Biological Theory (2020) 15:83–90
https://doi.org/10.1007/s13752-020-00341-y

CLASSICS IN BIOLOGICAL THEORY

Revisiting Burr and Northrop's "The Electro-Dynamic Theory of Life" (1935)

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Abstract

Harold Saxton Burr was a biologist working throughout the 1930s–1950s on an important set of problems related to biological organization and the origin of complex living forms. He was a profound thinker, suggesting a complementary focus on field concepts in addition to the emphasis on particle models and integrating concepts from physics and philosophy in his work. He developed innovations in electrophysiological technique and used them to perform a wide experimental survey of bioelectricity in normal and pathological growth. Here, I briefly review his classic paper with philosopher F. S. C. Northrop, "The Electro-Dynamic Theory of Life," in the context of advances in this field over the last few decades. Based on recent progress, it is now clear that Burr was a prescient and visionary thinker. His main hypothesis, that bioelectric gradients serve as prepatterns guiding morphogenesis, has been confirmed using modern molecular physiology, as have his ideas about the place of cancer and the nervous system in the question of biological organization. With limited technology but deep insight, he derived insights that anticipated many modern discoveries. Even more importantly, Burr's view of bioelectricity as a convenient entry point for rigorous investigation of the broader question of self-organizing properties of life highlights a frontier of inquiry that awaits today's researchers. Burr and Northrop's "The Electro-Dynamic Theory of Life," originally published in the Quarterly Review of Biology (10(3):322–333, 1935), is available as supplementary material in the online version of this essay.

Keywords Bioelectricity · Development · Embryogenesis · Voltage

> *Talent hits a target no one else can hit; genius hits a target no one else can see.*
>
> —Arthur Schopenhauer

Throughout history, there have been thinkers who displayed a remarkable degree of prescience—deriving a vision of the world that is ultimately borne out by scientific advances long after they are gone, from very limited information and tools available at the time. Harold Saxton Burr (Fig. 1) was one of those. A tireless researcher, he worked at the Yale University School of Medicine and published five decades' (from 1916 to the 1960s) worth of primary papers and opinion/analysis pieces (Anonymous 1957). He is a founding figure in developmental bioelectricity—an interdisciplinary field that now spans areas including the origin of multicellularity, the relationship between genome and anatomy, regenerative medicine, bioengineering, soft body robotics, and basal cognition (McCaig et al. 2005; Funk 2013; Knox and Funk 2014; Levin and Martyniuk 2018; Mathews and Levin 2018; Levin 2019).

Burr was fascinated by bioelectricity—the voltages and electric fields produced naturally within living tissues (aside from the spiking of excitable nerve and muscle which were already the subject of considerable investigation by then). These bioelectrical signals derive from the activity of ion channel and pump proteins in cell membranes, and spread throughout cell networks via electrical synapses known as gap junctions. But Burr didn't know any of this – at the time he was active, the molecular source of bioelectric gradients was not known, and the relationship between heredity and cell function was just beginning to be worked out. He produced the first millivoltmeter usable for investigation of bioelectricity (Burr et al. 1936), and used it to explore a wide

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13752-020-00341-y) contains supplementary material, which is available to authorized users.

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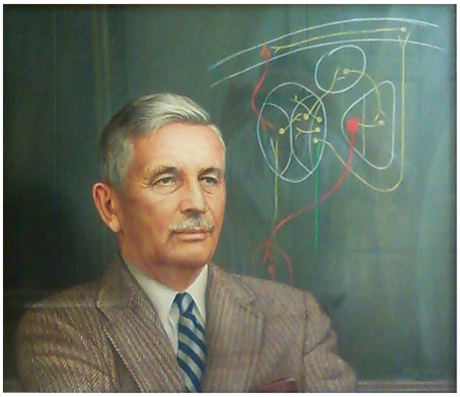

Fig. 1 Harold Saxton Burr. (Portrait provided courtesy of Manuscripts and Archives at the Yale University Library.)

sample of the biosphere. For example, as early as 1955 he had already seen the promise of unusual model systems such as slime molds (Burr 1955; Burr and Seifriz 1955), which have recently become popular contexts for understanding the decision-making capacities for cells and the role of biophysical forces therein (Adamatzky and Jones 2010; Kasai et al. 2015; Iwayama et al. 2016; Adamatzky 2018; Miranda et al. 2018; Vogel et al. 2018; Zhu et al. 2018; Boussard et al. 2019; Dussutour et al. 2019; Ray et al. 2019).

