Constitutive Control: How Experimental Control Strategies Co-Evolved with Biological Knowledge in 19th-Century Physiology

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How do different experimental control strategies shape the production of biological knowledge? This paper examines Emil du Bois-Reymond's electrophysiological investigations and Claude Bernard's toxicological research in 19th-century physiology. Rather than viewing these as opposing methodologies, I analyze their approaches to nerve-muscle communication as complementary responses to shared epistemic challenges. Using Schickore's framework for experimental control (2025), I show through a detailed historical analysis that experimental control functioned constitutively rather than merely technically in both research programs. Both scientists engaged in extensive second-order experimentation, systematically exploring their experimental setups to determine what factors needed controlling. Du Bois-Reymond's nonpolarizable electrodes made possible new ways of understanding biological electricity as quantifiable phenomena, while Bernard's ligature preparation constituted a method for understanding physiological functions as systematically separable within integrated organisms. Control practices and theoretical commitments co-evolved such that what counted as legitimate operationalization of theoretical principles was shaped by experimental practice. This analysis shows how experimental methodology and biological knowledge co-develop, suggesting implications for understanding methodological tensions in contemporary biological research.

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1. Introduction

Why do experiments generate more compelling evidence than other forms of empirical investigation? What distinguishes experimentation from mere observation in producing reliable knowledge about natural phenomena? The answer that I will explore in this paper points to experimental control, understood broadly as the systematic management of conditions which enables reliable causal inference.[1] To unpack this intuitive idea I will examine the epistemic functions that experimental control has played in concrete historical scientific contexts and how specific control strategies have developed over time.

In contemporary science, finding a control is often treated as "equivalent with figuring out what the experiment is doing" (Schickore 2025, p. 1), which in turn suggests that experimental control involves something more than methodological housekeeping. Despite being invoked as markers of experimental rigor and epistemic reliability, Schickore argues that control experiments remain "routinely taken for granted and rarely defined." To address this conceptual gap, she has put forward a multilevel framework (2019, 2025) which distinguishes between broad control (managing experimental conditions) and narrow control (comparative experimental designs), while identifying different levels of analysis: control strategies, practices, and methodological ideas. Through the lens of her analytical framework, this paper uses detailed historical investigation to understand how different strategies for managing experimental conditions shaped scientific investigation during a crucial period of methodological development. Rather than testing philosophical theories against historical evidence, this approach treats historical analysis as "explication work for philosophy" (Schickore 2018)—clarifying what various experimental control strategies accomplish in different research contexts by examining how they have emerged and developed historically.

My analysis unpacks two key episodes from nineteenth-century physiology, where biological phenomena increasingly became accessible to experimental manipulation. I will focus my inquiry on two leading figures whose experimental approaches addressed related aspects of nerve-muscle function through markedly different methodological commitments: Emil du Bois-Reymond and Claude Bernard. Du Bois-Reymond's systematic investigation of the "negative variation" (the decrease in electrical current accompanying nervous and muscular excitation) established key electrophysiological evidence about nervous activity that would prove significant

1. For a different stance on tackling more directly these questions about the epistemic privilege of experiments, see e.g., Levy and Currie 2019; Potochnik, Colombo, and Wright 2018.

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for understanding nerve-muscle relationships. When Bernard's toxicological research led him to conclude that curare abolished motor nerve function, the continued presence of electrical activity in curarized nerves that had lost all motor function (as demonstrated by du Bois-Reymond's methods) created a paradox that Bernard and his contemporaries had to address: if the nerves retained electrical function, why couldn't they activate muscles? This empirical puzzle arose precisely because the two physiologists approached nerve-muscle relationships through different experimental traditions—electrical measurement versus toxicological intervention. Yet their findings intersected around key questions about the nature of nervous transmission, revealing both the possibilities and limitations of their respective control strategies.

Comparing how du Bois-Reymond and Bernard conceptualized and implemented experimental control allows me to track how their approaches evolved over time and examine the specific functions that different control strategies served in their research programs. Rather than treating their methodological differences as reflecting incompatible experimental cultures, this analysis reveals how both developed sophisticated responses to shared epistemological challenges.

The argument proceeds through several stages. Section 2 introduces Schickore's analytical framework for understanding experimental control and contrasts this approach with interpretations that emphasize methodological opposition between the two physiologists (Finkelstein 2023). Sections 3 and 4 present detailed case studies of each physiologist's experimental practice. I start with du Bois-Reymond's investigations of animal electricity, emphasizing his systematic development of the negative variation experiments and the control innovations that enabled reliable electrophysiological measurements. I then examine Bernard's toxicological research on curare, focusing on his ligature experiments and his struggles to develop an explanation of nerve-muscle transmission that could accommodate electrophysiological evidence. Section 5 compares the sophisticated control strategies both scientists developed for managing similarly challenging experimental conditions. The analysis reveals that experimental control functioned constitutively rather than merely technically in both research programs—that is, control strategies and practices proved inseparable from the development of knowledge claims and explanations. Du Bois-Reymond's precision-oriented approach focused on developing technical solutions to control known sources of experimental error, while Bernard's integrative methodology favored systematic exploration to identify what factors might influence physiological processes under specific experimental conditions. Both approaches developed over time, with control strategies evolving in response to experimental challenges and

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theoretical developments. Section 6 draws out broader implications for contemporary biological research.

Examining the relationships between these experimental methodologies illuminates not only the historical development of experimental physiology but also continuing methodological tensions in contemporary biological research. Current debates in systems biology, for instance, reflect similar challenges in balancing reductionist precision with integrative approaches to complex biological networks. Likewise, contemporary discussions about reproducibility and experimental standardization often involve tensions between technical control of known variables and exploratory investigation of unknown factors—tensions that parallel those evident in 19th-century physiology. Rather than representing incompatible experimental cultures, this historical analysis suggests that understanding them as different control approaches to shared epistemic challenges may clarify current methodological discussions without prescribing universal solutions.

2. Analytical Framework: Experimental Control in Historical Context

The concept of experimental control occupies a curious position across both scientific practice and philosophical analysis: standardly recognized as essential for reliable experimentation, yet rarely subjected to systematic examination in either domain (cf. Schickore 2025; Schickore and Newman 2024). Scientists routinely invoke experimental controls as markers of methodological rigor while leaving the concept largely unexamined. On the other hand, philosophers of science have provided surprisingly few systematic analyses of what experimental control actually accomplishes across different research contexts.[2]

Recent historical studies (e.g., Schickore 2023; Schickore and Newman 2024) have shown how addressing this conceptual imprecision through detailed historical analysis can foreground important aspects of experimental methodology that remain obscured by more generalist philosophical approaches. Rather than treating experimental control as a methodological

2. This is not to say that experimental control has been entirely neglected in philosophical analysis. Edwin Boring's "The Nature and History of Experimental Control" (1954) is one of the few systematic philosophical treatments, distinguishing three meanings of control in experimentation: restraint (keeping conditions constant), guidance (manipulating variables), and comparison (checking results). More recently, Potochnik, Colombo, and Wright (2018) have offered formal definitions of "perfectly controlled experiments" within broader discussions of scientific methodology. However, as Schickore (2025) argues, even these contributions tend to focus on idealized epistemological conditions rather than examining how experimental control actually functions and develops in concrete research contexts.

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overlay applied to pre-existing knowledge, Schickore (2025) argues that understanding the epistemology of experimental control requires examining its design phase or the "making" of controlled experiments. This process, she contends, is simultaneously constitutive of the knowledge gained in experimentation, contingent on specific research situations, and historically shaped by evolving traditions and available technologies.

This perspective proves particularly fruitful for reexamining apparent methodological conflicts in nineteenth-century physiology, where focusing on surface-level contrasts may obscure more complex relationships between seemingly competing experimental approaches. By applying Schickore's framework to the alleged opposition between the experimental work of Emil du Bois-Reymond and Claude Bernard, this analysis aims to refine and extend her general claims by examining how different control strategies evolved to address shared epistemic challenges in early experimental physiology.

Schickore's most recent analysis (2025) shifts attention from the more familiar and narrow notion of control experiments understood as comparative experimental trials to the broader notion of control concerned with the management of background factors, including the systematic probing of experimental conditions that enables reliable causal inference. While acknowledging both notions as important, her work establishes that controlling for background factors represents an epistemologically complex and dynamic process involving multiple layers of conceptualization and material manipulation. For biological systems, where complex integration means that multiple factors will affect experimental outcomes, this distinction becomes crucial for understanding how scientists were able to build robust experimental knowledge. Importantly, Schickore shows that managing background factors involves both material-technical and conceptual-epistemic dimensions that intertwine rather than follow sequentially—technical innovations often constitute new conceptual possibilities, while theoretical developments reshape what technical solutions become necessary.

To enhance analytical precision, Schickore develops a three-level framework distinguishing between control strategies, control practices, and methodological ideas. Control strategies represent general designs and plans for approaching experimental problems, encompassing both managing experimental conditions and implementing comparative trials. Control practices are the concrete actions (specific techniques, instruments, and protocols) by which experimenters implement strategies in particular contexts. Methodological ideas encompass broader notions about how to study nature, including philosophical commitments about the nature of phenomena, assumptions about adequate experimental evidence, and beliefs

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about relationships between different scales of organization. This framework avoids conflating different levels of analysis while recognizing their interconnections, enabling examination of how philosophical commitments shaped general strategies, how strategies were implemented through specific practices, and how both evolved in response to experimental challenges and theoretical developments. Applying these categories to du Bois-Reymond's and Bernard's work allows precise analysis of how their apparent methodological opposition may reflect different but complementary approaches to experimental rigor.

Central to Schickore's framework is recognizing that experimental control represents an evolving process rather than static achievement. Experimental control and understanding of phenomena co-evolve through historical processes, with experimenters gradually learning what must be controlled through 'second-order experimentation'—systematic exploration of experimental setups themselves. In her earlier work, Schickore (2019) distinguished between diagnostic probing (exploring what factors might affect outcomes) and determinative probing (controlling factors already identified as relevant). Whether these represent distinct epistemic functions or complementary phases in all experimental programs remains an open question.

Du Bois-Reymond's and Bernard's experimental work on nerve-muscle physiology provides an opportunity to examine these issues. Finkelstein (2023) has characterized their relationship as reflecting a strong methodological opposition, emphasizing du Bois-Reymond's reductionist, instrument-based approach versus Bernard's holistic, observational methodology. However, examining their control strategies through Schickore's framework enables a more precise analysis: How did each approach manage background factors? What second-order experimental work did they undertake? How did their control strategies relate to their broader methodological ideas? Do different control strategies constitute different ways of understanding phenomena, or different technical approaches to the same phenomena? How do disciplinary backgrounds and available technologies shape what control strategies investigators can pursue? Addressing these questions reveals that rather than straightforward opposition, their different strategies for experimental control emerged and functioned as complementary responses to shared epistemic challenges. This historical analysis potentially refines our understanding of how experimental control develops while illuminating continuing tensions in contemporary biological methodology.

