To appear in S. Normandin and C. Wolf (Eds.). *Vitalism and the scientific image in post-enlightenment science, 1800-2010*. Springer

Addressing the Vitalists' Challenge to Mechanistic Science: Dynamic Mechanistic Explanation

William Bechtel[1]
Department of Philosophy, Center for Chronobiology, and
Interdisciplinary Programs in Science Studies and Cognitive Science
University of California, San Diego

1 Introduction

The vitalists-mechanist controversy of the 18th and 19th centuries is often portrayed in terms of the progressive mechanists being opposed by the reactionary vitalists. As far as the mechanists were concerned, the picture is basically correct—the mechanists were charting a new path, one that would prove immensely productive in generating biological knowledge. They were, in carrying out the program that Descartes had envisaged but only pursued speculatively, showing how many of the phenomena exhibited in living organisms could be explained in terms of the component parts of those organisms carrying out component operations in much the same manner as is the case in human-engineered machines. Many of the vitalists, however, were astute critics, recognizing the limitations of the mechanistic accounts of their day. The limitations were not just incidental but went to the core of the mechanistic project as it was pursued—they recognized that the mechanist accounts lacked the resources to account for some of the most fundamental features of living organisms. Unlike the human-engineered machines that provide the model for mechanistic accounts, organisms build, sustain, and repair themselves. In doing this they are not just reactive—they are endogenously active.

While correctly identifying the complexity of the phenomena associated with life, the vitalists were in worse shape than the mechanists they criticized when it came to explanation for they had no research program to pursue to explain these distinctive features of living systems. Those vitalists who availed themselves of non-mechanistic forces or powers didn't provide explanations but merely labeled the difference. Ultimately, I will argue, mechanistic biology can and is being extended to address the vitalists' objections. This requires taking seriously the importance of the way organisms are organized and, as is currently being done in parts of systems biology, drawing upon mathematical tools such as those of dynamical systems theory to understand how appropriate modes of organization can give raise to endogenously active mechanisms.

The challenges to mechanistic biology take on new currency in the wake of the emergence of the new mechanistic philosophy of science. As I will argue, the accounts of the new mechanists provide an accurate philosophical analysis of mechanistic biology as it has been

[1] The paper was partly written while I was a fellow at the Institute for Advanced Studies of the Hebrew University of Jerusalem. I am most grateful for their support and the valuable exchanges with colleagues there.

practiced. But while noting the importance of organization, they tend to focus on rather simple modes of organization, emphasizing sequential execution of operations from "start or set-up to finish or termination conditions." I will contrast this *basic* conception of mechanism with one that recognizes that the organization of biological mechanisms is often nonsequential and that this gives rise to ways of behaving (especially when the component operations are nonlinear) that cannot readily be captured in the qualitative and intuitive analyses offered by the basic accounts. Rather, they require developing mathematical representations and invoking the resources of dynamical systems theory to appreciate how such mechanisms will behave. Abrahamsen and I refer to accounts integrating mechanistic decomposition of systems into parts and operations with the quantitative tools provided by dynamical systems theory as *dynamic mechanistic explanations*.

I begin in section 2 with a characterization of mechanistic biology as it developed in the 19th and 20th centuries and in section 3 develop the account of basic mechanistic explanation, showing how it not only correctly characterizes mechanistic science but also offers significant advantages over the previously dominant tradition in philosophy of science that appealed primarily to laws in explanation. In section 4 I introduce what I take to be the most serious vitalist challenge to mechanistic biology—the fact that living systems seem to resist external forces imposed on them—and describe a first step in the mechanist's response—the introduction of a mode of non-sequential organization, negative feedback, to explain homeostasis. In section 5 I explore a further response, one that recognizes that living systems are endogenously active and that such activity serves to maintain the autonomous existence of living organisms. Finally, I show in section 6 such endogenously active systems require non-sequential modes of organization, and that understanding the effects of such organization in mechanisms requires mathematical representation and modeling that results in dynamic mechanistic explanations. While the project of understanding the behavior of non-sequential organization through mathematical modeling is still in its infancy, I describe some of the tools being developed that promise to enable the mechanistic to finally offer explanations that address the vitalist's challenge.

2 Mechanism's Forte: Identifying Parts and Operations

In articulating the original mechanistic philosophy Descartes attempted to explain all features of material objects in terms of their being composed of corpuscles of particular size, shape, and motion. His speculative account of magnetism in terms of screw-shaped corpuscles whose motion pulled the attracted material to the magnet both exemplify his strategy and its limitations. Corpuscles were presumed to be too small to be seen and as a result researchers could not determine their properties through empirical inquiry. Moreover, the catalog of acceptable properties was too limiting to provide plausible accounts of the phenomena exhibited of living systems. But the machine metaphor was potent. Just as machines, from the simple classical machines such as the lever and pulley to the machines being developed by Descartes' contemporaries (weapons often exhibit the most inventiveness, but other devices such as flush toilets were being developed; Da Vinci's many inventions are illustrative), provided a model of how phenomena might be generated

by the coordinated action of parts that carried out different tasks. By reversing the process through which the machine was put together—decomposing it into its parts and examining the operations they could perform—someone other than the inventor could explain how a machine worked. Moreover, the parts from which such a machine might be made, or into which it could be decomposed, need not be primitive parts, but simply anything, including other machines, that were already available.

One of the early successes of developing mechanistic explanations of biological phenomena actually preceded Descartes. Harvey (1628) offered a mechanistic account of the circulation of blood, with the heart serving as a pump and the valves serving to restrict the flow of blood in one direction.[2] Ironically, Descartes dissented from Harvey and advanced his own mechanistic explanation in which the lungs were construed as a furnace that heated and thereby expanded the blood and so forced it out to the tissues. Descartes offered other speculative proposals for physiological mechanisms. Intrigued by the statues in the Royal Gardens that moved by hydraulic processes, for example, he proposed that the nervous system is a hydraulic mechanism in which animal spirits are forced to flow through one set of nerves from the senses to the ventricles of the brain and then, in another set of nerves, back the muscles, causing them to move.

Many of the mechanistic proposals advanced in physiology in the 150 years after Descartes were also highly speculative. But by the end of the 18th century researchers were developing experimental techniques that provided empirical evidence about the component parts of organisms and how they behaved on which they could base their proposals. I will briefly review two of the great success cases of mechanistic biology over the two ensuing centuries.

The first involved identifying the chemical constituents of organisms and appealing to reactions involving them to explain physiological phenomena. This project had actually begun in the era of phlogiston chemistry, but took new form with Lavoisier's demonstration that oxygen was a basic element. He generalized his account to other elements, several of which—oxygen, carbon, and hydrogen—he also showed to be primary constituents of living organisms. Berthollet (1780) soon added nitrogen. Based on their distinctive ratios of these basic elements, Prout (1827) proposed and Liebig (1831) refined the catalog of proteins, carbohydrates, and fats as the basic types of animal nutrients and initiated inquiry into how they were used in animals. The result was that during the 19th century proposed chemical theories could appeal either to basic elements or to proteins, carbohydrates, and fats in their theorizing about the chemical events in organisms. Liebig himself worked at both levels. Reasoning that plants already synthesized proteins, carbohydrates, and fats,[3] he hypothesized that animals only carried out catabolic reactions. More specifically, he hypothesized that proteins were incorporated into the body and used for muscle contraction whereas fats and carbohydrates were burned to produce animal

[2] As Hall (1969, Chapter 17) argues, Harvey was not a mechanist at a micromechanical level; for example, he construed blood as the vital fluid that directs the organization of descendent organisms in reproduction.

[3] He offered chemical accounts of how they did so in Liebig (1840).

heat (Liebig, 1842). This proposal was effectively refuted by physiological experiments (Fick & Wislicenus, 1866; Frankland, 1866), but this led to ever more intense inquiry into the actual processes in which foodstuffs were utilized in animals.

In his accounts of both the synthesis of organic compounds in plants and their breakdown in animals Liebig had stressed the importance of balanced chemical equations, but it constructing these he and subsequent chemists for most of the 19th century could only work at the level of chemical elements and speculate how they were added or removed from compounds in hypothesized reactions. A new level of explanation emerged towards the end of the 19th century with the identification of chemical groups (hydroxyl, phosphate, etc.); this enabled physiological chemists to identify a set of fundamental reactions (oxidations, reductions, phosphorylations) that could figure in physiological processes. Once Buchner (1897) showed that fermentation could be achieved in a cell-free preparation, researchers began trying to identify a pathway of reactions from glucose to alcohol or lactic acid. The initial efforts (Neuberg & Kerb, 1914) encountered a number of empirical obstacles but with the determination that the intermediates were phosphorylated compounds (Embden, Deuticke, & Kraft, 1933), researchers soon succeed in constructing an empirically well-supported account (Meyerhof & Lohmann, 1934; Meyerhof & Kiesslling, 1936; see Bechtel, 2006, for a discussion of this history).

