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"It takes two to make a thing go right": The coevolution of technological and mathematical tools in neuroscience

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Abstract

Some philosophers of neuroscience have recently argued that the history of neuroscience is principally a history of technological tool development. Across these claims, there is little to no mention of data analysis methods nor their underlying assumptions. Here, I argue that mathematical tools have played crucial roles in the history of neuroscience. First, I present the Hodgkin-Huxley model as an example of research constrained by technological limitations and mathematical assumptions. Second, I highlight scale-free neuronal dynamics and explain how that discovery required both technological and mathematical advancements. I conclude by discussing consequences for explanations in neuroscience.

Keywords: Hodgkin-Huxley model, mechanism, neuronal dynamics, scale-free, tool development

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It takes two to make a thing go right.

—Rob Base (Ginyard) and DJ E-Z Rock (Bryce), *It takes two*

1. Introduction

There should be no doubt that technological developments have played significant roles throughout the history of scientific discoveries and progress. This is as true in the physical sciences (e.g., particle accelerators in physics) as in the life sciences (e.g., microscopes in biology). What is less apparent is the role mathematical developments have played in facilitating and supporting many of those discoveries. Mathematical tools for analyzing data may not be at the forefront of discoveries centering on the physical structure of investigative targets of interest (e.g., cells); but they certainly are crucial in research focused on the dynamics of phenomena (e.g., planetary motion). In short, for science to progress, research on the movement and temporal aspects of phenomena often require the coevolution of technological *and* mathematical tools.

Recently, it has been increasingly argued by some philosophers of neuroscience that experimental tools are not just important but are fundamental to neuroscience research (e.g., Bickle, 2016). Put in its most extreme terms, the line of thought goes like this: From Golgi's staining technique to functional magnetic resonance imaging, and from deep brain stimulation to optogenetics, the history of neuroscience is principally a history of tool development. Moreover, it has been argued that this history is best characterized as one that exhibits reductionist (Bickle, 2006, 2016) and mechanistic explanations (Craver, 2002, 2005). Across

these claims, little to no mention of data analysis methods are mentioned nor the underlying assumptions of those methods. Here, I argue that the mathematical assumptions of applied data analyses have played crucial roles in the history of neuroscience. First, I present the Hodgkin and Huxley model of action potentials as an example of research constrained by technological and mathematical limitations of the time. Second, I draw attention to a feature of neurons that is overlooked by the Hodgkin-Huxley model: scale-free dynamics. After describing scale-free dynamics, I then point out a consequence scale-free neuronal dynamics has for mechanistic explanations of neuronal activity. I conclude by discussing the necessity of mathematical developments in providing appropriate accounts of scale-free neuronal activity.

2. Hodgkin-Huxley model and scale-free neuronal dynamics

The canonical Hodgkin and Huxley (1952) model of action potentials in the squid giant axon is considered "the single most successful quantitative model in neuroscience" (Koch, 1999, p. 171). The majority of the details of the model are not essential for my current aims. For detailed explanations of this model see Gerstner, Kistler, Naud, and Paninski (2014), as well as Koch (1999) for discussion and further references. For now, it is important to understand that this model treats the action potential as an event that is "all-or-none" in that it occurs within distinctly defined timescales (e.g., ; Bear et al., 2016; Figure 1). Moreover, those timescales have a lower boundary, specifically, 10 milliseconds (ms) in the canonical Hodgkin-Huxley model (Hodgkin & Huxley, 1952, p. 528; Koch, 1999,

p. 334; Marom, 2010, p. 23). What that means is that the action potential of a neuron (i.e., its "spike" of activity) is treated within the Hodgkin-Huxley model as occurring at least 10 ms from initiation to termination of all involved processes (Marom, 2010, p. 22).