3. The Case of Emil du Bois-Reymond

3.1. The Scientific Debate over "Animal Electricity"

When Emil du Bois-Reymond entered the field of electrophysiology in 1841, he confronted a set of unresolved questions that had divided natural

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philosophers for over half a century (Clarke and Jacyna 1988; Bresadola and Piccolino 2013; Barbara 2013; Barbara and Corvol 2012, p. 22; Bechtel and Vagnino 2022, p. 7). The dispute over "animal electricity" originated in the competing explanations offered by Luigi Galvani and Alessandro Volta for the phenomenon of muscular contractions in prepared frog legs when connected by metallic arcs. Galvani's hypothesis proposed that living organisms generated their own electricity through a "nervous fluid" that flowed between nerve and muscle tissue.[3] Volta's alternative explanation attributed observed electrical effects to "contact electricity"—currents generated by the contact between dissimilar metals rather than intrinsic biological processes.

By the 1840s, the empirical landscape had grown even more complex. Galvani himself had conducted experiments demonstrating electrical effects in frog preparations without metallic contact, and these findings were later confirmed by Alexander von Humboldt (1799) and Leopoldo Nobili (1827–1830). Nobili's work proved particularly significant—he replaced the galvanoscopic frog leg preparation with his sensitive astatic galvanometer, enabling quantitative measurement of what he termed the "courant de grenouille" or "proper current." Building on this work, Carlo Matteucci systematically documented what he in turn called "demarcation currents"—electrical currents flowing between the intact surface and cut cross-section of striated muscles—and establishing their consistent polarity using both galvanoscopic frog legs and galvanometric measurements (Matteucci 1840, 1842a, 1842b). More puzzling still, he had observed that these currents appeared to diminish or disappear entirely during tetanic muscle contractions, a phenomenon he described as early as 1838 (Matteucci 1838a, 1838b).

This latter observation presented Matteucci with a theoretical problem that he could not resolve. If muscular activity generated electrical phenomena (as suggested by his discovery of the "induced twitch" in 1842[4], where contraction in one muscle preparation could trigger contractions in a

3. Hoff (1936) points out that Galvani was not the first to study the electrical stimulation of muscles or the physiological effect of a bi-metal, nor did he invent the hypothesis of muscular contraction. In fact, according to Hoff, Galvani's main contribution is to have systematically pursued experimental efforts to establish the truth of a current scientific hypothesis. Kipnis (1987) also provides a more nuanced historical account of Galvani's contributions to early electrophysiology showing the pitfalls of evaluating it solely through the lens of modern scientific theories or by reducing it to the Galvani-Volta controversy.

4. Matteucci first announced the induced twitch phenomenon in a sealed communication to the Académie des Sciences de Paris on February 28, 1842, opened during the October 24 session (C. R. Acad. Sci. (Paris) 15 1842, pp. 797–798). He published detailed results in "Sur un phénomène physiologique produit par les muscles en contraction" (Ann. Chim. Phys. ser. III 6 1842, pp. 339–343) and provided comprehensive documentation in chapter X of his Traité des phénomènes électro-physiologiques des animaux (1844).

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second, connected preparation), how could the same muscular activity simultaneously eliminate existing electrical currents? Matteucci found himself "trapped in apparent contradictions that his experimental methodology could not resolve" (cf. Moruzzi 1996, p. 85).

So when Johannes Müller assigned his student, du Bois-Reymond, to investigate and extend Matteucci's work, the field was still facing difficult experimental control challenges. First, there was the issue of *artefact control*: "contact electricity" generated by metal electrodes made it impossible to distinguish experimental artefacts from genuine biological currents. Second, existing galvanometers lacked sufficient sensitivity to detect weak biological signals reliably, which fueled debates about whether biological currents could be detected in the first place. Finally, no investigator had been able to demonstrate decisively whether electrical currents played a genuine causal role in nerve-muscle communication or remained mere epiphenomena of other physiological processes. These were not merely technical obstacles but epistemological challenges about how to establish reliable experimental knowledge about biological electricity.[5]

Du Bois-Reymond aimed to resolve these control challenges and establish that electricity governed the action of the nerves. This ambitious goal required not merely detecting "animal electricity" but proving that electrical phenomena in biological tissues operated according to the same quantitative principles as inorganic electrical phenomena—meaning they could be measured with the same instruments, showed reproducible patterns across different species and tissue types, and responded predictably to the same experimental manipulations. The following sections examine how du Bois-Reymond's approach to experimental control evolved in response to these interconnected problems.

3.2. From "Demarcation Currents' to the "Negative Variation"

To address the control challenge of establishing whether electrical phenomena played a genuine causal role in nerve-muscle communication, du Bois-Reymond began by systematically reproducing and extending some of the most promising earlier findings. One of his first steps was to confirm and extend Matteucci's observations using more sensitive instrumentation. His enhanced astatic galvanometer enabled him to detect

5. My analysis of du Bois-Reymond's experimental work relies on both primary sources (particularly his *Untersuchungen über thierische Elektricitä*, 1848-1884) and Gabriel Finkelstein's authoritative historical studies (2003, 2013, 2023), which provide comprehensive accounts based on extensive archival research. Where I describe experimental procedures and historical details, I draw substantially on Finkelstein's detailed reconstructions while analysing them through Schickore's framework for understanding control strategies.

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the same baseline currents that Matteucci had previously reported[6], confirming the presence of continuous weak currents in both muscle and nerve preparations, with current flowing from the exterior surface to the axial cross section.

Du Bois-Reymond's systematic methodology is evident in the structure of his 1843 *Preliminary Abstract*[7], where each finding is presented as building on the previous: confirming baseline electrical currents, establishing their spatial organization, demonstrating analogous phenomena in nerve tissue, and culminating in establishing the phenomenon of the "negative variation" (*die negative Schwankung*)—a decrease in baseline electrical current during tetanic contraction. This discovery transformed what Matteucci had noted as a puzzling contradiction into the centerpiece of a new theory: systematic changes in electrical phenomena became for him the mechanism by which nerves communicated with muscles (Figure 1).

The basic experimental arrangement (as reconstructed by Finkelstein 2003, p. 274) du Bois-Reymond developed to demonstrate the phenomenon of the negative variation involved three key components. First, he prepared biological specimens (typically frog gastrocnemius muscle with attached nerve) and placed them across his newly developed non-polarizable electrode system—conducting vessels filled with saturated salt solution, with multiple layers of filter paper creating conducting pads that eliminated direct metal-tissue contact.[8]

6. Du Bois-Reymond preferred in this case to use galvanometers over Matteucci's rheoscopic frogs for three reasons. First, his use of the astatic galvanometer reflected his philosophical commitment to demonstrating the unity of organic and inorganic electrical phenomena required physical rather than biological detection instruments. Second, there was the technical superiority of the instrument, as galvanometers could measure electrical direction, intensity, and variation while frog preparations provided only binary responses. And finally, enhanced astatic galvanometers were supposed to secure some measure of competitive strategy, since Matteucci had already established extensive work with rheoscopic methods, leaving instrumentation as the domain where du Bois-Reymond could distinguish his contributions (cf. Finkelstein 2013, pp. 66–7).

7. The publication of du Bois-Reymond's "Preliminary Abstract" (January 1843) in Poggendorff's *Annalen der Physik* was strategically orchestrated by his advisor Johannes Müller to establish priority over Matteucci. Du Bois-Reymond deliberately made the abstract cryptic and sparse, revealing his discoveries without disclosing his methods, and sent an expanded French translation to Paris to ensure his findings reached continental competitors. The publication compressed six months of breakthrough research into a priority-establishing outline designed to demonstrate what had been accomplished without facilitating experimental replication (Finkelstein 2013, pp. 68–9).

8. Du Bois-Reymond claimed that Matteucci's use of weak saline solutions soaked into cotton wool, rather than proper conducting vessels, had prevented detection of currents in isolated muscles. By developing precise electrode protocols with controlled electrolyte depth and strength, du Bois-Reymond transformed what Matteucci saw as species-specific "frog currents" into universal bioelectrical phenomena governed by systematic spatial relationships—current flowing not from interior to exterior as Matteucci had claimed, but from long-section to cross-section, with long-section referring to surfaces parallel to the muscle grain and cross-section to surfaces perpendicular to it.

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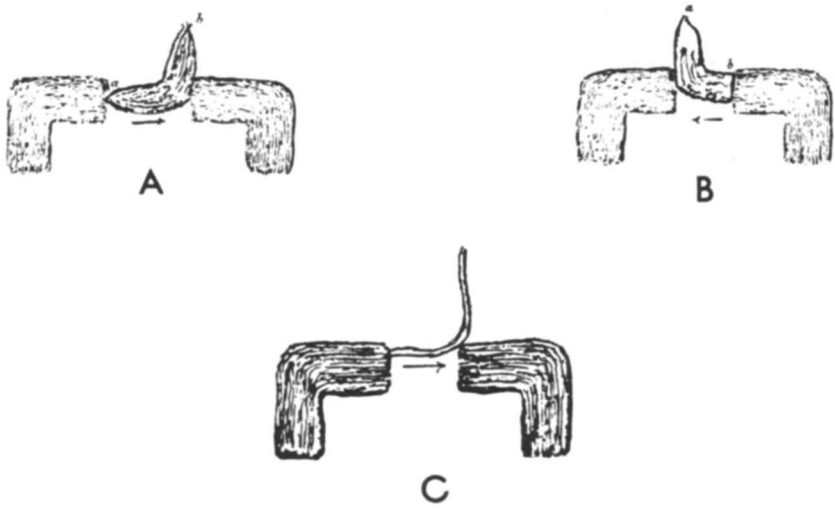


Figure 1. Du Bois-Reymond's demonstration of muscle and nerve currents from his 1843 *Preliminary Abstract*. (A) Muscle current: electrodes placed on the exterior surface of the muscle and the cut tendon detect current flowing from the longitudinal surface to the cross-section, with the surface electropositive relative to the tendon. (B) Nerve current: electrodes positioned on the exterior surface of nerve fibers and their cross-sectional area (after cutting) show current flowing from the intact surface to the damaged cross-section, with the exterior surface electropositive relative to the axial section. (C) Combined preparation demonstrating the relationship between nerve and muscle currents. These systematic measurements established du Bois-Reymond's baseline observations that preceded his discovery of the negative variation, illustrating his precision-oriented approach to controlling and quantifying electrical phenomena in biological tissues. Reproduced from du Bois-Reymond (1848) vol I.