A second major advance in mechanistic science was the discovery of cells as basic living units and mechanistic accounts of their function. Although reports of cells and theorizing about them goes back to Hooke's (1665) identification of cells in cork and Leeuwenhoek's (1719) identification of single-celled organisms, the microscopes available up through the early years of the 19th century introduced sufficient spherical and chromatic aberrations that one must assume that most of the cells researchers claimed to see during this period were artifacts. With improved microscopes that reduced these distortions, Brown (1833) observed the nucleus in orchids and this provided one of the foundations on which Schleiden (1838) argued that plant tissue generally consisted of cells. Schwann (1839) both extended the claim to animal tissue and developed a theoretical argument that cells were the fundamental unit in which the processes of life transpired. Although his insistence on cells as fundamental units suggested to some that he was a closet vitalist (Schwann, 1836, had argued that cells were necessary for fermentation, drawing the wrath of Wöhler and Leibig), a critical feature of Schwann's account of cells was that they were formed by a mechanical process of chemical precipitation analogous to crystal formation. He attributed the fact that some reactions only seemed to occur within cells to the distinctive chemical constituted they acquired through this precipitation process. When von Mohl (1835) and ultimately Virchow (1855) made a compelling case that cells arise by division of existing cells, it was they who seemed to abandon the attempts to ground cell formation in mechanical processes. A mechanistic account of these processes had to await further improvements in the optics of microscopes and the introduction of stains that revealed the complex behavior of chromosomes within the nucleus (Fol, 1873; Flemming, 1878). While there were controversial claims as to other organelles within cells, especially mitochondria (Altmann, 1890) and the Golgi apparatus (Golgi, 1898), the question of whether these were

artifacts was unresolved until the application of the electron microscope.[4] Determining what function mitochondria, the endoplasmic reticulum, the Golgi apparatus, etc., played required relating the observations made using electron micrographs with techniques such as cell fractionation that could localize enzymes in particular structures. With these new tools, though, cell biology developed, offering mechanistic explanations of a host of cellular phenomena by identifying basic operations with organelles and determining the enzymes within them that catalyzed the critical reactions (see Bechtel, 2006, for discussion of this history). The understanding of oxidative phosphorylation as resulting from the interaction of cytochromes with the inner mitochondrial membrane that allowed for the generation of a proton gradient that drove ATPase in reverse to synthesize ATP represents a crowning achievement of this endeavor.

These are just two of the research fields in which mechanistically oriented biologists made great progress in the 19th and 20th centuries. To those engaged in such progressive research, the vitalist's concerns that living processes might not be susceptible to mechanistic explanation seemed of little point. Some problems proved more challenging than others, but eventually each seemed to give way to a mechanistic account.

3 The New Mechanistic Philosophy of Science

During the period when mechanistic biology was achieving great successes in the 20th century, the dominant philosophical accounts of science provided little illumination. Highly influenced by Newton's success in articulating laws of motion that could subsume many phenomena from the terrestrial to the astronomical (consider, for example, the application of these laws to the motion of the pendulum), and comparable discovery of laws in other domains (the laws of thermodynamics, Olm's law and the Nernst equation for electrodynamics), the natural focus of philosophers was on laws of nature. Explanation on the accounts they offered involved showing how a given phenomenon represented an application of a law of nature. This became enshrined in the deductive-nomological (D-N) account advanced and defended by Hempel (1965, 1966) according to which one explained a phenomena by deriving a description of it from statements specifying one or more laws and initial conditions:

Law(s) (Newton's law of attraction)
Initial conditions (distance of object from the center of the earth)
$\therefore$ Phenomenon to be explained (object accelerates at 32 feet/sec^2)

While philosophers offered many illustrative examples from the physical sciences that fit this model, the attempts to provide examples from biology were generally uncompelling. A major reason for this is that there are few distinctively biological laws. When biologists speak of explaining a phenomenon, they only occasionally avert to laws (typically those of

[4] On of the pioneers in electron microscopy continued to challenge the reality of the Golgi apparatus (Palade & Claude, 1949a, 1949b) until research in his own laboratory revealed its role in packaging newly synthesized proteins for excretion (Jamieson & Palade, 1966).

physics and chemistry[5]) but commonly refer to discovering or identifying the mechanism responsible for the phenomenon. Wimsatt (1976) was one of the first philosophers to draw attention to this[6] and beginning in the 1990s a number of philosophers of biology and neuroscience began to focus on the role of mechanisms in explanations in these fields. Building on Wimsatt's insight as well as those of Simon (1962) and Kauffman (1971), Bechtel and Richardson (1993/2010) emphasized the processes by which scientists decompose mechanisms structurally into their parts and functionally into their operations. Emphasizing the same distinction between parts and operations (which they call *entities* and *activities*), Machamer, Darden, and Craver (2000, p. 3) proposed their widely cited characterization of mechanisms: "Mechanisms are entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions."[7] Skipper and Millstein (Skipper & Millstein, 2005) coined the label *new mechanistic philosophy of science* for this perspective.

All philosophical accounts of mechanisms emphasis that the parts and operations are organized and part of what this organization requires is that the different parts and operations are connected to each other, achieving what Machamer, Darden, and Craver speak of as "productive continuity." But the last phrase of their characterization of a mechanism—"from start or set-up to finish or termination conditions"—goes beyond insisting on productive continuity to impose a sequential ordering on the operations in the mechanism. This requirement, as we will see, is extremely problematic, and is a large part of what makes explanations that fit their characterization insufficient to explain many biological phenomena. Although the phrase is not employed in other characterizations of mechanism,[8] it does reflect the practices of many mechanistic biologists, who attempt to envisage sequentially the qualitative changes occurring in the mechanisms they investigate. More fundamentally, it also reflects the sequential nature of human mental processes that are employed in the attempt to understand the functioning of mechanisms. In particular, scientists rely on their processes of imagination, and research in cognitive neuroscience (see, e.g., Kosslyn, 1994) has revealed that in imagination we redeploy perceptual processes and so imagine changes sequentially.

---

[5] Laws of physics and chemistry are, of course, widely employed in explaining biological phenomena. While they are certainly important, a crucial question is whether it is the laws that are performing the crucial explanatory work. For a sustained argument that they are the vehicle of explanation in biology, see Weber (2005).

[6] He contended: "At least in biology, most scientists see their work as explaining types of phenomena by discovering mechanisms, rather than explaining theories by deriving them from or reducing them to other theories, and *this* is seen by them as reduction, or as integrally tied to it" (Wimsatt, 1976, p. 671).

[7] For related characterizations of mechanism, see Glennan (1996, 2002) and Thagard (2003, 2006).

[8] In particular, it was not part of Bechtel and Richardson's account, as part of their emphasis was on how research that started trying to fit parts and operations into a sequential order often lead researchers to abandon the quest and embrace more complex modes of organization. Bechtel and Abrahamsen (2005, p. 423) speak of the "orchestrated functioning of the mechanism."

Although in what follows I will focus on the shortcomings of this approach (which I call the *basic mechanistic approach*), it not only characterizes much of mechanistic biology but also provides a foundation on which one can fruitfully recast many of the fundamental issues in philosophy of science. I note three here. First, while in philosophical accounts laws are typically represented in propositions[9] and reasoning from laws is viewed as logical inference, mechanisms are often best represented in diagrams, and reasoning about them conducted in mental or computational simulations. In simple cases the diagram may just project a sequence of operations and the scientist can simulate the mechanism by rehearsing these in her head. In more complex cases, the diagram can represent multiple simultaneous reactions and when simulating these exceeds human capacity, the quantities depicted in them can be represented in equations and these used to conduct computational simulations. Second, while in philosophical accounts, reduction consists in the derivation of laws of one science from those of another (Nagel, 1961), mechanistic inquiry is reductionistic in another sense—it focuses on the constituent parts and operations of a mechanism. Such reductionistic mechanistic research does not promise to explain everything at the lowest level—rather, it recognizes that to explain the behavior of a mechanism the scientists must also determine how the mechanism as an organized whole engages other entities in its environment. If there is systemic organization between these entities and the mechanism, research must analyze it as well to understand how the mechanism will behave over time. As a result, mechanistic explanations are always multi-level accounts, integrating information about parts, operations, and organization within the mechanism with how the mechanism is situated in an environment (Bechtel & Abrahamsen, 2009; Craver, 2002, 2007; Craver & Bechtel, 2007). Finally, whereas the nomological tradition largely eschewed philosophical analysis of scientific discovery (for exceptions, see Langley, Simon, Bradshaw, & Zytkow, 1987; Thagard, 1988), the mechanistic approach has made discovery a focal concern and identified a range of strategies scientists employ in discovering mechanisms (Bechtel & Richardson, 1993/2010; Craver & Darden, 2001; Darden, 2006). (For further discussion of these and other differences between mechanistic and D-N explanations, see Bechtel & Abrahamsen, 2005.)