While interest in recording the bioelectrical correlates of morphogenesis was already apparent by 1903 (Mathews 1903), Burr's work was the only dataset big enough to permit generalization beyond one organism. Burr quantitatively recorded and analyzed the bioelectric properties of embryos, adult organisms, tumors, and trees, of a wide range of species including human beings. As a kind of informal "meta-analysis" of these extensive measurements, he thought deeply about the meaning of the universal occurrence of spatiotemporal patterns of bioelectric states in diverse tissues, and the fact that changes in these states correlate with important morphogenetic and patterning events.

Techniques for testing the functional role of these gradients (as contrasted with an epiphenomenal nature as a housekeeping byproduct of physiology) had begun to be available. Indeed, people including T. H. Morgan were already applying electric fields to developing and regenerating systems as early as 1904 (Morgan and Dimon 1904). However, Burr was well aware of the difficulty in making predicable changes to endogenous bioelectric properties with applied electrode approaches. He analyzed the measurement data from both neural and nonneural tissues, and proposed that the distributed pattern of electric potentials served as a kind of scaffold – a prepattern (in the modern language of molecular embryology) that guides cell behavior and thus controls growth and form.

The Electro-Dynamic Theory of Life

Burr's 1935 paper[1] (Burr and Northrop 1935) is, in many ways, his masterwork. Written with philosopher F. S. C. Northrop, it comprises many of Burr's key ideas, although he continued to refine many of the details after its publication. It begins with a philosophical stage setting, arguing for the greater emphasis on *organization* in addition to "entities"—a concern that is increasingly relevant in today's debates in systems biology and the proliferation of exhaustive profiling data (Noble 2010, 2012; Bizzari et al. 2019). Burr discusses the utility of field concepts, as a complement to what was already in his day apparent as the overwhelming direction of biological research—chemistry-based models focused on purely local interactions. He saw earlier than most that an important aspect of understanding biological systems was a rigorous appreciation of the nonlocal nature of control in morphogenesis and physiology. Burr weaves in concepts from physics, discussing the bidirectional feedback between field and particle. This paper (and Burr's overall body of work) is focused on bioelectric fields as a specific example, but this is (as I'm sure he realized) a much bigger issue, currently playing out in state-of-the-art discussions about agent-based models and downward causation from global "virtual governors" and global, distributed dynamics that emerge from relatively simple local rules governing proteins, subcellular structures, cells, and tissues (Pezzulo and Levin 2016; Torday and Miller 2016; Walker et al. 2016; Albantakis et al. 2017; Flack 2017; Ashikaga et al. 2018; Juel et al. 2019).

The first eight pages of the paper are devoted to a general introduction to a kind of informal dynamical systems theory for biology (Jaeger et al. 2012; Bizzarri et al. 2013; Jaeger and Monk 2015), arguing for the import of deep ideas (not merely computational methods) from physics to help address the major mysteries of biology. Burr then moves to a specific example: the establishment of anatomy during embryogenesis. Reliable, robust self-assembly of complex form is used here as a setting to discuss the ideas of Spemann, Weiss, and Driesch, and emphasize the importance of cellular context (cytoplasmic machinery) in addition to the nuclear genome. As in other works of his, Burr uses the example of the nervous system to illustrate his ideas and open problems in the field—a pairing that would not again be seriously explored until much later (Grossberg 1978; Pezzulo and Levin 2015).

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[1] For the journal's *Classics in Biological Theory* collection, this essay introduces Burr and Northrop's "The Electro-Dynamic Theory of Life," originally published in the Quarterly Review of Biology (vol. 10, no. 3, Sept. 1935, pp. 322–333); the article is available as supplementary material in the online version of this introduction.

Interestingly, he discusses the need to understand the *potential* forms that a given biochemical system can adopt (anticipating future efforts to map out additional attractors in cellular state space that exist beside the default ones (Levin 2014; Sullivan et al. 2016)). He concludes thus: "The pattern of the organization of the molecular and atomic constituents of protoplasm is an even more important problem to biology than the physico-chemical nature of the entities themselves. It is not enough to know the chemical formula of protoplasm. It is of vital importance to understand how the elements are related to each other, how they are gathered together in a single 'whole' system" (Burr and Northrop 1935, p. 331). The paper is a clear call for what today is embodied in complexity theory and dynamical systems approaches to biological control (Kauffman 1993; Kauffman and Clayton 2006; Seoane and Solé 2018), making it clear that bioelectricity is an experimental entry point into important philosophical and methodological issues in the biosciences.