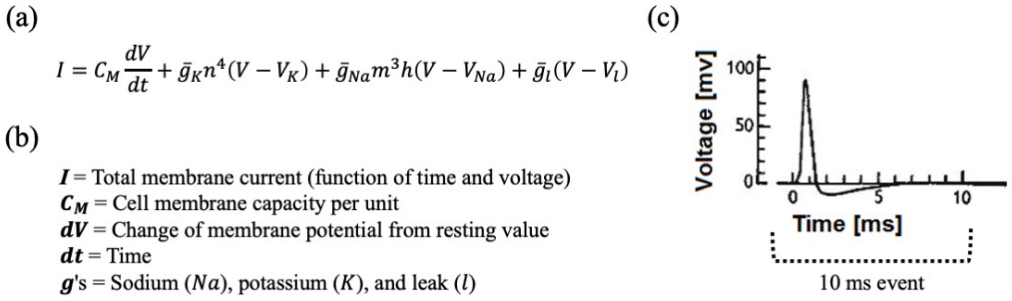

Figure 1. Hodgkin-Huxley model. (a) The canonical Hodgkin and Huxley (1952) model of action potentials in the squid giant axon. (b) Definitions of key model variables. (c) The basic shape of an action potential as produced by Hodgkin-Huxley model. (Modified and reprinted with permission from Wikipedia. CC BY-SA 4.0.) The x-axis captures the entire range of time in which an action potential occurs. According to the model, the lower temporal boundary of an action potential is 10 ms. This means that the entire event, from start to finish, occurs within that time frame.

As is well-known (e.g., Marom, 2010), although there were empirically justifiable reasons at the time (e.g., Adrian & Zotterman, 1926), defining the "action potential" as a 10 ms event was due to investigator observational preferences in combination with technological limitations. Observational preferences were constrained by the limits of the recording technology, namely,

the voltage clamp. Although the voltage clamp was instrumental in providing the data that lead to the development of the Hodgkin-Huxley model, it was limited in its ability to record the full range of ion channels, charged particles, and other physiologically relevant features of neuronal activity (Schwiening, 2012). This resulted in the need to sum across molecular activity (Gerstner et al., 2014)—certainly a necessity when calculating at the molecular scale—and collapse other physiological features into imprecise "leak" terms, a sort of "catch all" variable used in models that have causally relevant features that have not been precisely measured. Other limitations involved the manner in which the data was calculated. Hodgkin and Huxley calculated data from the voltage clamp via hand calculators (Koch, 1999, p. 160). Specifically, Hodgkin and Huxley utilized a mechanical calculator, the Brunsviga 20 (Figure 2), which required them to spend a few weeks and many thousands of rotations of the mechanical calculator's crank (Schwiening, 2012).

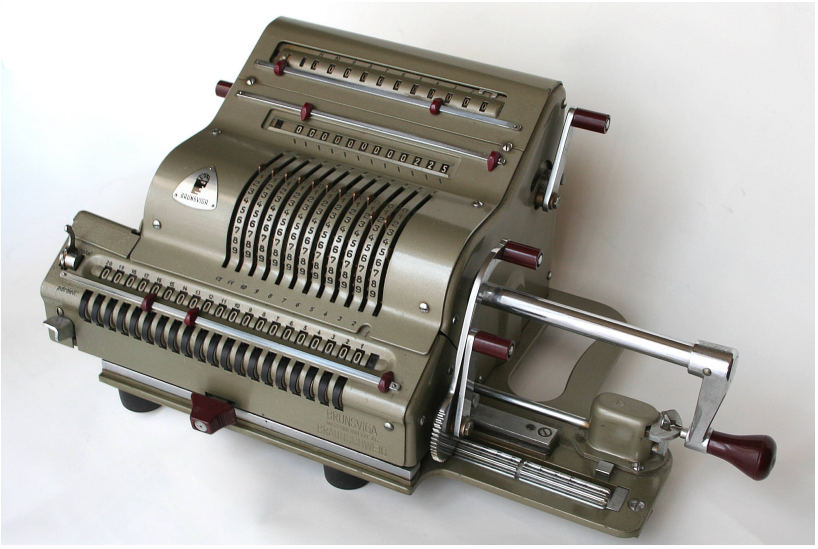

Figure 2. The Brunsviga 20, "one of the most popular mechanical calculators. It was produced up to the early 1970s and marketed with the slogan 'Brains of

Steel'" (Schwiening, 2012). (Reprinted with permission from Wikipedia. CC BY-SA 2.0 DE).