Below I will argue that the basic account of mechanistic explanation must be enriched in important respects to handle the vitalist's challenge. But for now it is important to note that it fits well the main threads in mechanistic science that I highlighted in section 1. Two major accomplishments of these mechanistic sciences were (1) to identify the parts of organisms, such as the parts of cells and the various types of molecules out of which they are composed, and (2) to determine the sorts of operations each performed. In the case of cell division, once the chromosomes were discovered, researchers identified the sequence of operations occurring in cell division. In the case of fermentation, after Buchner demonstrated that it could be accomplished in a cell-free extract, researchers sought the three carbon compounds into which glucose could be broken and these transformed in steps in the generation of alcohol or lactic acid. The same was true of other biochemical reactions, and when electron microscopy and cell fractionation were developed,

[9] In most scientific contexts they are represented as equations.

researchers took advantage of them to determine where in the cell various reactions occurred and how internal membranes contributed to phenomena such as oxidative phosphorylation. The triumph of mechanistic science has been the discovery of legions parts and determination of the operations they perform in generating important phenomena exhibited in living organisms.

4 The Vitalist's Challenge and Initial Responses: Homeostasis and Negative Feedback

As mechanistic biologists were seeing the promise of developing mechanistic explanations of phenomena exhibited by living organisms and eagerly trying to exploit it, vitalists were pointing out features of life that seemed beyond the scope of mechanistic explanation. Xavier Bichat provides an illuminating example. In part he seemed to embrace the mechanist project as he went so far as decomposing human organs into 21 different types of tissue and appealed to the different properties of these tissues to explain the properties of the various organs. But for him the efforts at decomposition could go no further—in particular, one could not explain the properties of the tissues by decomposing them into their chemical parts and operations. He offered two reasons for rejecting such further decomposition. He claimed, first, that the behavior of living organisms is too variable to be explained mechanically: "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). Second, he claimed that this behavior involves distinctive forces that actively resist those forces operative in the inorganic world that would destroy the living tissue if left unopposed: "life is the sum of all those forces which resist death."

For the most part, vitalists and mechanists talked past each other. Mechanists focused on phenomena for which it seemed possible to develop mechanistic explanations and saw in their success reason to carry on. As I noted above, some problems proved temporarily challenging, but these could safely be set aside until new strategies or techniques made it possible to pursue them. Thus, for the most part, mechanists did not address the vitalists' challenges—they ignored them. On this score Bernard (1865) was an exception—he took the vitalists' challenges, especially those of Bichat, seriously enough to address them. One of his objectives was to defend a deterministic physiology. For him a phenomenon was explained only when it could be demonstrated to occur in all situations in which the conditions specified in the explanation were satisfied and accordingly he directly responded to Bichat's claims about the irregularity of the behavior of living systems. In part his strategy was to show how to set up experiments that always produced the same result. But another part of his response was to provide a framework that explained the apparent indeterminacy in the behavior of organisms. He distinguished two environments—the internal environment in which the organs of an organism functioned and the external environment in which the organism as a whole functioned. The variability in the response of the organism to an external stimulus was due, he claimed, to the failure to properly consider the conditions in the internal environment. When one insured that the same conditions were maintained in the internal environment, responses to conditions in the external environment became deterministic.

The distinction between the internal and external environment also enabled Bernard to begin to develop a response to Bichat's claims about living organisms as resisting death. It is important for the functioning of components of the organism that the conditions in the internal environment are kept relatively constant. A prominent example from his own research was the process by which the liver converts glycogen to glucose whenever concentrations of glucose in the blood decline. This maintains a constant condition in which there is a supply of glucose to provide energy for energy-demanding operations. From examples such as these Bernard concludes: "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, 1929, p. 400). As a result of these processes directed at maintaining the constancy of the internal environment, organisms appear to resist the natural processes that would result in death (e.g., those that would deplete them of available glucose). Walter Cannon (1929) named this capacity *homeostasis* (from the Greek words for *same* and *state*).

Cannon identified a number of processes by which organisms maintain homeostasis. Some were as simple as accumulating surplus supplies in selected tissues (e.g., water in muscle or skin), or by converting them into a different form (e.g., glucose into glycogen) from which reconversion in time of need is possible. Others involved 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.

What underlies the processes Cannon identified is a mode of organization known as negative feedback, a mode of organization whose importance was only coming to be generally recognized at the time Cannon was working. Although most people are today familiar with the notion of negative feedback, it was an extremely challenging concept for humans to grasp and many still fail to grasp its full consequences. As far as we can tell, it was first introduced by Ksebios in about 270 BCE as part of his design for a water clock. To keep time accurately, he needed to ensure that water entered the recording vesicle at a constant rate. He accomplished this by inserting a second vesicle between the water intake and the recording vesicle, and added a floating plug that would rise up and close the intake when water reached the target level. The plug would drop to open the intake as soon as the water fell below the target. The solution in which behavior (closing the water supply) was dependent on a downstream effect (the rise of water above its target level) is elegant, but it wasn't readily generalized. When a way to regulate other technologies such as windmills and furnaces was required, the procedure of inserting something that would alter a process in light of its effect had to be invented *de novo* (Mayr, 1970). So when in 1788 Watt needed a governor to regulate the flow of steam in a steam engine to ensure that the appliances ran at a constant rate, he once again invented the process of negative feedback. In this instance the solution (discussed further below) attracted the attention of Maxwell, who provided a mathematical analysis of governors (Maxwell, 1868). Maxwell's analysis, the increasingly need for control in engineered mechanisms, and the discovery that biological systems often relied on the same procedure to regulate themselves, combined to make negative feedback a general principle of organization that was championed by the cyberneticists

as a general control architecture for biological as well as social and engineered systems (Wiener, 1948).[10]

What the legacy of theorizing from Bernard through the cyberneticists served to make clear is that the key to addressing many of the limitations of basic accounts of mechanistic explanation is attention to modes of organization beyond sequential organization. As momentous as is the step from sequential organization to negative feedback in allowing for the maintenance of a desired state within a mechanism, it represents only the first step beyond sequential organization, and many others are required to address the concerns of the vitalists and to demonstrate that mechanism is capable of explaining the distinctive features of living systems.

5 Beyond Cybernetics: Endogenous Activity and Autonomous Systems

In some ways a negative feedback system is quite easy to understand. Consider the governor Watt designed (Figure 1). Watt needed to insert within the steam engine some means of detecting whether the engine was running too fast or too slow that could be used to change the setting of the steam valve. He inserted a spindle that would revolve proportionally to the speed of the engine and attached to it arms with weights at the end that were free to move out or in by centrifugal force. When the engine sped up, the spindle rotated faster, and the arms moved out; when it slowed down, the spindle rotated more slowly, and the arms dropped. Now all he needed was a linkage mechanism that worked to close a valve on the steam supply when the arms moved out and open it when the arms moved in. From this verbal description and the diagram, most people are able to understand how the governor works. But there is an additional feature of negative feedback systems that such a verbal account fails to capture but with which engineers are only too familiar. Such systems oscillate. Sometimes when the system is allowed to run long enough it will reach a stable configuration; for instance, the valve will reach the setting at which the arms of the governor will cease to move. This constitutes a dampened oscillator, but even it generates interesting dynamics as it approaches the stable state, described in dynamical systems theory as a *fixed attractor*.

