them. But they need to create and maintain all the mechanisms upon which they rely in order to use these resources. Second, each addition to the basic system involves a cost in that the system must generate and repair these mechanisms itself. Evolution is not just a matter of introducing and selecting new genes, but requires a system that builds and maintains new traits (i.e., new mechanisms).

I have been emphasizing the value of focusing on organization as it subserves autonomy in understanding biological mechanisms. In concluding, I must acknowledge that in practice a great deal of significant biological research has proceeded without considering how the mechanisms investigated subserve the autonomy of a living system. From this research we have acquired substantial understanding of the mechanisms involved in living systems. This is possible since a researcher can focus on a mechanism as operating in a specified way without considering it as subserving the autonomy of the organism. What, then, is the value of emphasizing autonomy and the demands it imposes on organisms? This can be answered in two ways. First, despite its many successes, when mechanistic science fails to attend to organization it often reaches a point of identifying the parts but not understanding how they succeed in producing the phenomena exhibited in living organisms. Such frustration is part of the explanation of the current appeal of developing a systems approach to biology where tools for mathematically modeling systems complement those for identifying components. Second, discovery of the mechanisms actually operative in nature is often fostered by understanding the constraints under which they work. Lacking constraints, there are often too many possibilities and it is difficult to determine which possibility is the actual one being sought. Maintaining autonomous functioning is a critical constraint on any biological mechanism, and considering the requirements autonomy imposes provides constraint for investigators trying to figure out the mechanisms at work.

accounts that treat as functional only traits that have been selected in the past (adaptations) or traits that enable the organism to meet current selection forces (adaptive traits).

³¹ Ruiz-Mirazo and Moreno argue that before evolution can function to produce systems with greater autonomy, an autocatalytic replication system that is independent of the catalytic metabolic system is required: “hereditary autonomous systems have no other possibility but to start producing two types of macromolecular components that will take up different but complementary functions in the organization of those systems. The two types of components (informational records and highly specific catalysts or, equivalently, genotype and phenotype) strongly depend on each other, and their (code-mediated) complex interrelation changes profoundly the organization of autonomous systems, at both the individual (metabolic) and the collective (ecological) level” (Kepa Ruiz-Mirazo & Moreno, 2004, p. 251). In Ruiz-Mirazo, Peretó, and Moreno (2004, p. 330), the authors add evolutionary potential to autonomy in characterizing living beings: “*a living being’ is any autonomous system with open-ended evolutionary capacities.*”

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