Second, this preparation was connected to his astatic galvanometer, which measured the baseline electrical current flowing from the muscle's longitudinal surface to its cross-section. Third, a separate set of stimulating electrodes, connected to a magneto-electromotor, was positioned to deliver tetanizing electrical shocks to the nerve. With the muscle preparation in place and the galvanometer needle settled at its baseline deflection (indicating the normal muscle current), du Bois-Reymond would activate the magneto-electromotor. As tetanic contractions seized the muscle, the galvanometer needle would reverse direction, "passing straight through the zero point of the dial into the negative quadrant."[9] Du Bois-Reymond interpreted the

9. Du Bois-Reymond's laboratory notebooks, 1841–2, and *Untersuchungen über thierische Elektricität*, vol. ii, pp. 50–1, as cited in Finkelstein 2013, pp. 73–4.

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negative variation as demonstrating that nervous activity produced measurable changes in tissue electricity—providing the crucial link between electrical phenomena and biological function (Figure 2).

This demonstration raised a crucial methodological challenge: since du Bois-Reymond used electrical stimulation to investigate electrical phenomena, sceptics could reasonably question whether the galvanometer deflections reflected genuine nervous activity or merely artefacts of the stimulation apparatus itself. Through systematic second-order experimentation (i.e., experiments designed to probe the experimental setup itself), du Bois-Reymond developed a sophisticated control using two galvanometers positioned at opposite ends of a single nerve preparation, with stimulating electrodes placed at the midpoint (du Bois-Reymond 1848, ii.300–303; cf. Finkelstein 2003, p. 278). When he applied alternating current stimulation, both galvanometer needles deflected simultaneously into the negative quadrant, demonstrating that the electrical changes occurred throughout the entire nerve rather than being confined to the stimulation site. This control

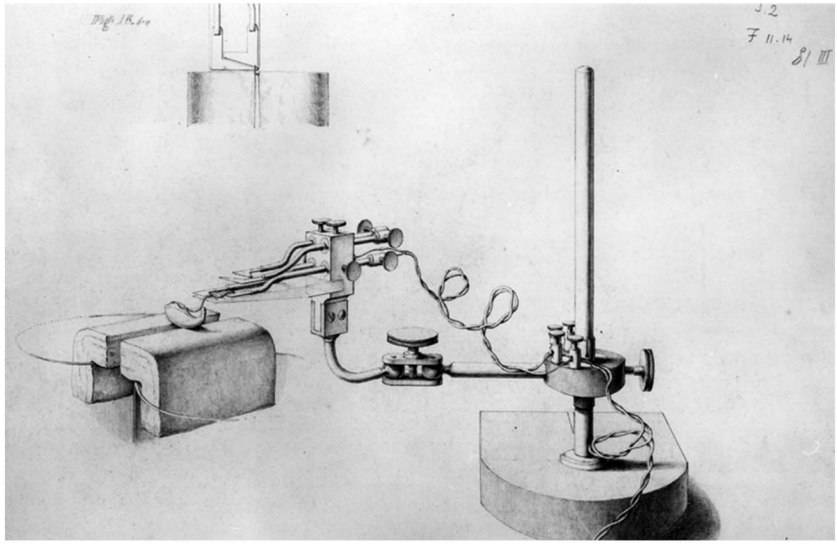


Figure 2. Du Bois-Reymond's laboratory apparatus for detecting the negative variation. The frog gastrocnemius-sciatic preparation rests across two pads of blotting paper bent over the edges of the conducting vessels (the rest of the circuit extending to the galvanometer is not shown). Metal electrodes, held in place by an adjustable stand, stimulate the nerve. The twisted wires trail off to some source of electricity, probably a magneto-electrometer. Reprinted from Emil du Bois-Reymond (1848) vol 1, plate II, figure 20.

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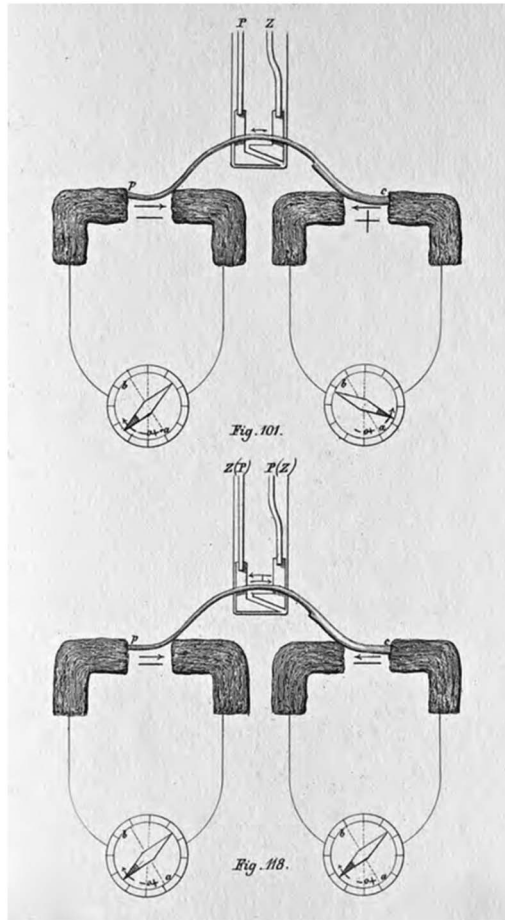


Figure 3. Du Bois-Reymond's experiment with two galvanometers demonstrating negative variation in the nerve. Metal electrodes Z and P stimulate the middle section of the preparation. Arrows indicate current direction. Stimulation with direct current gives rise to electrotonus in the nerve, deflecting each galvanometer needle in opposite directions from position a. Bottom: Stimulation with alternating current gives rise to a negative variation in the nerve current, deflecting both galvanometer needles into the negative quadrant from position a. Reprinted from Emil du Bois-Reymond (1848) vol. 2, plate II, figure 101 and 118.

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experiment ruled out the possibility that the negative variation merely reflected local electrical disturbances around the electrodes, establishing it instead as a distributed property of nervous activity (Figure 3).

The success of these experiments depended on du Bois-Reymond's instrumental innovations, which addressed two of the control problems identified in Section 3.1. His astatic galvanometer, containing up to 24,160 turns of wire—nearly four times more than previous devices—solved the signal sensitivity problem. The design incorporated two magnetized needles in reversed orientation to compensate for Earth's magnetic field, with small magnets correcting for iron traces in the coils, rendering the instrument "astatic" and free from spurious responses. More critically, his non-polarizable electrode system addressed the artefact control problem. Previous experimenters faced the problem that metal electrodes in contact with tissue generated their own electrical currents, making it impossible to distinguish artefacts from genuine biological electricity. Du Bois-Reymond's elegant solution used wet filter paper as a buffer between metal electrodes and tissue, maintaining electrical contact while eliminating direct metal-tissue contact. Electrodes were placed in separate varnished glass vessels containing saturated salt solutions, with multiple layers of filter paper bent over the vessel lips to create conducting pads.

Beyond these technological innovations, du Bois-Reymond developed exhaustive protocols for eliminating sources of experimental error. His galvanometer required elaborate calibration procedures, with delicate needles enclosed in glass bells to protect them from air currents. Electrode preparation followed rigorous protocols: platinum plates were washed in successive chemical baths, rinsed with distilled water, heated until they glowed, and handled only with glass rods to avoid static charge contamination. Even his biological preparations required careful attention—he chose saline as his electrolyte after testing more caustic solutions and covered filter paper with pig bladder soaked in egg white to prevent prolonged salt contact from damaging preparations (cf. Finkelstein 2013).

Du Bois-Reymond's extensive second-order experimentation (which I take to correspond to what he called "variation of circumstances") exemplifies his systematic approach to identifying what factors affected experimental outcomes. As documented in his Untersuchungen (1848) and analyzed by Finkelstein (2003, 2013), testing across "various orientations of muscle and apparatus," "various muscles," "various fragments of tissue down to a single isolated fibre," and "various animals, including rabbit, guinea-pig, mouse, pigeon, tortoise, lizard, water frog, grass frog, leaf frog, salamander, tench and crab" served multiple functions: determining which factors needed controlling, demonstrating the generality of his findings, and establishing that electrical phenomena in biological tissues followed

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quantitative principles comparable to inorganic electricity. This systematic exploration of experimental conditions simultaneously refined his control strategies and strengthened his causal claims about the role of electricity in nerve-muscle communication.

Yet this confirmation procedure revealed another important methodological problem. Du Bois-Reymond was convinced that the phenomenon reflected discrete electrical events—individual nerve impulses that only appeared continuous because his galvanometer could not resolve rapid bursts of current into their constituent events (cf. Lenoir 1986). But demonstrating this discreteness required a different kind of instrument and detection approach.

3.3. The Electrophysiological Rheoscope: Overcoming Instrumental Limitations

Having established that electrical phenomena accompanied nerve-muscle communication, du Bois-Reymond faced a new challenge: demonstrating that these phenomena were discrete rather than continuous. His theoretical commitments, built around electromagnetic analogies to Faraday's work on induced currents and the electrotonic state[10], implied that nerve transmission consisted of discrete electrical events—individual impulses triggering corresponding muscular responses. Yet his galvanometer registered only smooth, continuous deflections during tetanic stimulation. For du Bois-Reymond, the challenge was thus one of methodological innovation rather than one pertaining to second-order experimentation[11]: he needed to develop a detection approach that could resolve individual electrical events that were too brief and subtle for any available physical instrument to detect.

Du Bois-Reymond's innovative solution was to reconceptualize biological tissue itself as a detection instrument. He proposed that the excitability of living nerve and muscle tissue would prove more sensitive to brief

10. The electrotonic state was a concept du Bois-Reymond borrowed directly from Faraday's electromagnetic theory. Faraday had postulated that a current-carrying wire and the matter in its vicinity are put into a "peculiar condition" as long as current continues, and that changes in this condition cause current to flow—the basis for understanding electromagnetic induction. Du Bois-Reymond applied this concept to nerve physiology after discovering that when a constant current was passed through a middle segment of a nerve, the normal nerve current increased at one end (in the direction of the applied current) and decreased at the opposite end. He termed this polarized condition of the nerve "electrotonic," drawing a direct analogy to Faraday's electrotonic state. This allowed him to interpret nerve excitation and inhibition as consequences of changes in the nerve's electrotonic condition, much as electromagnetic induction resulted from changes in the electrotonic state of conducting materials (cf. Lenoir 1986).

11. *UTE*, 2 (1849), pp. 90–93, also discussed in Lenoir 1986, p. 9.

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electrical changes than any physical galvanometer he could construct.[12] The proposed setup, which he termed an "electrophysiological rheoscope," involved arranging biological preparations to function as their own indicators of discrete electrical activity. The apparatus consisted of two nerve-muscle preparations positioned so that the electrical activity of one could directly stimulate the other. Although the experimental design was simple in principle, it required precise execution. Du Bois-Reymond arranged one nerve-muscle preparation (which he designated as the "primary") with its nerve positioned parallel to the muscle fibers of a second preparation (the "secondary"). The nerve of the primary preparation made electrical contact between the muscle surface and the tendon cross-section of the secondary preparation, ensuring that current would flow from the primary to the secondary when the first muscle was activated.