---

[10] Wiener himself had been engaged with Bigelow in the 1930s in the design of negative feedback systems for controlling anti-aircraft fire. In this endeavor they encountered a serious challenge: 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 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. Inspired by the ability of negative feedback to direct a mechanism toward a target, Rosenbleuth, Bigelow, and Wiener (Rosenblueth, Wiener, & Bigelow, 1943) argued that it provided a framework for employing such notions as teleology and purpose without invoking vitalism. Wiener secured support from the Macy Foundation for a series of twice-yearly conferences known as the Conference for Circular Causal and Feedback Mechanisms in Biological and Social Systems that attracted some of the leading theorists in biology and the social sciences; after he coined the term *cybernetics* from the Greek term for steersman, the movement adopted it as its name.

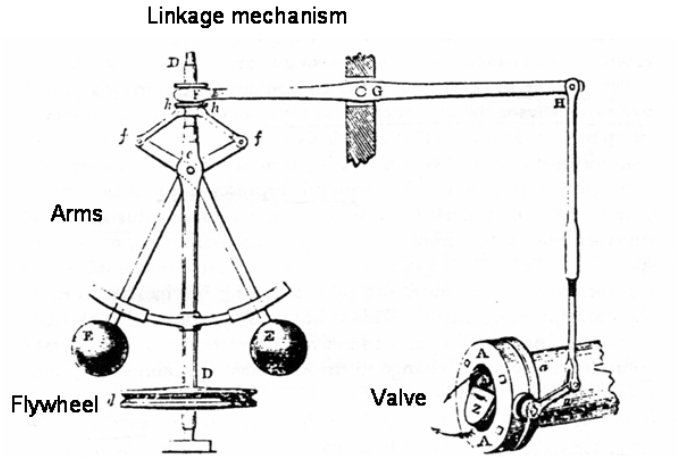

Figure 1: A schematic representation of the governor James Watt designed for his steam engine. The speed of the flywheel determines how far out the angle arms move by centripetal force. They are in turn linked to the valve in such a way that when the flywheel is turning too quickly, the steam supply 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.

Many negative feedback systems, however, fail to dampen but continue to oscillate. This is especially the case if there are delays within the system such as in the case of a furnace controlled by a thermostat. The temperature will drop below the target temperature before the furnace begins to produce heat, and will rise above it before the furnace is turned off. In many human engineered systems such oscillations are considered undesirable, and engineers strive to minimize them. But biological systems often make use of such oscillations. I briefly note three such systems:

1. *Circadian rhythms.* Organisms from cyanobacteria to us depend on internal clocks that represent time of day and regulate a great variety of physiological and behavioral processes (Bechtel, 2011). The operations required for these activities often require extensive time to prepare and organisms rely on being able to act in advance on the basis of tracking time endogenously. They do so through oscillatory processes that utilize multiple feedback loops (discussed further below).
2. *Central pattern generators.* Although the standard view of motor activities is that they are responses to sensory stimuli, pioneering research on decorticate preparations by Brown (1911, 1914) showed that stepping behavior occurs without input from cortex. Wilson (1961) showed that the isolated locust nervous system generated rhythmic output comparable to that produced in flight. Although in many cases the details of the mechanism are still not known, the paradigm cases involve what is referred to as a *half-center oscillator* involving two neurons that reciprocally inhibit each other in such a manner that after one neuron is inhibited by the other, it gradually depolarizes, reaches threshold, and begins to fire, now inhibiting the other (Hooper, 2001).
3. *Brain rhythms.* Research beginning with Berger (1929) revealed electrical activity that can be detected by electrodes placed on the scalp. The dominant frequency changes depending on the state of activity or sleep (alpha rhythms between 8-12 Hz

> dominate while sitting quietly, higher frequency rhythms are more evidence while performing cognitive activities, and slower rhythms while in various stages of sleep) but there is always oscillatory activity. More recently synchronized oscillatory activity at even lower frequencies (<.1 Hz) across networks of areas that are elicited together in task conditions have been detected in fMRI while subjects are at rest (Fox & Raichle, 2007). These rhythms are increasingly being recognized as playing important roles in various cognitive activities (see Buzsáki, 2006).

In Abrahamsen and Bechtel (in press) we speak of systems that continue to generate activity, such as oscillations, independently of input stimuli as *endogenously active*. Biological organisms are primary examples of endogenously active systems. The examples of circadian, motor, and brain rhythms are all instances of endogenous activity. But endogenous activity is far more ubiquitous. It is a notorious feature of humans that they have a very hard time sitting still. And it takes extensive training to stop one's mind from spontaneously generating thoughts. The active state is seemingly the default state. But endogenous activity is not limited to humans. Look at a bacterial cell in a microscope—it is constantly in motion, and it is a challenge to keep it within the range of view. There are times when organisms seem less active than at others, and there are organisms whose activity seems minimal. A sleeping or hibernating animal exhibits fewer spontaneous movements, and is harder to arouse it with stimuli. But even during sleep or hibernation, fundamental metabolic activities are continuing. Moreover, there is ongoing slow-wave oscillatory activity in the brain that can be detectable by EEG (and is regarded as the signature of sleep in mammals). Plants seem not to move except to grow, but time-lapse photography can reveal their movement to orient with the sun, and this continues even in the absence of exogenous cues such as sunlight. And again, basic metabolic activities including the transport of water, capturing energy, and building new tissue, are ongoing.

Endogenous activity is not a merely incidental feature of living organisms. It is crucial for living organisms to maintain themselves as living systems. Unlike many physical objects, which exist in relatively stable configurations due to the strength of the physical and chemical bonds that hold their parts together, living organisms are not stable structures. But nonetheless they maintain themselves by continually executing the operations needed to build or rebuild themselves. This was the point of Bichat's characterization of life as resisting death, a point that was developed in Varela's conception of the identity of living system as constituted by the organization which they maintain "through the active compensation of deformations" (Varela, 1979, p. 3). In articulating this idea Varela expands upon Cannon's notion of homeostasis to develop his own concept of *autopoiesis*. The extension involves two steps: (1) "making every reference for homeostasis internal to the system itself through mutual interconnections of processes" and (2) 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 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).

For current purposes, the critical feature in Varela's notion of autopoiesis is that the causal processes that build and rebuild the organism originate within it; they are not just the effects of external forces impinging on it.

Varela goes on to characterize autopoietic systems as autonomous systems: "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" (p. 15). He later elaborates

> 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).

The concept of autonomy requires features of endogenous activity I noted earlier—operations that build and maintain the living organism are controlled from within it and are not merely responses to conditions presented to it. The concept thus provides a helpful way to characterize what is distinctive about living systems and why they are able to resist death. In calling living systems autonomous, one is not denying that they interact with their environments in many ways and are dependent on these interactions. What autonomy does draw attention to is that these interactions with the environment are in part regulated from within the organism so that the organism directs the interactions in ways that maintain its own identity as an organism.

In characterizing autopoietic systems as autonomous, Varela does not draw attention to one of the most noteworthy features of such systems—a feature which in fact necessitates the internal regulation of activity. This is the fact that biological organisms are, as highly organized systems, far from thermodynamic equilibrium with their environments. As such they dissipate Gibbs free energy. Moreover, since they are chemical systems, not solid systems, such dissipation will be relatively rapid. As a result, organisms must draw free energy as well as matter from sources in their environments and after consuming the energy and the useful matter, release waste-products, now in a lower energy state, back into their environment. The free energy and material that is secured from the environment must be utilized to build and repair the organism (restoring what was lost through dissipation), and this requires channeling it appropriately to the reactions that carry out the synthesis and repair. In animals captured free energy is typically stored in the phosphate bonds of ATP that can then be broken down in energy demanding operations. Managing the creation and distribution of these molecules is thus a critical task.

Kepa Ruiz-Mirazo and Alvaro Moreno (2004) have made these energetic considerations central to their account of autonomy. They begin with the recognition that as organized systems, living organisms are far from thermodynamic equilibrium and that preserving that organization entails maintaining themselves far from equilibrium (cf. Schrödinger, 1944). Many of the chemical reactions required to maintain such a system are endergonic (require 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, Ruiz-Miorazo and Moreno focuses on how the system *manages* the flow of energy so as to provide for its own construction and reconstruction. The membrane presents 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, they 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 (Ruiz-Mirazo & Moreno, 2004, p. 240; see also Ruiz-Mirazo, Peretó, & Moreno, 2004, p. 330).

I contend that with the concept of autonomy theorists such as Ruiz-Mirazo and Moreno have captured the phenomenon that vitalists thought defied mechanistic explanation. But they have not just relabeled that phenomena—they have shown what is required of an organism, consisting of mechanisms, to realize it. The key is coordinated organization so that the various operations performed within mechanisms and by overall mechanisms are directed at building and maintaining the overall identity of the organism as an entity that, as a result of that very organization, is far from equilibrium with its environment. The challenge for the mechanist is to develop appropriate ways to understand how such organization generates the requisite effects.