This paper, and Burr's work in general, received limited attention. As molecular biology took off, most workers (and their students) gravitated toward emphasis on the more easily studied biochemical and genetic mechanisms, which—unlike bioelectricity—could be studied in fixed, chemically fractionated preparations. This of course was in line with precisely what Burr warned about—an overly exclusive focus on those aspects of cellular structure and function that could be studied in isolation, at the expense of holistic aspects. Even prominent thinkers who were making similar points at the time (Haldane 1917; Woodger 1930, 1931; Bertalanffy and Woodger 1962; Bertalanffy 1967, 1968) did not publicly support Burr's insight that bioelectricity represented a set of mechanisms that would, in time, become an immensely tractable entry point into supporting the organicist philosophical position. Weiss cited Burr's work, but mainly as a warning against thinking that bioelectricity *addressed as a mechanism* will resolve all of the organization questions (Weiss 1950) (a point which Burr well appreciated). Not until circa 2000, when bioelectricity began to be integrated into mainstream molecular genetics, did the paper begin its exponential increase in citations.

Bioelectricity: State of the Art

While subsequent decades saw an explosion of work on ion currents (Jaffe and Nuccitelli 1974; Nuccitelli 1980, 1986b; Kline et al. 1983) and electric fields (Robinson and McCaig 1980; Hinkle et al. 1981; McCaig 1986a, b, 1987, 1988), it was not until the 1970s that endogenous voltage was shown to be critical for single-cell proliferation by C. D. Cone (Cone 1970, 1971, 1974; Cone and Tongier 1971, 1973; Stillwell et al. 1973; Cone and Cone 1976) and ion currents implicated in embryo polarity by Lionel Jaffe (Bentrup et al. 1967; Jaffe 1981), and not until 2000 that the first tools were created to examine the role of voltage in a multicellular context (Levin et al. 2002) using fluorescent molecules that function as in vivo voltmeters.

In the last 20 years, a variety of Burr's specific predictions have come true. Spatiotemporal patterns of bioelectric gradients are indeed prepatterns that, along with chemical gradients and biomechanical forces, specify large-scale anatomy of the body (Bates 2015). This has been shown in the context of eye development (Pai et al. 2012), brain shape (Pai et al. 2015), fin length (Perathoner et al. 2014), skin coloration (Iwashita et al. 2006), left–right axial patterning (Levin et al. 2002), and anterior–posterior axial patterning (Durant et al. 2019). Prepatterns of bioelectric properties that predict large-scale patterning in cucurbits (Burr and Sinnott 1944) have been studied and functionally implicated using molecular tools (Vandenberg et al. 2011; Adams et al. 2016) (Fig. 2). Moreover, it is now clear that the bioelectric signaling layer is an important aspect of physiological software that enables genome-specified hardware to exhibit the remarkable *plasticity* observed during regeneration and remodeling (Bryant et al. 2017; McLaughlin and Levin 2018).

Also confirmed have been a variety of Burr's ideas about the relationship between the nervous system and nonneural bioelectricity (Burr 1932). Neural structures are indeed exquisitely sensitive to bioelectric cues provided by the neighboring tissue, as he predicted (Grenell and Burr 1947), seen by the modulation of host cell electric potentials to control outgrowth of transplanted neurons (Blackiston et al. 2015) and by the patterning of the brain by preexisting bioelectric patterns (Burr 1932; Pai et al. 2018). Similarly, Burr's idea that the nervous system carries a significant portion of instructive bioelectric signaling has recently been confirmed in the discovery of the brain's directing of tissue morphogenesis in development via ionic signaling (Herrera-Rincon et al. 2017) and the role of the central nervous system in directing planarian regeneration polarity (Pietak et al. 2019). Remarkably, Burr even partially anticipated the computational neuroscience techniques being applied to nonneural bioelectricity (Friston et al. 2015; Pezzulo and Levin 2015), by inquiring about the design principles of the brain and its information-processing functions (as distinct from the implementation mechanisms). Consistently with Burr's ideas of the evolutionary process shaping brain and somatic tissues, it is now increasingly beginning to be appreciated how neural computation evolved by speed-optimizing information processing tasks that cells were already doing long before nervous systems evolved (Keijzer et al. 2013; de Wiljes et al. 2015; Jekely et al. 2015; Keijzer 2017; Keijzer and Arnellos 2017; Fields et al. 2020).