When the primary preparation was tetanized through electrical stimulation of its nerve, the secondary preparation also became tetanized and remained so until the end of the stimulation. This demonstrated that the electrical activity associated with tetanic contraction could indeed be transmitted from one preparation to another through purely electrical means. However, the most revealing results emerged when du Bois-Reymond modified the experimental conditions to produce less intense stimulation.

By exciting the nerve of the primary preparation less frequently, so that the muscle did not become completely tetanized, du Bois-Reymond discovered that every individual contraction of the primary preparation was answered by a corresponding contraction in the secondary preparation. Meanwhile, a galvanometer attached to the secondary preparation registered a continuous reduction in current during the stimulation period. This combination of discrete muscular responses with apparently continuous electrical changes provided the evidence du Bois-Reymond was after (Figure 4).

The experimental results allowed him to conclude that each variation in current intensity leading to a muscular contraction was accompanied by a

12. This approach superficially resembled Matteucci's earlier work on "induced contractions" (1842), where contraction in one muscle preparation triggered contractions in a second, connected preparation. However, du Bois-Reymond's rheoscope differed significantly in both purpose and execution. Where Matteucci used the phenomenon to demonstrate that muscular activity generated electrical effects, du Bois-Reymond employed it to resolve a specific methodological problem: demonstrating that the negative variation consisted of discrete electrical events rather than continuous phenomena. Moreover, du Bois-Reymond systematically combined the rheoscope with galvanometric measurements to establish the contrast between discrete muscular responses and apparently continuous electrical deflections—a deliberate experimental design guided by his electromagnetic theoretical framework. Thus, while building on Matteucci's empirical observations, du Bois-Reymond transformed them into a sophisticated detection method addressing a different epistemological challenge.

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Figure 4. A primary muscle, P, is tetanized from the nerve. A second nerve-muscle preparation, S, with the nerve making contact between the muscle surface and the tendon (insuring that current will flow from P to S), contracts with each shock administered to P. Reprinted from du Bois-Reymond, *Untersuchungen über thierische Elektricität* (hereafter *UTE*), 2 (1849).

brief, temporarily separate negative variation of the muscle current. The electrophysiological rheoscope had succeeded where his galvanometer could not: it resolved the apparently smooth negative variation into its constituent discrete events. Each individual contraction in the secondary preparation indicated a separate electrical discharge from the primary, even though the galvanometer registered only a continuous deflection.

This experimental arrangement illustrated du Bois-Reymond's reconceptualization of biological systems as experimental instruments. The secondary preparation functioned simultaneously as indicator and amplifier, responding to electrical changes too subtle for galvanometric detection while producing visible muscular contractions that could be easily observed and counted.

The electrophysiological rheoscope served as a model of du Bois-Reymond's proposed mechanism for nerve-muscle communication. The experiment demonstrated that electrical variations in one muscle could directly trigger responses in another, supporting his hypothesis that nervous transmission operated through discrete electrical discharges rather than continuous currents. The spatial separation between the two preparations ruled out mechanical transmission, leaving for du Bois Reymond electrical communication as the only plausible explanation.

Du Bois-Reymond extended these findings through related experiments that seemed to provide further support for the electrical nature of nerve transmission. He demonstrated that the magnitude of response in the secondary preparation corresponded to the intensity of stimulation in the primary, and that the timing of contractions in the secondary consistently followed those in the primary with minimal delay. These results provided additional evidence that nerve-muscle communication operated through measurable electrical phenomena that could be systematically investigated and quantified.

The rheoscope experiments illustrate how du Bois-Reymond's control strategies and theoretical understanding co-evolved through sustained

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experimental work. As his laboratory notebooks accumulated data, he found it "impossible to have an instantaneous overview of the entire subject" (*UTE* 1 (1848), pp. xii–xiii). His solution was to construct material analogies—copper cylinders with galvanized zinc exteriors submerged in electrolytic solutions—that mimicked the electrical behavior he observed in biological preparations. These physical models generated currents flowing from their positively charged surfaces to their negatively charged cross-sections, paralleling the phenomena he measured in muscles and nerves. To represent his hypothesis about discrete "voltaic cells," he assembled bundles of small copper cylinders, each modelling individual muscle fibers. These material analogies both depended on and reinforced his experimental findings, exemplifying the reciprocal relationship between control practices and theoretical understanding. While experimental methods shaped how he conceptualized phenomena, theoretical commitments guided his methodological refinements (Figure 5).

Still, the persuasive power of these material analogies depended entirely on du Bois-Reymond's fundamental assumption that uninjured muscles and nerves maintained permanent electrical currents. This assumption would later face serious empirical challenges when scientists questioned whether these baseline currents were genuine biological phenomena or artefacts of tissue damage and preparation methods.[13]

3.4. Du Bois-Reymond and the Quest for Precision-Oriented Control

The previous analysis told the story of how du Bois-Reymond addressed the three control challenges identified in Section 3.1 through what might be summarized under the umbrella terms of *precision-oriented control*—the systematic effort to manage experimental conditions by identifying and eliminating known sources of error and interference. His non-polarizable electrode system addressed the artefact control problem, his enhanced galvanometer tackled the signal detection problem, and his systematic demonstration of the negative variation established the causal role of electrical phenomena in nerve-muscle communication. I take this overall approach to reflect a commitment to isolating specific causal

13. The main challenge came from du Bois-Reymond's former student Ludimar Hermann, who argued that the "resting currents" were artefacts of tissue injury rather than genuine biological phenomena. Hermann contended that electrical activity arose only in dying or damaged organs through chemical decomposition, so that there was no muscle current at all in intact resting bodies. This critique, supported by earlier theoretical concerns from Helmholtz about the impossibility of measuring currents in truly uninjured tissues, undermined du Bois-Reymond's fundamental assumption and forced reconceptualization of nerve-muscle systems as capacitor-like rather than battery-like structures (cf. Finkelstein 2006, pp. 342–344; Lenoir 1986, p. 20).

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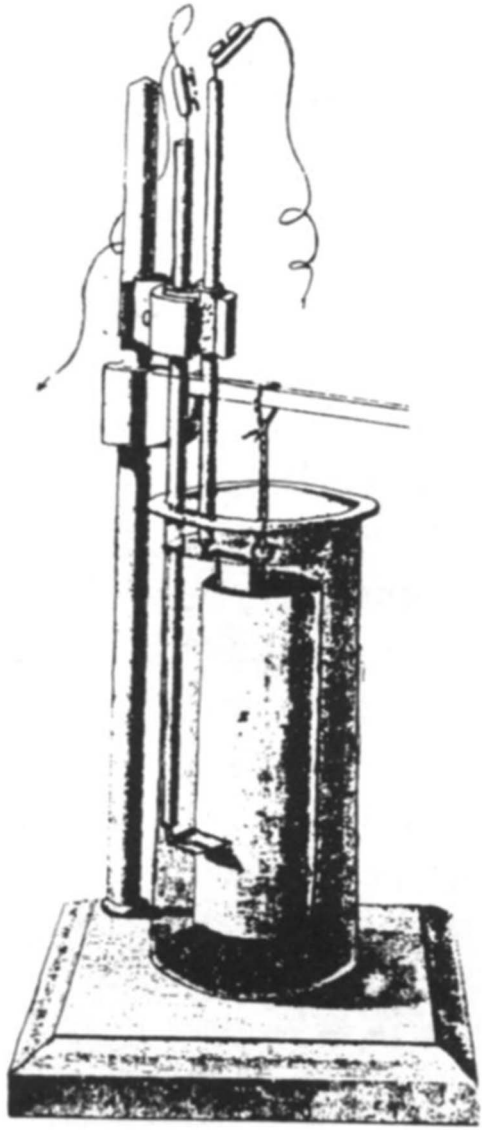


Figure 5. Du Bois-Reymond's physical model of the muscle current. A hollow copper cylinder, galvanized on the outside, hangs in a beaker containing an electrolytic fluid. Leads from a galvanometer run to the outside and to the interior of the cylinder. Reprinted from du Bois Reymond (1848, *UTE* 1).

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relationships from the complex web of factors operating within living systems, which in turn facilitates the establishment of quantitative relationships that might hold consistently across different contexts.

Viewed through Schickore's three-level framework, du Bois-Reymond's precision-oriented approach was implemented via methodological ideas (quantification as epistemically superior to qualitative observation), control strategies (systematic isolation of causal relationships through instrumental precision), and control practices (specific techniques like non-polarizable electrodes, enhanced galvanometers, and exhaustive calibration protocols). These levels were interconnected rather than independent: his commitment to quantification shaped his instrumental innovations, while successful control practices reinforced his methodological convictions about the superiority of precision-oriented approaches.

Du Bois-Reymond's approach can also be taken to exemplify what Schickore calls 'broad control'—the systematic management of background factors that might confound experimental results. His work involved both diagnostic probing (his extensive "variation of circumstances" across species, tissues, and experimental conditions to identify what factors affected measurements) and determinative probing (developing specific technical solutions like non-polarizable electrodes once contact electricity was identified as a problem). Importantly, these aspects did not occur sequentially but developed together. For instance, his systematic testing revealed that metallic contact, galvanometer sensitivity, and stimulation artefacts all required controlling. That is, diagnostic work simultaneously guided his determinative innovations (electrode design, galvanometer refinement, two-galvanometer controls). I emphasize this progression from detecting baseline currents to demonstrating the negative variation to resolving discrete electrical events as an instance of Schickore's co-evolution thesis. In this historical episode we can see that control practices and theoretical understanding developed together, with methodological innovations creating new ways of conceptualizing phenomena rather than merely providing better access to them.

To disambiguate the meaning of this co-evolution thesis I focus on how du Bois-Reymond's instrumental developments functioned in the context of his inquiry. Before the introduction of his non-polarizable electrodes, scientists could not conclusively claim that biological electricity was a genuine tissue property rather than an instrumental artefact. The conceptual possibility was foreclosed by methodological uncertainty. Du Bois-Reymond's technical solution did not just provide better access to pre-existing phenomena but enabled a new way of understanding: biological electrical phenomena could now be conceptualized as quantifiable intrinsic properties of living tissues governed by physical laws. So, the control innovation was

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epistemologically constitutive—it made possible a theoretical claim that was unthinkable under previous experimental conditions.

In addition, the case of the electrophysiological rheoscope allows us to articulate a different form that this constitutive relationship can take. Here, rather than solving a diagnostic control problem through determinative means, du Bois-Reymond developed a methodological innovation in response to a known instrumental limitation. He recognized that no physical instrument could resolve individual electrical events, so he reframed biological excitability itself as a detection mechanism more sensitive than any galvanometer. So this innovation enabled the investigation of discrete electrical events by changing what counts as an 'experimental instrument' to include living tissue as a detector. The control strategy and theoretical understanding co-evolved as he interpreted the experimental findings as evidence that nerve transmission operated through discrete discharges rather than continuous phenomena.