6 From Basic to Dynamic Mechanistic Explanations

I turn now to the implications of this perspective on biological organisms as endogenously active autonomous systems for the sorts of mechanisms found in biology and the challenges for scientists in understanding them. A mechanism that operates sequentially to carry out operations only when their start conditions are realized and stops when their termination conditions are reached cannot generate the sustained, endogenous behavior that is required to keep the organism far from equilibrium. Only a mechanism with cyclic organization, such as a feedback system, has the capacity to keep itself going by supplying the various operations with the conditions needed for their operation. As a result, it is not surprising that the organization found in biological organisms (either in the organisms as a whole or within its individual mechanisms) is nonsequential (Bechtel & Abrahamsen, 2011).

Understanding how a nonsequentially organized mechanism behaves is challenging. In mentally rehearsing individual operations, researchers lose track of how the functioning of other components affects these operations. As I noted, even with simple negative mechanisms researchers cannot determine whether the mechanism will generate ongoing oscillations or settle into a stable state. The project of identifying the parts and characterizing the operations of a mechanism explanation must be complemented by that of mathematically and computationally modeling to show how such a mechanism will operate. The result is dynamic mechanistic explanation (Bechtel & Abrahamsen, 2010).

I illustrate the project of dynamic mechanistic explanation first in the case of simple negative feedback. Figure 2 shows the mechanism Hardin, Rosbash and Hall (1990) proposed for the circadian clock in animals. In it a gene, *period* or *per* is transcribed into its mRNA, which then is transported to the cytoplasm where it is translated into the corresponding protein PER. PER then is transported back into the nucleus and in some manner impairs its own transcription. (Although many additional constituents have been identified in the two subsequent decades, this is still thought to constitute the core intracellular mechanism underlying circadian rhythms.)

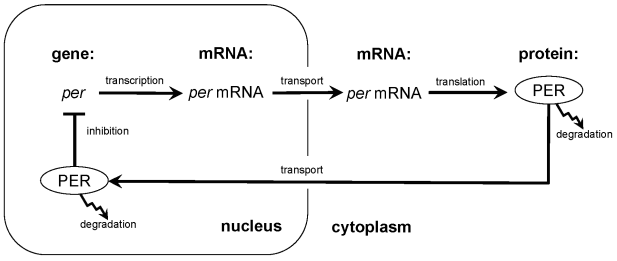

Figure 2. The mechanism for generating circadian rhythms through a transcription, translation feedback loop as proposed by Hardin et al. (1990).

A critical question is whether such a mechanism could generate sustained oscillations of approximately 24 hours, or will it dampen to a steady state. To address this question, Goldbeter (1995) first represented the mechanism in terms of variables and parameters and then wrote a set of five differential equations to characterize the functioning of the mechanism. The left side of Figure 3 shows the relation between one of these equations and an operation shown in Figure 2. Goldbeter was then able to numerically simulate the functioning of the mechanism and show that with plausible parameter values it would produce what in dynamical systems terms is known as a *limit cycle*: as shown on the right of Figure 3, the values of two parameters (*per* mRNA and PER) change over time but approach a cycle in which the rise in the quantity of *per* mRNA is followed by the rise in the quantity of PER. Only then does the quantity of *per* mRNA drop, followed in turn by the drop in the quantity of PER.

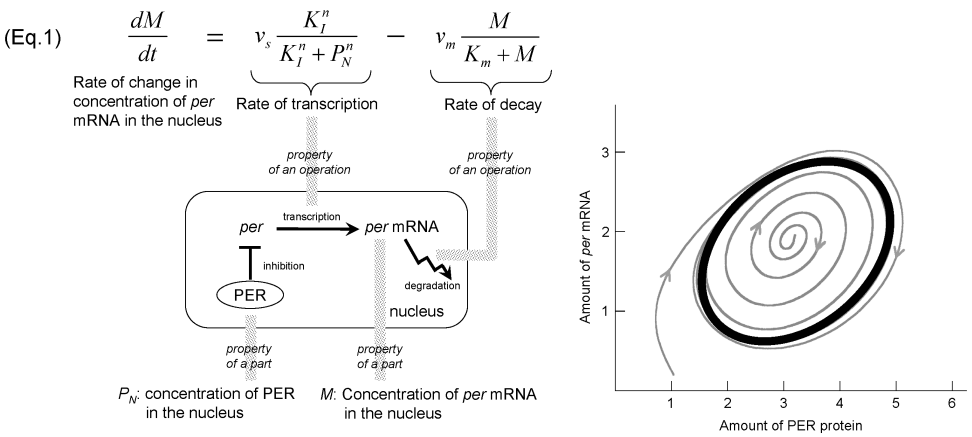

Figure 3. On the left the first equation in Goldbeter's (1995) model is related to the relevant components of the mechanism, as illustrated on the right of Figure 2. On the right is the limit cycle generated from the model with what Goldbeter claimed were plausible parameter values.

With nonsequential organization, especially when the operations are nonlinear, any change could potentially affect the behavior of the mechanism. Thus, the discovery of additional components in the animal circadian clocks and the determination that there are probably three feedback loops that interact with each other, demanded further modeling endeavors with much more complex models to assess how such a mechanism will behave (see, e.g., Leloup & Goldbeter, 2008).

A cursory examination of the current understanding of biological mechanisms reveals that the circadian case is far from exceptional and that sequential execution of operations is the exception rather than the rule. One of the products to emerge from mechanistic science in the past two decades has been the development of massive databases identifying the components (genes, proteins, neurons, etc.) of even relatively simply biological organisms such as bacteria. Although our knowledge of the operations in which these particulate is far from complete, when they are presented in networks in which in which nodes represent the components and edges the interactions, one gains an appreciation of the complexity of the system. The overall organization is far from sequential. A returning vitalist might become convinced that they were right all along (see Kirschner, Gerhart, & Mitchison, 2000). The mechanistic project of decomposing the mechanism into its parts and operations simply cannot show how the parts will behave as a result of receiving various inputs from across the network and how such a network as a whole will behave. Even if science could identify all the parts, determine all the operations in which they participated, and from equations simulate the operation of the whole organism, the modern day vitalist might complain that one would have no explanation of why the organism behaved as it did. In identifying such complexity, mechanism might have finally generated its own undoing.

While the task is daunting, the prospects for dynamic mechanistic explanation are a good deal more promising than this suggests. There appears to be order in the complexity, and this order is precisely what is required for dynamic mechanistic explanation to make progress. Let's consider first the overall structure of the sorts of large networks researchers encounter. Initially mathematicians in the field of graph theory focused on two

sorts of networks, regular lattices and randomly (or completely) connected graphs. Two important measures were developed for characterizing these two forms of organization: a clustering coefficient which indicates to how many of its neighbors an individual node is typically connected and a characteristic path length which indicates the average shortest path between two randomly selected target. Regular lattices have, not surprisingly, both a high clustering coefficient and characteristic path length while random networks have both a low clustering coefficient and characteristic path length.

While regular lattices and random networks are the easiest to analyze mathematically, Watts and Strogratz (1998) found that many real-world networks fall into a class that lies between them, which they designated *small worlds*. In these networks most connections are between neighbors, thus generating a high clustering coefficient close to that of a regular lattice. A few connections are long-distance, though; adding just a few of these radically reduces the characteristic path length so that it approximates that of a random network. Thus, small worlds exhibit both local clusters of nodes and high levels of integration across the whole network. These conditions, as Watts and Strogatz indicated in their initial paper, are precisely what is desired for processing information.[11]

The occurrence of local clusters or modules brings us back within the context of mechanistic explanation, which emphasizes decomposition of the mechanism. Local clusters can perform specific operations even as this performance is modulated by the long-distance connections that integrate them into a larger small-world network. But what is the organization of these local clusters? A common finding is that within large networks, such as a cell signaling system or the mammalian brain, the local clusters themselves have small-world organization, allowing, as in the mechanist project, for further decomposition. But how are components, at whatever level of organization on which one focuses (individual molecules or neurons, or small-world networks of these) organized into the next larger structure? Here a complementary tool is being developed—the analysis of motifs—which offers great insight into how mechanisms are organized.