Although the canonical Hodgkin-Huxley model is described by some as being linear in nature (e.g., Gerstner et al., 2014; Hodgkin & Huxley, 1952, pp. 538-540), there is debate about whether or not it is able to capture the relevant types of nonlinearities exhibited by feedback that are now established as occurring during action potentials (e.g., Marom, 2010; Schwiening, 2012). Regardless whether or not the canonical Hodgkin-Huxley model is linear or nonlinear, or can capture particular forms of feedback, it is clear now that even single neurons are appropriately understood as nonlinear systems (e.g., Izhikevich, 2007).

Advancements in recording technologies have facilitated the ability of neuroscientists to obtain more detailed data on neuronal activity (e.g., multielectrode arrays; Gross, 2011), making it possible to record more detailed and accurate data from longer timescales of neuron activity. As a result, it is becoming increasingly evident that the relevant timescales for explaining even "basic" single-neuron activity requires looking below and above that 10 ms window. Action potentials do not appear to have strictly defined windows of activity, specifically, nonlinearities in the forms of feedback and hysteresis significantly contribute to the event. Instead of viewing action potentials as having clear startup and finish conditions (Figure 1), it is more accurate to view action potentials as continuous, nonlinear cycles. This is clearly depicted in early

models, such as the FitzHugh-Nagumo model (FitzHugh, 1961; Nagumo et al., 1962; Figure 3a) and more recent models, such as the Izhikevich model (Izhikevich, 2007; Figure 3b).

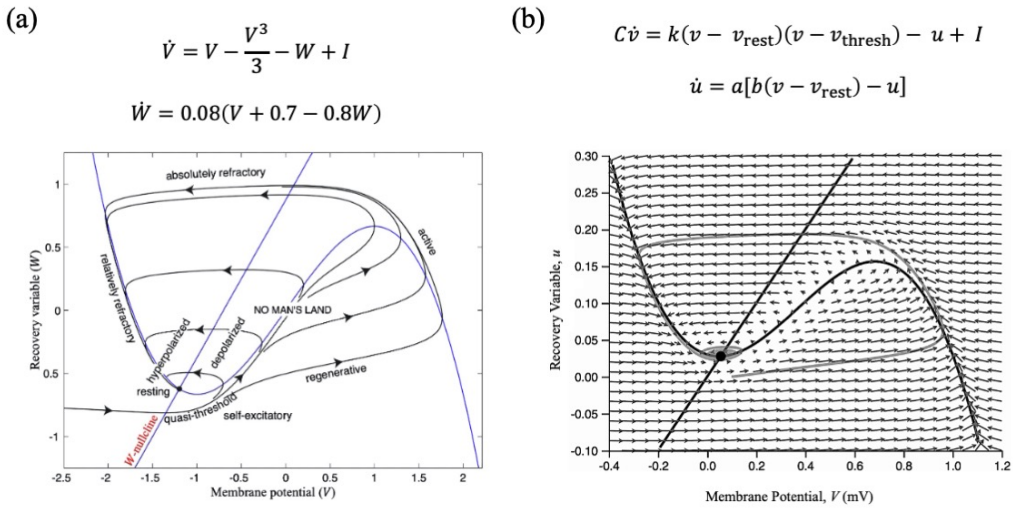

Figure 3. Models of single-neuron activity. (a) FitzHugh-Nagumo model and phase space portrait. (Modified and reprinted with permission from Scholarpedia. CC BY-NC-SA 3.0.) (b) Izhikevich model and phase space portrait. (Modified with permission from J. Terwilliger, 2018.)