Du Bois-Reymond's control practices were thus inseparable from his evolving understanding of bioelectrical phenomena. His theoretical commitment to electrical reductionism (Finkelstein 2023) both motivated specific technical innovations and was reinforced by their experimental success. Moreover, this reciprocal relationship is evident in his material analogies, where copper cylinders modelling biological tissues simultaneously depended on his experimental findings and guided further theoretical development.[14]

So far I have insisted that this co-evolutionary relationship between technical innovation and theoretical development proved highly productive for du Bois-Reymond's investigations. But there is another side of the story which highlights the constraints inherent in his precision-oriented approach. Du Bois-Reymond's control strategy required systematic isolation—from the elaborate electrode preparation protocols and galvanometer calibration procedures to the artificial experimental arrangements that removed nerve-muscle preparations from normal physiological contexts. This reductive approach enabled precise quantitative measurements but also created significant practical barriers. Investigations required sophisticated instrumentation and extensive technical expertise, while the highly artificial experimental conditions raised questions about whether the findings reflected normal biological function.

14. It could also be argued that competitive pressures also played an important role in this co-evolution: du Bois-Reymond's comprehensive testing across species, tissue types, and experimental conditions served simultaneously as precision control, empirical validation, and strategic demonstration of his findings' generality. This suggests that professional rivalries influenced what kinds of methodological rigor became necessary for establishing credible knowledge claims.

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Drawing attention to these multiple constraints—reductive requirements, quantification demands, and technical barriers—allows us to ask important questions about the scope and applicability of precision-oriented control in biological research. Can experimental control operate effectively without systematic isolation and quantification, or do some biological phenomena require maintaining rather than eliminating physiological complexity? How do different control strategies shape what counts as adequate experimental evidence—do they provide neutral access to phenomena or constitute particular ways of understanding what biological knowledge should look like?

These questions point towards the need to examine alternative experimental traditions that developed different methodological commitments while confronting similar epistemic challenges. Claude Bernard's toxicological research faced the same fundamental control problems as du Bois-Reymond—distinguishing genuine biological effects from artefacts, establishing causal relationships, and managing complex physiological systems. Yet Bernard's integrative methodology approached these challenges primarily through diagnostic rather than determinative strategies, preserving physiological complexity rather than systematically isolating factors.

4. The Case of Claude Bernard

Claude Bernard's toxicological research provides an alternative approach to the questions raised by du Bois-Reymond's precision-oriented control: can experimental control operate effectively without systematic isolation and quantification? Bernard investigated nerve-muscle communication through a markedly different experimental tradition. Where du Bois-Reymond used electrical measurements to establish that the negative variation accompanied nervous activity, Bernard used the South American poison curare to probe how nerves activated muscles, concluding that curare eliminated motor function by acting on motor nerve tissue while preserving sensory function.

These investigations intersected in the 1860s when French physiologists applied du Bois-Reymond's electrophysiological methods to curarized preparations, revealing a fundamental contradiction: electrical negative variations persisted in curarized nerves that had completely lost their ability to activate muscles (Vulpian 1866; cf. Fessard 1967; Barbara 2009). This empirical puzzle exposed the limitations of both approaches. Du Bois-Reymond's electrical measurements detected persistent nervous activity but could not explain why this activity failed to produce motor function, while Bernard's toxicological approach documented the loss of motor function but could not detect the electrical activity that apparently continued. Rather than tracing historically how this puzzle was eventually

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resolved (Barbara 2009), I examine how Bernard's control strategies constituted an alternative approach to establishing reliable experimental knowledge about nerve-muscle communication—one that preserved physiological complexity rather than systematically isolating factors.

4.1. The Scientific Context: Poisons as Epistemic Tools

Claude Bernard's investigation of curare emerged from the toxicological research tradition established by his mentor François Magendie at the Collège de France. Working within this framework, Bernard pursued systematic investigation of the South American poison across several years, from early observations in the 1840s through his presentations to the French Academy of Sciences in the 1850s.[15] This research was summarized in the eight lessons of his course on *Les effets des substances toxiques et médicamenteuses*, delivered in 1856 and published the following year, alongside detailed experimental records preserved in his *Cahiers de notes* (1850–1860) which document his evolving understanding of the curare mechanism.

Bernard entered a field marked by considerable disagreement about curare's mechanism of action (Barbara 2013; Barbara and Corvol 2012). Earlier work had established that rapid death in curare poisoning was "due at least in part, to a central action," (cf. Fessard 1967) yet investigators disagreed about the specific sites and mechanisms involved. Kölliker independently favored action upon motor nerve terminals, while von Bezold thought nerve trunks were directly affected. Many others believed the loss of reflex activity resulted from depression of sensory nerves. Adding to this confusion, some curare preparations provoked strychnine-like convulsions—an effect Bernard correctly identified as resulting from actual strychnine contamination in certain preparations.

However, an important clue already existed: Brodie had demonstrated in 1811 that artificial respiration could maintain curarized animals alive and result in their complete recovery once the poison was eliminated, establishing that death resulted from asphyxia due to paralysis of respiratory muscles. This observation posed Bernard's central control challenge: how to determine curare's specific site and mechanism of action within intact, functioning organisms where multiple physiological systems

15. Bernard's first recorded curare observation appears in his notebook entry dated June 19, 1844: "A poisoned arrow obtained from a friend who had had connections with South America natives was thrust into the subcutaneous tissue of a rabbit at the internal part of the thigh and maintained there for 30 seconds. The animal was then observed. At first, nothing happened. But after six minutes it became totally paralyzed: no reflex movements were observed on pinching the rabbit, although the heart continued to beat. The animal subsequently died and at autopsy it was not possible to find any lesion capable of explaining paralysis and death."

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interact. Unlike isolated tissue preparations where the scientists could eliminate confounding factors, living animals required distinguishing direct from indirect effects. Bernard needed to determine whether curare acted on nerves, muscles, or some intermediate structure while all remained connected through circulation and innervation.

For Bernard, curare research was part of a broader project to understand integrated physiological function. His concept of the "*milieu intérieur*"—developed in his 1854 lectures at the Sorbonne and thus predating his systematic curare investigations[16]—emphasized that complex organisms maintain stable internal environments protecting tissue elements from external variations. Poisons like curare could then be treated as intervention tools for probing this system: substances that accessed the *milieu intérieur* through circulation could selectively disrupt specific physiological networks. In addition, Bernard's conviction that pathological phenomena represented exaggerated versions of normal processes meant studying how poisons systematically dismantled integrated functions could reveal normal physiological organization.

As Bernard explained in his 1856 communication on curare at the French Academy of Sciences, toxic agents allowed researchers to study "not the death of organs, as Bichat did, but the death of organic systems" (cited in Shideman 1967, p. 125). Thus, rather than focusing on individual organ failure, Bernard aimed to understand how integrated physiological networks coordinated their functions by observing how poisons systematically dismantled them. Curare was ideal for this approach because it systematically shut down physiological systems in predictable sequences, enabling temporal analysis of the underlying mechanisms.

4.2. From Methodological Commitments to Experimental Strategies

Bernard's theoretical commitments shaped an experimental approach that contrasted with the precision-oriented methodology du Bois-Reymond pioneered in German electrophysiology. Where du Bois-Reymond's control strategy emphasized systematic isolation—eliminating confounding

16. Holmes (1986) argues that Bernard first formulated the "*milieu intérieur*" concept publicly in his 1854 inaugural lectures at the Sorbonne, noting that "the concept emerged instead from his concern with very general biological principles" rather than from specific experimental discoveries (Holmes 1986, pp. 4–6). Bernard's systematic toxicological work on curare, presented to the French Academy in 1856 and published in his 1857 *Leçons*, was thus conducted within the conceptual framework of the *milieu intérieur* rather than generating that concept. This chronology suggests that Bernard's theoretical commitments about integrated physiological systems guided his experimental approach to curare rather than emerging from it (Bernard 1855; Barbara 2013; Barbara and Corvol 2012, p. 22; Bechtel and Vagnino 2022, p. 7).

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factors through non-polarizable electrodes, elaborate calibration protocols, and experimental protocols involving tissue preparations—Bernard developed control strategies that preserved physiological complexity. His conviction that biological phenomena could be properly understood only within integrated, living systems led him to reject approaches that, as Barbara (2009: 233) notes, relied "principally on anatomical or electrophysiological indices" divorced from integrated physiological function.

Bernard's integrative methodology translated into specific control strategies that exploited rather than eliminated physiological complexity. Consider, for instance, his approach to localizing curare's site of action. In contrast to du Bois-Reymond, who used isolated preparations to control for interfering factors, Bernard used the intact organism as both experimental subject and analytical instrument. His systematic exploration of curare's effects on blood circulation—investigating whether the poison affected gas exchanges in the lungs or tissues—exemplifies this approach. These investigations, while showing no such effects, served a diagnostic control function. By ruling out circulatory mechanisms, Bernard was able to localize curare's action without requiring the artificial isolation that would destroy the integrated relationships he aimed to study (Bernard 1857; cf. Fessard 1967, p. 111).

Bernard's integrative methodology comprised three distinctive control strategies that map onto Schickore's categories. First, route-of-administration protocols served as diagnostic probing to trace how toxic substances accessed and disrupted the *milieu intérieur*. Bernard's systematic exploration of intravenous injection, oral ingestion, and skin application aimed not simply to test potency but to map the pathways through which poisons reached their sites of action—diagnostic work that identified which physiological systems mediated curare's effects.

Second, temporal sequencing analysis provided a control strategy unique to integrated systems. By observing the sequential breakdown of organ systems during poisoning—respiratory function failing before cardiac, motor responses disappearing before sensory—Bernard used time as an experimental variable that revealed underlying relationships between systems in healthy animals. This temporal approach to control was unavailable to experimenters using isolated preparations where such sequential relationships were destroyed.

Finally, comparative toxicology protocols established systematic control through contrast. Bernard's parallel investigations of curare and strychnine, which he viewed as having "exactly opposite effects," used systematic comparison of contrasting disruptions to reveal the normal organization of integrated physiological networks. This represented a form of determinative control achieved through comparative analysis rather than systematic

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isolation. The following section examines Bernard's ligature experiment to illustrate how these control strategies operated in practice.

4.3. The Ligature Experiment

Bernard's investigation began with a puzzling observation: when he applied electrical stimulation to a motor nerve in a curarized frog, no muscle contraction occurred, whereas the same muscles contracted normally when stimulated directly. This result suggested that curare interrupted nerve-muscle communication without affecting either tissue independently. Bernard's control challenge was to determine precisely where this interruption occurred—nerve, muscle, or junction—without destroying the physiological relationships through which curare exerted its effects.