Motifs are characterized as patterns of connections between components that occur far more often than would be expected in a randomly generated network with the same number of nodes and edges (Alon, 2007). Alon and his collaborators developed an algorithm for detecting motifs and applied it first to the transcription factors and the operons they regulate in *Escherichia coli* (Shen-Orr, Milo, Mangan, & Alon, 2002). What is particularly interesting is that analysis of these motifs can reveal how small networks with these designs will behave. The feedforward loops they identified are especially interesting and will serve to illustrate their approach.[12] In feedforward loops an initial transcription

[11] Subsequent research by Barabási and his colleagues (Barabási & Albert, 1999; Barabási & Bonabeau, 2003) has shown that in many real world networks the number of edges per node is not randomly distributed but follows a power-law such that most nodes have few connections but a very few are highly connected. These constitute hubs.

[12] Although these motifs do not involve feedback and so cannot generate on their own oscillations or other complex behavior which is crucial for maintaining endogenously

factor X regulates a second transcription factor Y, and X and Y jointly regulate operon Z. Regulation at any step can be positive or negative. Although there are eight possible combinations of positive and negative connections, only the consistent loop illustrated with two examples on the left and the inconsistent loop illustrated with an example on the right in Figure 4 are realized in the *E. coli* network much more often than they occur in randomly-generated networks. (A loop is consistent if the two routes to the output both operate in the same manner—accelerate or inhibit, and inconsistent if they operate in the opposite manner—one accelerates and one inhibits.) To analyze these networks, Alon and his colleagues treat the regulation of Z as involving either an OR and an AND operation, which are sufficiently close approximations of the continuous functions that occur in actual operons not to affect the accuracy of the analysis.

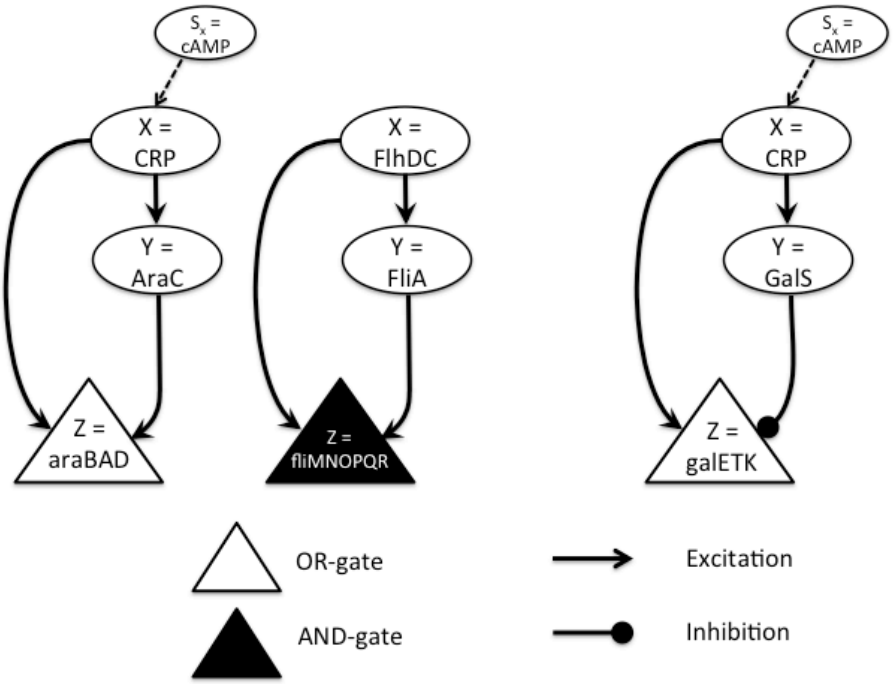

Figure 4. Left: Two consistent feedforward loops of type 1, one employing an AND-gate and one an OR-gate in the regulation of Z. Right: Inconsistent feeedforward loop of type 1.

The consistent feedforward loop functions as what Alon characterizes as a sign-sensitive delay. In the example feedforward loop with an AND-gate (Mangan, Zaslaver, & Alon, 2003) (employed in the system for converting to use of arabinose as a fuel source), when the input cAMP is supplied to X it begins to generate its product CRP (cyclic response protein). After a sufficient quantity is generated to exceed a threshold, Y=AraC begins to be synthesized, but only when it reaches a threshold does Z=araBAD begin to be synthesized. The production of the output araBAD is delayed by the time it takes for sufficient Y to accumulate (approximately 20 minutes). Alon proposes that the utility of this is to prevent

---

active mechanisms, they do generate interesting behaviors which require mathematical analysis.

responses to spurious pulses of cAMP, which can last about the same period as the delay. This can be important since vital resources may be utilized in generating araBAD when it is not needed. With an AND-gate there is no delay in terminating the response but when an OR-gate is employed (as in the mechanism controlling the generation of the flagellum motor), the response will continue until the supply of Y (FliA) is also depleted (Kalir, Mangan, & Alon, 2005). This allows fliLMNOPQR to continue to be generated even during a temporary interruption of the input signal (active FlhDC), leading Alon to characterize it as a persistence detector. It, however, operates with no delay after the initially appearance of the input signal. The inconsistent feedforward loop using an OR gate shown on the right (used in the mechanism regulating galactose utilization) results in pulses of the output product galETK due to the fact that the production of CRP initially begins generation of galETK, but after GalS reaches threshold, it inhibits galETK production (Mangan, Itzkovitz, Zaslaver, & Alon, 2006). A further consequence of this arrangement is that the output can initially be produced at a very high rate without significantly overshooting the target because of the subsequent suppression by the intermediate.

I have characterized the feedforward loop motif in qualitative terms since as they are sufficiently simple that one can understand these behaviors in such a manner. However, the importance of computational modeling is not thereby negated as the details of how any particular mechanism employing the motif will behave depend upon the particular parameter values found in an actual mechanism. In the above descriptions I assumed that the parameter values were such that the direct path to Z produce its effect before the indirect path. If that were violated, the mechanism would behave differently. Moreover, under particular parameter values these motifs can generate more complex behavior, and Alon and his colleagues are still engaged in such a process of discovery, in part by experimenting with additional biological mechanisms exhibiting the motif and in part by sampling parameter values in computational models. Further, while the feedforward motif does not employ feedback, others of the motifs they have identified do, including motifs involving single nodes that feedback positively or negatively on themselves. Multiple motifs can be combined. Although apparently not in bacterial transcription networks, feedforward loops can be included within larger networks employing feedback.

The strategy of identifying motifs and analyzing how they affect the operation of a mechanism provides a means to generate understanding of how organization affects the behavior of biological mechanisms. Motif analysis, together with the analysis of the overall connectivity pattern of larger networks, and the more complex dynamics that arise with feedback loops, are instances of dynamic mechanistic explanation—explanation that focuses on modes of organization and uses computational modeling and dynamical systems tools to analyze the consequences of such organization for the behavior of a mechanism.

Having introduced the framework of dynamic mechanistic explanation and sketched some of the ways it can be pursued, I finish with a brief discussion of some of the issues to which it gives rise. In one respect dynamic mechanistic explanations are closer to D-N explanations than are basic mechanistic explanations. In characterizing the effects of different modes of organization they are generalizing beyond a specific mechanism to the generic features of such organization. Thus, the focus is on networks in which one

considers only the connectivity represented by the edges, not the specific features of the components that occupy the nodes, and tries to ascertain how such a network will behave. For the purposes of the analysis, it does not matter whether the occupants are genes, proteins, neurons, neural columns, brain regions, people, or social groups. There are parameter values in the model that must be satisfied before it applies to any given mechanism, but often the focus is on developing models that are robust over a broad range of parameter values. Thus, in utilizing the mathematical equations developed in the dynamical models, one is applying them to specific mechanisms, much as the D-N model applies laws to different sets of initial conditions. The mathematical equations one uses in dynamic models, however, are not presented as general laws. While they are not specific to individual mechanisms, they are specific to particular modes of organization (change a node or an edge in a motif, and a different set of equations will be required). Moreover, unlike D-N accounts, dynamic mechanistic explanation is still anchored in the mechanism in that the mathematical representation is characterizing how a mechanism with a specific form of organization will behave.[13]