Finally, Burr also correctly identified cancer as the flip side of multicellular organization, equally dependent on

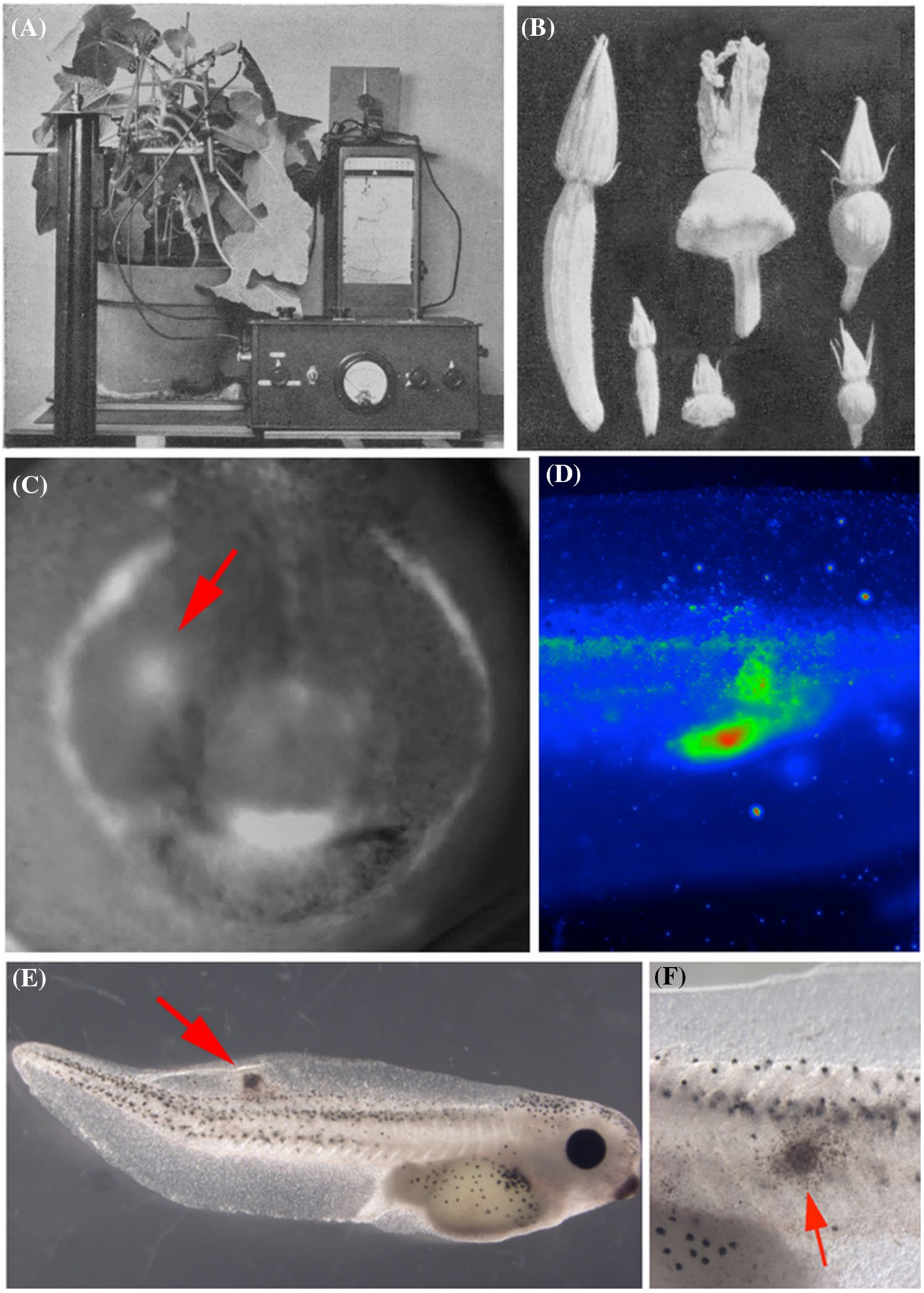

Fig. 2 Bioelectric prepatterns, then and now. **a** An electrophysiology rig allowed Burr to measure bioelectric patterns existing in embryos of cucurbit fruits (taken with permission from Fig. 3 of Burr and Sinnott 1944). **b** These fruits occur in different shapes and sizes based on strain, enabling him to correlate the initial bioelectric state with the subsequent anatomy, and leading to the suggestion that these bioelectric states provide instructive information about growth and form—that they serve as a prepattern that guides morphogenesis (taken with permission from Fig. 1 of Burr and Sinnott 1944). **c** Modern work in frog embryos using voltage-sensitive fluorescent dyes supported Burr's prescient idea, revealing the "electric face" (Vandenberg et al. 2011): a distinct pattern of resting potentials (light gray) which show where the eyes (arrow indicates the first eye to form), mouth, and various other organs of the face will form. Functional experiments to modify these patterns showed that they regulate gene expression and resulting anatomy (Adams et al. 2016), exactly as Burr predicted, and when reproduced elsewhere in the body, can even initiate the formation of whole ectopic organs such as eyes (Pai et al. 2012). **d** Similarly, Burr's ideas about the importance of bioelectric signaling in tumors (Burr et al. 1938; Burr 1940) have been validated by recent data (Yang and Brackenbury 2013; Bates 2015) showing that precancer in tadpoles (induced by human oncogene misexpression) can be detected by its abnormal bioelectric signature (Chernet and Levin 2013b), before it becomes anatomically apparent (E,F: arrow indicates tumor)

bioelectric cues (Chernet and Levin 2013a; Moore et al. 2017). Moreover, he found out that the disturbances of normal bioelectric pattern by tumorigenesis can be detected at long-range (Burr et al. 1938, 1940; Burr 1941), presaging by more than 70 years the discovery that nonlocal imposition of bioelectric states by optogenetic techniques can normalize cancer (Chernet and Levin 2014; Chernet et al. 2016). It is clear that evolution discovered the unique properties of bioelectric circuits, implementing the communication needed to bind competent individual cells toward a common organ-level morphogenetic purpose, as far back as bacterial biofilms (Prindle et al. 2015; Lee et al. 2017; Liu et al. 2017).