More specifically, if curare paralyzed motor responses, how could Bernard determine whether it also affected sensory nerves? The motor paralysis had "deprived him of a means of testing the excitability of the sensory side of the nervous system" (Fessard 1967, p. 112; Bernard 1942, p. 25). Bernard's solution—the ligature preparation—demonstrates his first control strategy (route-of-administration protocols) by creating differential exposure within a single organism. A tight ligature passed around a frog's waist isolated the posterior limbs from general blood circulation while carefully preserving the sciatic nerve trunk connecting anterior and posterior regions. This created what amounted to a living control experiment within a single animal: two body regions that shared neural connections but differed in their exposure to circulating toxins.

When curare was introduced under the skin of the back, it poisoned the anterior part of the body and prevented movement there, but stimuli applied to this paralyzed portion caused energetic reflex movements in the isolated posterior half. As Bernard concluded, "curare is thus a poison which not only produces physiological separation of nerves and muscles, but also separation of two major kinds of nervous manifestations. It suppresses movement but has no action on sensation" (cited in Fessard 1967, p. 110).

Bernard's subsequent experiments attempted to localize curare's action more precisely, but also revealed the constraints of his theoretical framework. He devised two preparations: in one, he soaked the sciatic nerve directly in curare solution while keeping the muscle protected; in the second, he applied curare to the muscle while keeping the nerve trunk protected. When he stimulated the nerve electrically in the first preparation, normal muscular contractions occurred. However, in the second preparation, electrical stimulation produced no response (Figure 6).

This result suggested that some junctional structure between nerve and muscle was affected. However, Bernard's commitment to his circulation-based theory—that curare acted by circulating through the

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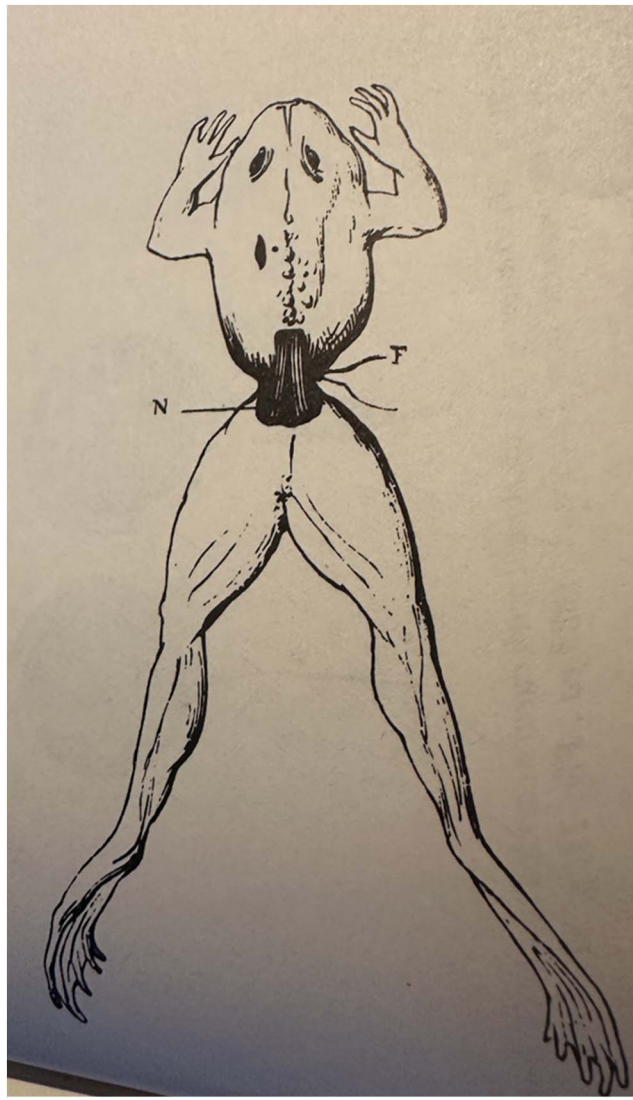


Figure 6. A frog preparation illustrating Bernard's ligature experiment. A ligature passed around the waist of the frog isolated the lower limbs from the rest of the body, except for the sciatic nerve trunk; reproduced from *Leçons* [1857] 1883, Fig. 26, p. 345.

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bloodstream to directly affect motor nerve tissue—prevented him from recognizing this interpretation (cf. Fessard 1967). He proposed instead that curare could travel retrograde up the nerve trunk from the nerve terminations in the muscle. This mechanistically implausible hypothesis preserved his core theoretical commitment that curare must act on nerve tissue itself rather than on intermediate structures.

Bernard also developed what may well be the first use of close arterial injection technique (Fessard 1967, p. 112). By isolating the vascular pathway, this intervention tested specific mechanisms through differential exposure. He injected curare directly into the artery supplying a specific muscle while creating a venous outlet that prevented the poisoned blood from reaching the central nervous system. This approach ensured curare reached the target muscle through blood circulation while preventing systemic distribution, allowing Bernard to test whether local blood supply alone was sufficient to produce paralysis. The resulting paralysis provided what Bernard viewed as confirmation that curare acted through circulation rather than through other routes (Figure 7).

Taken together, these experiments demonstrate both the power and the limitations of Bernard's integrative control strategies. The ligature preparation succeeded in distinguishing motor from sensory effects while preserving physiological relationships—an achievement unavailable to isolated tissue preparations. His route-of-administration protocols (ligature, arterial injection) and comparative observations (curarized vs. non-curarized regions) provided systematic control within intact organisms. However, his commitment to studying integrated physiological systems made it conceptually difficult to envision discrete structural intermediates like the neuromuscular junction. Where du Bois-Reymond's precision-oriented approach could isolate and measure electrical phenomena independently of their functional consequences, Bernard's integrative methodology was designed to preserve the very relationships that needed analytical separation to understand the curare mechanism. This tension became acute when investigators challenged Bernard's interpretations using electrophysiological evidence.

4.4. From Methodological Constraints to Adaptation

The most significant challenge came from Alfred Vulpian (1866), who incorporated findings from German electrophysiology into curare research. Vulpian pointed out that electrical activity—the "nervous current" and "negative variation" that du Bois-Reymond and others had identified as markers of nervous function—remained completely intact in curarized nerves even after they had lost their ability to activate muscles.

This dissociation between electrical and functional evidence could not be resolved within Bernard's theoretical framework, which conceptualized

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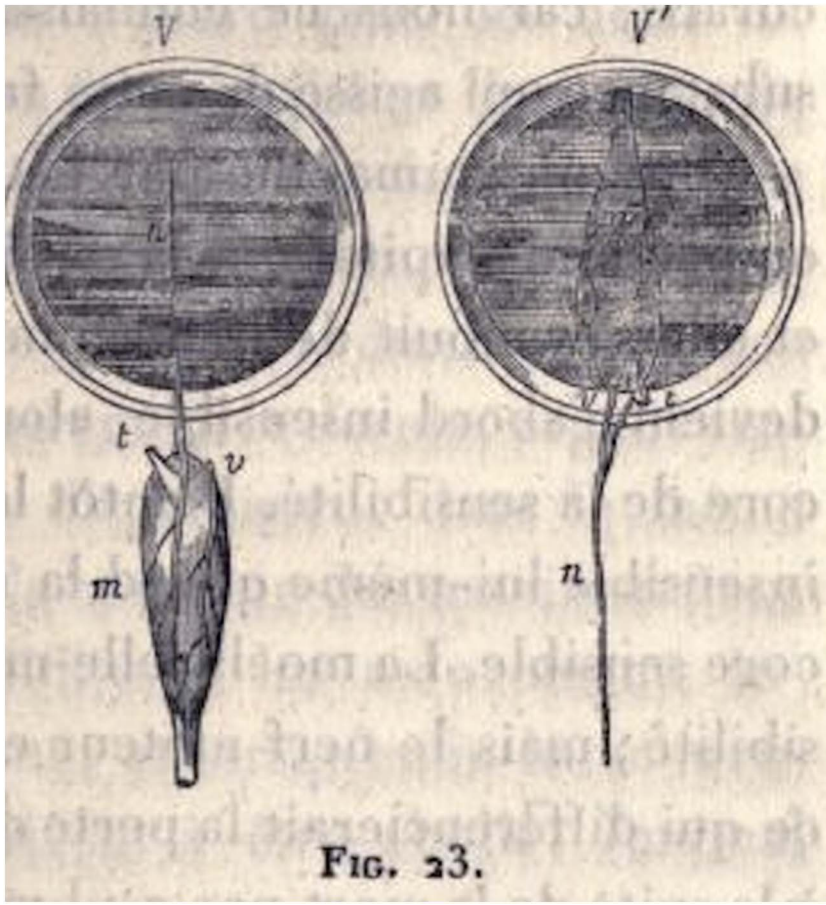


Figure 7. Illustration of an experiment with curare carried out by Bernard—reproduced from *Leçons* [1857] 1883, Fig 23, p. 329.

nerve-muscle relationships as direct tissue interactions mediated by circulating substances. The persistence of electrical activity in functionally paralyzed nerves suggested a level of physiological organization—discrete junctional structures—that Bernard's integrative approach was not equipped to investigate. Where du Bois-Reymond's precision-oriented methods could isolate and measure electrical phenomena independently of their functional consequences, Bernard's integrative methodology was designed to preserve the very relationships that needed to be analytically separated to understand this contradiction.

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Bernard's response to this challenge reveals the sophisticated yet constrained nature of his experimental reasoning. His private notebooks contain evidence that he was approaching the correct interpretation even while maintaining his public commitment to nerve-based action. Fessard (1967, p. 114) pointed out that in hastily written but explicit notes, Bernard recorded insights that anticipated later developments: "curare must act on the terminal plate of motor nerves" and "curare does no more than interrupt something motor which puts the nerve and the muscle into electrical relationship for movement". These observations suggest that Bernard possessed intuitions about junctional transmission that he could not reconcile with his broader theoretical framework emphasizing the integrated nature of physiological functions. This internal contradiction points to an important constraint of his methodological approach.

This challenge revealed how Bernard's methodological commitments both enabled and constrained his theoretical possibilities. His experimental approach, designed to preserve physiological relationships within intact systems, could not dissociate the discrete components of nerve-muscle communication that electrophysiological methods could detect. When stimulation failed to produce muscle contraction in curarized preparations, Bernard's integrative approach led him to conclude that nerve tissue had become unexcitable—a reasonable inference given his tools and theoretical commitments, but one that prevented recognition that nerve excitability and nerve-muscle communication represented separable physiological processes. His theoretical commitment to integrated physiological systems made it conceptually difficult to envision discrete structural intermediates—specialized junction sites that could mediate communication without direct tissue contact—leading to increasingly elaborate explanations like the mechanistically implausible hypothesis that curare could travel retrograde up nerve trunks.