7 Conclusions

The challenges of vitalists such as Bichat to mechanism, despite the evidence successes of mechanistic explanations for many biological phenomena, have been my focus. My contention has been that the phenomena to which vitalists appealed in objecting to mechanism are ones entwined with endogenous activity and autonomy and that biological organisms generate activity endogenously and acquire autonomy as a result of the modes of organization exhibited in them. A mechanism or an organized system of mechanisms that can maintain itself in a far from equilibrium condition is one that is organized so as to insure the appropriate relations between operations so that it can capture energy and deploy it in the continuing endeavor to construct and repair itself. Understanding the effects of such organization requires going beyond the approach of basic mechanistic explanation in which scientists attempt to simulate the sequential operation of parts in their heads. Rather, they must invoke a different set of tools, characterizing the mechanism mathematically and performing and analyzing computational simulations. Such an approach integrates the tools of traditional mechanistic science that facilitate decomposing the mechanism and generating basic mechanistic explanations with tools of dynamical analysis that facilitate recomposing the complexly organized mechanism in simulation. This integration of approaches is what Abrahamsen and I refer to as *dynamic mechanistic explanation*. Only such an integrated approach has the resources to deal with the type of

[13] The approach is thus different from that that advocated by some proponents of dynamical systems theory in psychology who propose dynamical explanation as an alternative to mechanistic explanation (Chemero & Silberstein, 2008; Stepp, Chemero, & Turvey, 2011). For responses to the proposal to cleave dynamics from mechanism, see Kaplan and Bechtel (2011) and Kaplan and Craver (in press). In Bechtel and Abrahamsen (2010) we argue that many computational models in cognitive science, especially neural network models, are mechanistic in spirit, but since little is known about the components and their actual operations, the models remain hypothetical and not accounts of actual mechanisms.

mechanisms that can account for the distinctive features of living systems to which the vitalists drew attention.

References

Abrahamsen, A., & Bechtel, W. (in press). From reactive to endogenously active dynamical conceptions of the brain. In T. Reydon & K. Plaisance (Eds.), *Philosophy of behavioral biology*. New York: Springer.

Alon, U. (2007). Network motifs: theory and experimental approaches. [10.1038/nrg2102]. *Nat Rev Genet, 8*, 450-461.

Altmann, R. (1890). *Die Elementaroganismen und ihre Beziehungen zu den Zellen*. Leipzig: von Veit.

Barabási, A.-L., & Albert, R. (1999). Emergence of scaling in random networks. *Science, 286*, 509-512.

Barabási, A.-L., & Bonabeau, E. (2003). Scale-free networks. *Scientific American*, 50-59.

Bechtel, W. (2006). *Discovering cell mechanisms: The creation of modern cell biology*. Cambridge: Cambridge University Press.

Bechtel, W. (2011). Representing time of day in circadian clocks. In A. Newen, A. Bartels & E.-M. Jung (Eds.), *Knowledge and representation*. Palo Alto, CA: CSLI Publications.

Bechtel, W., & Abrahamsen, A. (2005). Explanation: A mechanist alternative. *Studies in History and Philosophy of Biological and Biomedical Sciences, 36*, 421-441.

Bechtel, W., & Abrahamsen, A. (2009). Decomposing, recomposing, and situating circadian mechanisms: Three tasks in developing mechanistic explanations. In H. Leitgeb & A. Hieke (Eds.), *Reduction and elimination in philosophy of mind and philosophy of neuroscience* (pp. 173-186). Frankfurt: Ontos Verlag.

Bechtel, W., & Abrahamsen, A. (2010). Dynamic mechanistic explanation: Computational modeling of circadian rhythms as an exemplar for cognitive science. *Studies in History and Philosophy of Science Part A, 41*, 321-333.

Bechtel, W., & Abrahamsen, A. (2011). Complex biological mechanisms: Cyclic, oscillatory, and autonomous. In C. A. Hooker (Ed.), *Philosophy of complex systems. Handbook of the philosophy of science* (Vol. 10, pp. 257-285). New York: Elsevier.

Bechtel, W., & Richardson, R. C. (1993/2010). *Discovering complexity: Decomposition and localization as strategies in scientific research*. Cambridge, MA: MIT Press. 1993 edition published by Princeton University Press.

Berger, H. (1929). Über daas Elektroenkephalogramm des Menschen. *Archiv für Psychiatrie und Nervenkrankheiten, 87*.

Bernard, C. (1865). *An introduction to the study of experimental medicine*. New York: Dover.

Bernard, C. (1878). *Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux*. Paris: Baillière.

Berthollet, C. L. (1780). Recherches sur la nature des substances animales et sur leurs rapports avec les substances végétales. *Mémoires de l'Acadeâmie royale des sciences*, 120-125.

Bichat, X. (1805). *Recherches Physiologiques sur la Vie et la Mort* (3rd ed.). Paris: Machant.

Brown, R. (1833). On the organs and mode of fecundation in Orchideae and Asclediadeae. *Transactions of the Linnean Society, 16*, 685-745.

Brown, T. G. (1911). The Intrinsic Factors in the Act of Progression in the Mammal. *Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character, 84*, 308-319.

Brown, T. G. (1914). On the nature of the fundamental activity of the nervous centres; together with an analysis of the conditioning of rhythmic activity in progression, and a theory of the evolution of function in the nervous system. *The Journal of Physiology, 48*, 18-46.

Buchner, E. (1897). Alkoholische Gärung ohne Hefezellen (Vorläufige Mittheilung). *Berichte der deutschen chemischen Gesellschaft, 30*, 117-124.

Buzsáki, G. (2006). *Rhythms of the brain*. Oxford: Oxford University Press.

Cannon, W. B. (1929). Organization of physiological homeostasis. *Physiological Reviews, 9*, 399-431.

Chemero, A., & Silberstein, M. (2008). After the philosophy of mind: Replacing scholasticism with science. *Philosophy of Science, 75*, 1-27.

Craver, C. F. (2002). Interlevel experiments and multilevel mechanisms in the neuroscience of memory. *Philosophy of Science, 69*, S83-S97.

Craver, C. F. (2007). *Explaining the brain: What a science of the mind-brain could be*. New York: Oxford University Press.

Craver, C. F., & Bechtel, W. (2007). Top-down causation without top-down causes. *Biology and Philosophy, 22*, 547-563.

Craver, C. F., & Darden, L. (2001). Discovering mechanisms in neurobiology: The case of spatial memory. In P. K. Machamer, R. Grush & P. McLaughlin (Eds.), *Theory and method in neuroscience* (pp. 112-137). Pittsburgh, PA: University of Pittsburgh Press.

Darden, L. (2006). *Reasoning in biological discoveries: Essays on mechanisms, interfield relations, and anomaly resolution*. Cambridge: Cambridge University Press.

Embden, G., Deuticke, H. J., & Kraft, G. (1933). Über die intermediaren Vorgänge bei der Glykolyse in der Muskulatur. *Klinische Wochenschrift, 12*, 213-215.

Fick, A. E., & Wislicenus, J. (1866). On the origin of muscular power. *Philosophical Magazine & Journal of Science London, 4th ser., 31*, 485-503.

Flemming, W. (1878). Zur Kenntnis der Zelle und ihrer Theilungserscheinungen. *Schriften des naturwissenschaftlicher Verein für Schleswig-Holstein, 3*, 23-27.

Fol, H. (1873). Le premier développement de l'oeuf chez les Géronidés. *Archives des sciences physiques et naturelles, 2nd series. 48*, 335-340.

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience, 8*, 700-711.

Frankland, E. (1866). On the source of muscular power. *Royal Institution of Great Britain. Notices of the proceedings at the meetings of the members, 4*, 661-685.

Glennan, S. (1996). Mechanisms and the nature of causation. *Erkenntnis, 44*, 50-71.

Glennan, S. (2002). Rethinking mechanistic explanation. *Philosophy of Science, 69*, S342-S353.

Goldbeter, A. (1995). A model for circadian oscillations in the *Drosophila* Period protein (PER). *Proceedings of the Royal Society of London. B: Biological Sciences, 261*, 319-324.

Golgi, C. (1898). Intorno alla struttura delle cellule nervose. *Bollettino della Società Medico-Chirurgica di Pavia, 13*, 3-16.

Hall, T. S. (1969). *Ideas of life and matter; studies in the history of general physiology, 600 B.C.-1900 A.D.* Chicago: University of Chicago Press.

Hardin, P. E., Hall, J. C., & Rosbash, M. (1990). Feedback of the *Drosophila period* gene product on circadian cycling of its messenger RNA levels. *Nature, 343*, 536-540.

Harvey, W. (1628). *Exercitatio anatomica de motu cordis et sanguinis in animalibus*. Francofurti: Sumptibus Guilielmi Fitzeri.