Burr had a remarkable ability to foresee advances in this field, and his work was no doubt an inspiration to the major figures in this area who advanced this science in the 20th century (Nuccitelli and Jaffe 1975, 1976; Nuccitelli et al. 1975, 1977, 1986; Weisenseel et al. 1975; Borgens et al. 1977a, b, 1979a, b, c, 1980, 1981; Jaffe and Nuccitelli 1977; Jaffe 1979; Jaffe and Poo 1979; Robinson and McCaig 1980; Stump et al. 1980; Hinkle et al. 1981; Kline et al. 1981; Robinson et al. 1981; Borgens 1982, 1983; McCaig and Robinson 1982; McCaig 1986b; Nuccitelli 1986a). If he were alive today, Burr would have thrived in the context of the revolution in optogenetic reporters of bioelectric state and actuators that allow modulating tissue bioelectric patterns at will (Mutoh et al. 2012; Adams et al. 2014; Cohen and Venkatachalam 2014; Silic and Zhang 2018). Given his ability to see beyond the current mainstream and the willingness to embrace and extend the latest technology, we can only try to imagine the advances he would have made at the interface of molecular biology and developmental physiology. Due to his interest in philosophical issues of explanation in biology and the use of mathematical global field models as a complement to particles and forces, he would have been right at home with today's questions about the relationship between DNA, biochemistry, and dynamic form (Bischof 2000; Newman 2016; Manicka and Levin 2019). Interestingly, despite all of the progress since his work, Burr's emphasis on *field* models of bioelectric control have not yet been developed. Moving beyond local models of electrophysiology in development and regeneration represents an important area for future work (Goodwin and Pateromichelakis 1979; Goodwin and Trainor 1980; Goodwin and Lacroix 1984; Goodwin 1985; Hart et al. 1989; Brandts and Trainor 1990a, b; Brandts 1993). As of 2020, Burr's ideas have only begun to be mined.

Burr was an important thinker and pioneer, working at the very edge of contemporary technology to produce new data, and extrapolating to ideas that wouldn't be properly appreciated for decades thereafter. Equally important as the mechanistic insights into bioelectricity was a thread running through all of Burr's work: a rigorous appreciation of the unique information-processing, purposive, *meaning*ful activities that characterize life at all scales, the role of bioelectrics in this process, and the resulting relationship between life and mind (Burr and Northrop 1935; Burr 1944, 1956, 1957).

Acknowledgments M.L. thanks Stuart Newman and Richard Gawne for helpful suggestions on the manuscript, and Jessica Becker of Manuscripts and Archives at the Yale University Library for assistance with the portrait of H. S. Burr. M.L. also gratefully acknowledges support by the Allen Discovery Center program through The Paul G. Allen Frontiers Group (12171), and by the Barton Family Foundation.

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