By 1864, however, Bernard demonstrated the adaptive flexibility of his control strategy by effectively abandoning his original interpretation. In his course lectures, he made a remarkable theoretical concession: "it seems one could somehow compare what happens in this place [between nerve and muscle] to the rupture of a wire that would interrupt a communication or an electrical current. At the bottom of curare's action, there is the big question of the nature of nervous fluid and the influence of nerve on muscle" (Bernard 1865, pp. 435–40).[17] It is possible to read in this

17. "il semble qu'on pourrait en quelque sorte comparer ce qui se passe dans cet endroit [entre le nerf et le muscle] à la rupture d'un fil qui interromprait une communication ou un courant électrique. Au fond de l'action du curare, il y a la grosse question de la nature du fluide nerveux et de l'influence du nerf sur le muscle" (Bernard 1865, pp. 435–40, as cited in Barbara 2009, p. 232).

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admission Bernard's robust methodological adaptation—he maintained his integrative approach while incorporating insights that his original theoretical framework could not accommodate, demonstrating how control strategies can evolve in response to empirical challenges while preserving core methodological commitments.

Despite these constraints, the curare investigations reveal Bernard's distinctive experimental logic—one that achieved systematic control through fundamentally different means than du Bois-Reymond's precision-oriented methodology. Rather than viewing Bernard's limitations as methodological failures, examining how his control strategies function demonstrates a coherent alternative approach to establishing reliable experimental knowledge about biological phenomena.

The experiments examined above demonstrate that Bernard's control strategies exploited rather than eliminated biological complexity. His ligature preparation created differential exposure within single organisms, systematically separating circulatory and neural factors while preserving their organizational relationships. His temporal sequencing analysis treated the time course of physiological disruption as direct analytical information about normal system organization. His comparative toxicology used systematic perturbation—contrasting curare and strychnine's opposite effects—to map integrated physiological networks. His vascular isolation techniques achieved precise control over how substances accessed biological systems while maintaining the integrated relationships essential for understanding their effects. These strategies treated biological complexity as an essential experimental resource rather than a confounding factor to eliminate.

Bernard's integrative methodology thus constituted a legitimate alternative to precision-oriented control, though one with distinct epistemological constraints. Where du Bois-Reymond's systematic isolation enabled precise measurement of discrete phenomena like electrical currents, Bernard's preservation of physiological relationships revealed organizational principles unavailable to reductive approaches. However, as the curare case demonstrates, phenomena involving discrete structural intermediates—like the neuromuscular junction—required the analytical separation Bernard's approach was designed to avoid. The ultimate resolution of the curare puzzle came when later investigators combined Bernard's insights about integrated physiological function with the electrophysiological and histological precision his methodology had resisted. Understanding how both approaches functioned as sophisticated experimental control strategies, each with characteristic strengths and limitations, provides the basis for examining their broader significance for experimental physiology.

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5. Experimental Control: Upshots of a Comparative Analysis

The preceding analysis of du Bois-Reymond's and Bernard's experimental practices reveals how Schickore's co-evolution thesis operates in historical practice. Rather than representing fixed methodological oppositions, the two scientific approaches demonstrate that control strategies and theoretical understanding develop together through sustained experimental work. This section examines three aspects of this co-evolutionary relationship: how diagnostic and determinative probing function as complementary phases in control development (Section 5.1), how experimental control operates constitutively rather than merely as technical mediation in knowledge production (Section 5.2), and the implications of this analysis for understanding persistent methodological tensions in contemporary biological research (Section 5.3).

5.1. Complementary Functions in Control Strategies

Section 2 introduced Schickore's distinction between diagnostic probing (exploring what factors might influence outcomes) and determinative probing (managing factors already identified as sources of interference). The question now is whether these represent fixed methodological approaches or complementary phases within evolving experimental programs. The historical analysis suggests the latter: both du Bois-Reymond and Bernard employed diagnostic and determinative functions at different stages, though their approaches emphasized different aspects of experimental control.

Du Bois-Reymond's mature determinative solutions—non-polarizable electrodes, astatic galvanometers, calibration protocols—emerged from extensive diagnostic work. His systematic testing across tissue types, species, and experimental conditions revealed what required controlling: contact electricity, magnetic interference, and instrumental variables. His development trajectory moved from exploratory diagnostic work toward increasingly refined determinative control. Even his electrophysiological rheoscope emerged from the diagnostic recognition that galvanometers could not resolve discrete electrical events, leading him to explore biological systems as more sensitive detection mechanisms.

Bernard's approach, on the other hand, emphasized diagnostic exploration—systematically varying administration routes, comparing toxins, testing alternative preparations—but also developed determinative solutions when diagnostic work revealed specific control requirements. His ligature preparation emerged from systematic exploration of how to separate circulatory and neural factors, ultimately providing a precise determinative solution for testing sensory function in paralyzed animals. His comparative toxicology protocols evolved from initial observations into

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sophisticated determinative tools for distinguishing different mechanisms of physiological disruption. Finally, Bernard's trajectory maintained diagnostic exploration even as determinative elements emerged, reflecting his theoretical commitment to understanding integrated systems.

The key insight emerging from this comparative analysis is that diagnostic and determinative functions operated together within both experimental programs rather than representing opposing methodologies. Du Bois-Reymond's systematic exploration simultaneously revealed control requirements and theoretical possibilities; Bernard's variation of circumstances both identified what needed controlling and what causal relationships were detectable. Both scientists' extensive second-order experimentation exemplified how diagnostic and determinative work complement each other in practice. Furthermore, understanding how these functions operated within each approach can help us clarify how experimental control can play a constitutive function in knowledge production.

5.2. The Constitutive Function of Experimental Control

To unpack the constitutive function of control we need to start by addressing a potential circularity in the co-evolution thesis. If control strategies and theoretical understanding develop together, how do we distinguish genuine co-evolution from simple temporal correlation? The answer lies in recognizing that experimental control doesn't merely provide technical access to pre-existing phenomena but shapes what those phenomena can be understood to be.

Consider how du Bois-Reymond's case exemplifies this constitutive relationship. Before his non-polarizable electrodes, investigators could not definitively distinguish biological electricity from instrumental artefacts—not because they lacked sensitive instruments, but because the conceptual possibility of biological electricity as an intrinsic tissue property was foreclosed by methodological uncertainty. His technical solution didn't provide better access to a phenomenon that was already conceptually available; it made possible a new way of understanding. Biological electrical phenomena could now be conceptualized as quantifiable intrinsic properties governed by physical laws. The control innovation was epistemologically constitutive, enabling a theoretical claim that was not possible under previous experimental conditions. Similarly, his electrophysiological rheoscope constituted a new way of understanding nerve transmission as discrete rather than continuous. Without the rheoscope's ability to resolve individual events, the concept of discrete nerve impulses remained theoretically inaccessible regardless of investigators' theoretical commitments.

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Bernard's systematic perturbation approach operated similarly. His ligature preparation made possible a way of understanding physiological functions as systematically separable within integrated organisms. His route-of-administration protocols constituted a method for tracing causal pathways through living systems, enabling investigation of phenomena like selective nerve poisoning. Rather than merely observing pre-existing relationships, these control strategies constituted ways of conceptualizing specific features of physiological organization.

This constitutive function can explain the co-evolutionary pattern postulated by Schickore: when control strategies shape what can be meaningfully investigated, methodological innovations and conceptual developments must occur together rather than sequentially. Du Bois-Reymond's precision-oriented approach and Bernard's integrative methodology reflected different epistemological possibilities for understanding nerve-muscle communication, not merely different technical preferences.

But this raises another important question: could theoretical commitments be operationalized through different control strategies, with commitments merely constraining rather than determining experimental design? The historical cases suggest a tighter coupling. Du Bois-Reymond's electrical reductionism required the quantitative measurement and systematic isolation that characterized his approach—the control practices partly determined what would count as successfully demonstrating that biological processes follow physical laws. Bernard's commitment to integrated systems required preserving physiological complexity because the organizational relationships he sought only became conceptually accessible through his perturbation methods. In these cases, control practices and theoretical commitments co-evolved such that specifying how commitments could have been "differently operationalized" proves difficult.[18]

Whether this tight coupling represents a general feature of experimental control or reflects specific features of nineteenth-century biological research—where phenomena were less well-defined and experimental traditions still emerging—requires investigation of additional historical cases. The analysis suggests that control's constitutive role may be

18. These co-evolutionary processes occurred within specific disciplinary and technological constraints. Du Bois-Reymond's physics training and access to electrical apparatus oriented him toward precision-oriented control, while Bernard's medical background and physiological expertise enabled systematic exploration of integrated networks. These disciplinary differences shaped not just available skills but the epistemological possibilities each investigator could pursue. The curare controversy's eventual resolution through integrating insights from both experimental traditions illustrates how phenomena resistant to single disciplinary frameworks can drive methodological synthesis.

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strongest when investigating novel phenomena with emerging methods, where what counts as a legitimate operationalization of theoretical principles remains open to determination through experimental practice.

5.3. On the Modern Problem of Experimental Control

If experimental control functions constitutively and co-evolves with theoretical understanding, as this historical analysis suggests, what implications might this have for contemporary scientific practice? Current scientific education typically treats experimental control design as a technical skill learned through protocol mastery rather than as a methodological appendix to hypothesis formation rather than a constitutive element of knowledge production. The proliferation of control protocols supports this interpretation: Schickore (2025) notes over 2,500 titles in methodology manuals covering experimental procedures. Yet she also emphasizes that "there are no universal control procedures" and "what must be controlled, and how, is worked out anew for every project." (Schickore 2025, pp. 1–2) This tension between how control is taught (through standardized procedures) and how it functions in research practice (through constitutive experimental work) points to an important gap between methodological training and actual research demands.

This historical analysis reveals why protocol-based approaches may be insufficient. Du Bois-Reymond's precision-oriented control and Bernard's integrative approach didn't simply provide alternative technical routes to understanding nerve-muscle relationships—they constituted different ways of conceptualizing biological phenomena, with different explanatory possibilities and constraints. Methodological choices about experimental control are simultaneously choices about what kinds of biological knowledge become possible, a relationship that protocol-based training may inadvertently obscure.

Rather than treating methodological tensions in contemporary biological research as problems requiring resolution through better protocols or standardization, this analysis suggests that they may reflect the different but complementary epistemic functions that their associated control strategies serve. The continuing tension between reductionist precision and integrative understanding in fields like systems biology may represent not methodological confusion but the continuous scientific struggle to integrate knowledge claims about biological phenomena that have been differently controlled. Understanding experimental control as constitutive and evolving rather than static and technical could inform how such tensions are approached in interdisciplinary collaboration, suggesting the value of what might be termed methodological pluralism that

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acknowledges the legitimate epistemic functions of different experimental approaches (cf. Bolinska 2024).[19]

While these insights emerge from analysis of two historical cases, they suggest that incorporating historical and philosophical perspectives into methodology training could help researchers recognize that persistent difficulties in experimental control design may stem not from inadequate technical training but from the fundamental relationship between methodological choices and knowledge production. Understanding experimental control as both precision-oriented and integrative—different but equally necessary aspects of establishing reliable knowledge about complex biological phenomena—may prove useful for addressing the sophisticated control challenges facing contemporary biological research.