Hempel, C. G. (1965). Aspects of scientific explanation. In C. G. Hempel (Ed.), *Aspects of scientific explanation and other essays in the philosophy of science* (pp. 331-496). New York: Macmillan.

Hempel, C. G. (1966). *Philosophy of natural science.* Englewood Cliffs, NJ:: Prentice-Hall.

Hooke, R. (1665). *Micrographia: or some physiological descriptions of minute bodies made by magnifying glasses with observations and inquiries thereupon*. London: John Martin and James Allestry.

Hooper, S. L. (2001). Central Pattern Generators. *eLS*: John Wiley & Sons, Ltd.

Jamieson, J. D., & Palade, G. E. (1966). Role of the Golgi complex in the intracellular transport of secretory proteins. *Proceedings of the National Academy of Sciences (USA), 55*, 424-431.

Kalir, S., Mangan, S., & Alon, U. (2005). A coherent feed-forward loop with a SUM input function prolongs flagella expression in Escherichia coli. [10.1038/msb4100010]. *Mol Syst Biol, 1*.

Kaplan, D. M., & Bechtel, W. (2011). Dynamical models: An alternative or complement to mechanistic explanations? *Topics in Cognitive Science, 3*, 438-444.

Kaplan, D. M., & Craver, C. (in press). The explanatory force of dynamical and mathematical models in neuroscience: A mechanistic perspective. *Philosophy of Science*.

Kauffman, S. (1971). Articulation of parts explanations in biology and the rational search for them. In R. C. Bluck & R. S. Cohen (Eds.), *PSA 1970* (pp. 257-272). Dordrecht: Reidel.

Kirschner, M., Gerhart, J., & Mitchison, T. (2000). Molecular "Vitalism". *Cell, 100*, 79-88.

Kosslyn, S. M. (1994). *Image and brain: The resolution of the imagery debate*. Cambridge, MA: MIT Press.

Langley, P., Simon, H. A., Bradshaw, G. L., & Zytkow, J. M. (1987). *Scientific discovery: Computational explorations of the creative process*. Cambridge: MIT Press.

Leeuwenhoek, A. v. (1719). *Epistolae physiologicae super compluribus naturae arcanis*. Delft: Beman.

Leloup, J.-C., & Goldbeter, A. (2008). Modeling the circadian clock: From molecular mechanism to physiological disorders. *BioEssays, 30*, 590-600.

Liebig, J. (1831). Ueber einen neuen Apparat zur Analyse orgaischer Körper, und über die Zusammensetzung einiger organischer Substanzen. *Annalen der Physik und Chemie, 21*, 1-43.

Liebig, J. (1840). *Organic Chemistry in its Applications to Agriculture and Physiology*. London: Taylor and Walton.

Liebig, J. (1842). *Animal chemistry: or organic chemistry in its application to physiology and pathology*. Cambridge: John Owen.

Machamer, P., Darden, L., & Craver, C. F. (2000). Thinking about mechanisms. *Philosophy of Science, 67*, 1-25.

Mangan, S., Itzkovitz, S., Zaslaver, A., & Alon, U. (2006). The incoherent feed-forward loop accelerates the response-time of the gal system of *Escherichia coli*. *Journal of Molecular Biology, 356*, 1073-1081.

Mangan, S., Zaslaver, A., & Alon, U. (2003). The coherent feedforward loop serves as a sign-sensitive delay element in transcription networks. *Journal of Molecular Biology, 334*, 197-204.

Maturana, H. R., & Varela, F. J. (1980). Autopoiesis: The organization of the living. In H. R. Maturana & F. J. Varela (Eds.), *Autopoiesis and cognition: The realization of the living* (pp. 59-138). Dordrecht: D. Reidel.

Maxwell, J. C. (1868). On governors. *Proceedings of the Royal Society of London, 16*, 270-283.

Mayr, O. (1970). *The origins of feedback control*. Cambridge, MA: MIT Press.

Meyerhof, O., & Kiesslling, W. (1936). Über den Hauptweg der Milchsäurebildung in der Muskulatur. *Biochemische zeitschrift, 263*, 83-113.

Meyerhof, O., & Lohmann, K. (1934). Über die enzymatische Gleichgewichtsreaktion zwischen Hexosediphosphorsäure und Dioxyacetonphosphorsäure. *Die Naturwissenschaften, 22*, 220.

Nagel, E. (1961). *The structure of science*. New York: Harcourt, Brace.

Neuberg, C., & Kerb, J. W. (1914). Über zukerfreie Hefegärungen. *Biochemische Zeitschrift, 58*, 158-170.

Palade, G. E., & Claude, A. (1949a). The nature of the Golgi apparatus. I. Parallelism between intercellular myelin figures and Golgi apparatus in somatic cells. *Journal of Morphology, 85*, 35-69.

Palade, G. E., & Claude, A. (1949b). The nature of the Golgi apparatus. II. Identification of the Golgi apparatus with a complex of myelin figures. *Journal of Morphology, 85*, 71-111.

Prout, W. (1827). On the ultimate composition of simple alimentary substances; with some preliminary remarks on the analysis of organised bodies in general. *Philosophical Transactions of the Royal Society of London, 117*, 355-388.

Rosenblueth, A., Wiener, N., & Bigelow, J. (1943). Behavior, purpose, and teleology. *Philosophy of Science, 10*, 18-24.

Ruiz-Mirazo, K., & Moreno, A. (2004). Basic autonomy as a fundamental step in the synthesis of life. *Artificial Life, 10*, 235-259.

Ruiz-Mirazo, K., Peretó, J., & Moreno, A. (2004). A universal definition of life: Autonomy and open-ended evolution. *Origins of Life and Evolution of the Biosphere, 34*, 323-346.

Schleiden, M. J. (1838). Beiträge zur phytogenesis. *Archiv für Anatomie, Physiologie und wissenschaftliche Medecin*, 137-176.

Schrödinger, E. (1944). *What is life? The physical aspect of the living cell*. Cambridge: Cambridge University press.

Schwann, T. (1836). Über das Wesen des Verdauungsprocesses. *Archiv für Anatomie, Physiologie und wissenschaftliche Medecin*, 90-138.

Schwann, T. (1839). *Mikroskopische Untersuchungen über die Übereinstimmung in der Struktur und dem Wachstrum der Theire und Planzen*. Berlin: Sander.

Shen-Orr, S. S., Milo, R., Mangan, S., & Alon, U. (2002). Network motifs in the transcriptional regulation network of Escherichia coli. [10.1038/ng881]. *Nat Genet, 31*, 64-68.

Simon, H. A. (1962). The architecture of complexity: hierarchic systems. *Proceedings of the American Philosophical Society, 106*, 467-482.

Skipper, R. A., & Millstein, R. L. (2005). Thinking about evolutionary mechanisms: Natural selection. *Studies in History and Philosophy of Biological and Biomedical Sciences, 36*, 327-347.

Stepp, N., Chemero, A., & Turvey, M. T. (2011). Philosophy for the rest of cognitive science. *Topics in Cognitive Science, 3*, 425-437.

Thagard, P. (1988). *Computational philosophy of science*. Cambridge, MA: MIT Press/Bradford Books.

Thagard, P. (2003). Pathways to biomedical discovery. *Philosophy of Science, 70*, 235-254.

Thagard, P. (2006). *Hot thought: Mechanisms and applications of emotional cognition*. Cambridge, MA: MIT Press.

Varela, F. J. (1979). *Principles of biological autonomy*. New York: Elsevier.

Virchow, R. (1855). Cellular pathology. In L. Rather (Ed.), *Disease, life, and man: Selected essays of Rudolf Virchow*. Stanford: Standford University Press.

von Mohl, H. (1835). Über die Vermehrung der Pflanzenzellen durch Teilung.

Watts, D., & Strogratz, S. (1998). Collective dynamics of small worlds. *Nature, 393*, **440-442**.

Weber, M. (2005). *Philosophy of experimental biology*. Cambridge: Cambridge University Press.

Wiener, N. (1948). *Cybernetics: Or, control and communication in the animal and the machine*. New York: Wiley.

Wilson, D. M. (1961). The central nervous control of flight in a locust. *Journal of Experimental Biology, 38*, 471-490.

Wimsatt, W. C. (1976). Reductionism, levels of organization, and the mind-body problem. In G. Globus, G. Maxwell & I. Savodnik (Eds.), *Consciousness and the brain: A scientific and philosophical inquiry* (pp. 202-267). New York: Plenum Press.