6. Conclusion

This investigation of how Emil du Bois-Reymond and Claude Bernard developed experimental control strategies in nineteenth-century physiology reveals that their apparent methodological differences reflected complementary responses to shared epistemic challenges rather than a fundamental opposition. Applying Schickore's analytical framework allows us to see that both scientists engaged in extensive second-order experimentation—systematically exploring their experimental setups to determine what factors required controlling—while developing distinctive approaches that served different but equally necessary epistemic functions in establishing reliable knowledge about nerve-muscle communication.

The detailed historical analysis clarifies how experimental control functioned constitutively in both research programs. Du Bois-Reymond's non-polarizable electrodes didn't simply provide better technical access to biological electricity but made possible new ways of understanding: biological electrical phenomena could be conceptualized as quantifiable intrinsic properties governed by physical laws. His electrophysiological rheoscope enabled investigation of discrete nerve impulses by

19. The term "methodological pluralism" here follows Bolinska's (2024) distinction between different types of pluralism in scientific practice. Methodological pluralism refers specifically to the persistence of multiple experimental methods or techniques within a research domain, driven by the complexity of phenomena and the partiality of information provided by any single approach. This differs from epistemic or model pluralism, which concerns whether multiple models are necessary for adequate representation of particular phenomena, and from integrative pluralism, which seeks to maintain plurality while integrating models at the level of application. The focused historical analysis suggests that du Bois-Reymond's and Bernard's different control strategies should be viewed as methodologically pluralist approaches that serve complementary epistemic functions, rather than competing models of the same phenomena that require integration.

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reconceptualizing what counted as an experimental instrument. Similarly, Bernard's ligature preparation and comparative toxicology didn't merely solve practical problems but constituted ways of understanding biological systems as integrated networks amenable to systematic perturbation analysis. These cases demonstrate that different control strategies enabled different ways of conceptualizing biological phenomena. Methodological choices were simultaneously epistemological choices about what kinds of biological knowledge could become possible.

Understanding experimental control as constitutive and evolving rather than static and technical has implications for contemporary biological research. Current scientific education typically treats experimental control design as a technical skill learned through protocol mastery, yet as Schickore (2025) emphasizes, "what must be controlled, and how, is worked out anew for every project." Rather than viewing persistent methodological tensions in contemporary interdisciplinary research as problems requiring universal solutions through standardization, they may reflect different but complementary epistemic functions—much as du Bois-Reymond's precision-oriented isolation and Bernard's preservation of physiological complexity served complementary functions in nineteenth-century physiology. The lesson from this historical analysis is that experimental control represents an evolving, constitutive process central to knowledge production, suggesting the value of methodological pluralism that acknowledges the legitimate epistemic functions of different experimental approaches.

References

Barbara, J.-G. 2009. "Claude Bernard et ses suiveurs sur la question de curare: Enjeux épistémologiques." *Journal de la Société de Biologie* 203(3): 227–234. https://doi.org/10.1051/jbio:2009026, PubMed: 19833069

Barbara, J.-G. 2013. "Évolutions de la 'méthode scientifique' dans l'école de Claude Bernard." Pp. 83–104 in *Claude Bernard: La méthode de la physiologie*. Edited by F. Duchesneau, J.-J. Kupiec, and M. Morange. Paris: Éditions Rue d'Ulm.

Barbara, J.-G., and P. Corvol, eds. 2012. *Les élèves de Claude Bernard: Les nouvelles disciplines physiologiques en France au tournant du XXe siècle*. Paris: Hermann.

Bechtel, W., and R. Vagnino. 2022. "Figuring out What is Happening: The Discovery of Two Electrophysiological Phenomena." *History and Philosophy of the Life Sciences* 44(2): 20. https://doi.org/10.1007/s40656-022-00502-1, PubMed: 35581443

Bernard, C. 1855. *Leçons de physiologie expérimentale appliquée à la médecine, faites au Collège de France*. Paris: Baillière. https://doi.org/10.5962/bhl.title.1818

Downloaded from direct.mit.edu/posc/article-pdf/34/1/43/2577002/posc.a.572.pdf by UNIVERSITY OF EAST ANGLIA user on 30 October 2026

Bernard, C. [1857] 1883. *Leçons sur les effets des substances toxiques et médicamenteuses*. Paris: Baillière. https://doi.org/10.5962/bhl.title.1834
Bernard, C. 1865. *Introduction à l'étude de la médecine expérimentale*. Paris: Baillière.
Bernard, C. 1942. *Le cahier rouge*. Paris: Gallimard.
Bernard, C. 1965. *Cahier des notes, 1850–1860*. Paris: Gallimard.
Bolinska, A. 2024. "A Monist Proposal: Against Integrative Pluralism about Protein Structure." *Erkenntnis* 89(4): 1711–1733. https://doi.org/10.1007/s10670-022-00601-2
Boring, E. G. 1954. "The Nature and History of Experimental Control." *American Journal of Psychology* 67(4): 573–589. https://doi.org/10.2307/1418483, PubMed: 13228721
Bresadola, M., and M. Piccolino. 2013. *Shocking Frogs: Galvani, Volta, and the Electric Origins of Neuroscience*. Oxford: Oxford University Press.
Clarke, E., and L. S. Jacyna. 1988. *Nineteenth-Century Origins of Neuroscientific Concepts*. Berkeley: University of California Press. https://doi.org/10.1525/9780520352087
du Bois-Reymond, E. 1848–1884. *Untersuchungen über die thierische Elektricität*. 2 vols. Berlin: Reimer. https://doi.org/10.1515/9783111475325
Fessard, A. 1967. "Claude Bernard and the Physiology of Junctional Transmission." Pp. 105–124 in *Claude Bernard and Experimental Medicine*. Edited by F. Grande and M. B. Visscher. Cambridge, MA: Schenkman Publishing Company.
Finkelstein, G. 2006. Emil du Bois-Reymond vs Ludimar Hermann. *Comptes Rendus Biologies* 326(5–6): 340–347. https://doi.org/10.1016/j.crvi.2006.03.005, PubMed: 16731491
Finkelstein, G. 2013. *Emil du Bois-Reymond: Neuroscience, Self, and Society in Nineteenth-Century Germany*. Cambridge, MA: MIT Press. https://doi.org/10.7551/mitpress/9543.001.0001
Finkelstein, G. 2023. "Paris or Berlin? Claude Bernard's Rivalry with Emil du Bois-Reymond." *History and Philosophy of the Life Sciences* 45(2): 15. https://doi.org/10.1007/s40656-023-00567-6, PubMed: 36976381
Hoff, H. 1936. "Galvani and pre-Galvanian Electrophysiologists." *Annals of Science* 1(2): 157–172. https://doi.org/10.1080/00033793600200131
Holmes, F. L. 1986. "Claude Bernard, the 'Milieu Intérieur,' and Regulatory Physiology." *History and Philosophy of the Life Sciences* 8(1): 3–25.
Humboldt, A. von. 1799. *Expériences sur le galvanisme et en général sur l'irritation des fibres musculaires et nerveuses: Traduction de l'allemand, publiée avec des additions*. Translated by J.-F.-N. Jadelot. Paris: J.-F. Fuchs.

Downloaded from direct.mit.edu/posc/article-pdf/34/1/43/2577002/posc.a.572.pdf by UNIVERSITY OF EAST ANGLIA user on 30 October 2026

Kipnis, N. 1987. "Luigi Galvani and the Debate on Animal Electricity, 1791–1800." *Annals of Science* 44(2): 107–142. https://doi.org/10.1080/00033798700200151

Lenoir, T. 1986. "Models and Instruments in the Development of Electrophysiology, 1845–1912." *Historical Studies in the Physical and Biological Sciences* 17(1): 1–54. https://doi.org/10.2307/27757574, PubMed: 11622202

Levy, A., and A. Currie. 2019. "Why Experiments Matter." *Inquiry: An Interdisciplinary Journal of Philosophy* 62(9–10): 1066–1090. https://doi.org/10.1080/0020174X.2018.1533883

Matteucci, C. 1838a. "Des contractions et des sensations produites dans les animaux par le courant électrique." *Bibliothèque Universelle de Genève* 17: 357–364.

Matteucci, C. 1838b. "Sur le courant électrique ou propre de la grenouille." *Bibliothèque Universelle de Genève* 15: 157–168.

Matteucci, C. 1840. *Essai sur les phénomènes électriques des animaux*. Paris: Carilian-Goeury et Vr. Dalmont.

Matteucci, C. 1842a. "Deuxième mémoire sur le courant électrique propre de la grenouille et sur celui des animaux à sang chaud." *Annales de Chimie et de Physique*, ser. III, 6: 301–339.

Matteucci, C. 1842b. "Expériences rapportées dans un paquet cacheté déposé par M. Dumas, au nom de M. Matteucci, et dont l'auteur, présent à la Séance, désire aujourd'hui l'ouverture." *Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences* (Paris) 15: 797–798.

Moruzzi, G. 1996. "The Electrophysiological Work of Carlo Matteucci." *Brain Research Bulletin* 40(2): 69–91. https://doi.org/10.1016/0361-9230(96)00036-6, PubMed: 8724424

Potochnik, A., M. Colombo, and C. Wright. 2018. *Recipes for Science: An Introduction to Scientific Methods and Reasoning*. New York: Routledge. https://doi.org/10.4324/9781315686875

Schickore, J. 2018. "Explication Work for Science and Philosophy." *Journal of the Philosophy of History* 12(2): 191–211. https://doi.org/10.1163/18722636-12341387

Schickore, J. 2019. "The Structure and Function of Experimental Control in the Life Sciences." *Philosophy of Science* 86(2): 203–218. https://doi.org/10.1086/701952

Schickore, J. 2023. "Methodological Ideas in Past Experimental Inquiry: Rigor Checks around 1800." *Intellectual History Review* 33(2): 267–286. https://doi.org/10.1080/17496977.2021.1974225

Schickore, J. 2025. *Controlled experiments*. Cambridge: Cambridge University Press. https://doi.org/10.1017/9781009348966

Schickore, J., and W. R. Newman, eds. 2024. *Elusive Phenomena, Unwieldy Things: Historical Perspectives on Experimental Control*. Cham: Springer. https://doi.org/10.1007/978-3-031-52954-2

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Shideman, F. E. 1967. "Drugs as Tools in the Elucidation of Physiological Mechanisms." Pp. 107–128 in *Claude Bernard and Experimental Medicine*. Edited by F. Grande and M. B. Visscher. Cambridge, MA: Schenkman Publishing Company.

Vulpian, A. 1866. *Leçons sur la physiologie générale et comparée du système nerveux*. Paris: Baillière.

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