As mentioned above, there is debate as to the degree or not that the canonical Hodgkin-Huxley model accounts for a wide range of nonlinear features of action potentials, such as hysteresis. I am not entering that debate here. Instead, I focus on a particularly notable recent finding that has resulted from improved recording technologies. That finding is the apparently scale-free nature of neuronal activity. At its most general, a phenomenon is "scale-free" (or "scale invariant") when its structure (i.e., behavioral, spatial, and/or temporal) is statistically self-similar from various points of observation (Bak, 1996; Gisiger,

2001). Many illustrative examples of spatial scale-free structures are found in fractal geometry (Mandelbrot, 1983; Figure 4).

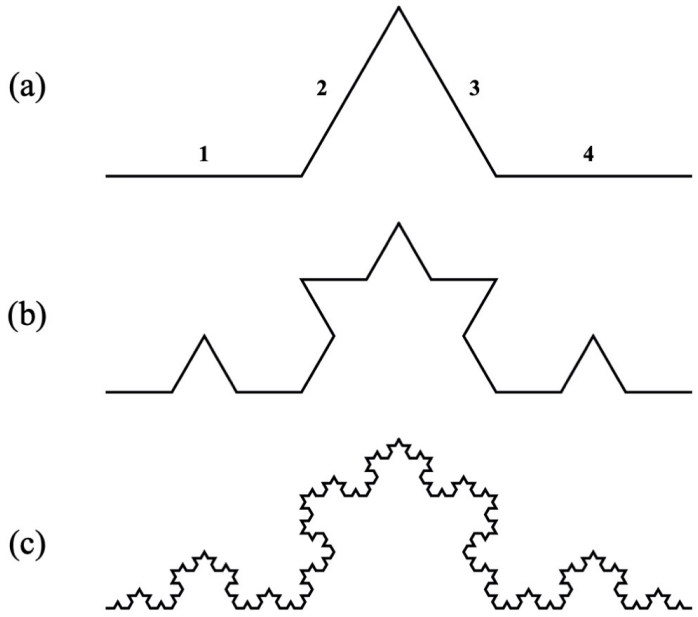

Figure 4. The Koch triangle is an example of a spatial fractal. Here, three iterations of self-similarity are depicted (a,b,c). (Modified and reprinted with permission from Wikipedia. CC BY-SA 3.0.)

Scale-free properties have become particularly popular in recent years in regard to network structure, where few nodes have many connections and many nodes have few connections. Consequently, such networks have no specific or average number of connections that characterize the entire system. Mathematically speaking, scale free structures can be characterized by their power-law distribution (He, 2014). It has become commonly accepted that many phenomena and systems of diverse composition are scale free in this way, for

example, cellular metabolism, Hollywood actors that have worked together, sexual relationships, and the World Wide Web (Barabasi & Bonabeau, 2003). There is increasing evidence that neural systems exhibit many scale-free properties (e.g., Boonstra et al., 2013; He, 2014). These properties are exhibited from neuronal network connections to neuron branching patterns. For current purposes, I focus on the scale-free dynamics exhibited by neuronal dynamics (for a wide range of examples see Boonstra et al., 2013). In short, neuronal dynamics are considered "scale free" when there is no single time scale that properly characterizes its activity, which includes attempting to define an event as occurring within specific windows of time. There are a number of consequences that result from the fact that many neural systems exhibit scale-free spatial or temporal structure. In the next section I explore one such consequence, specifically, the inability of mechanistic explanations to account for scale-free neuronal dynamics.

3. Consequences of scale-free dynamics for explanations in neuroscience

In a recent paper, Bechtel (2015) argues against the claim that scale-free biological phenomena cannot be explained mechanistically. He rejects the following argument, which I summarize as follows:

1. Mechanistic explanations require that the phenomena being explained have well-defined boundaries, such as a temporal boundary.
2. Many biological phenomena exhibit scale-free features.
3. Scale-free phenomena have no well-defined temporal boundaries.

4. Therefore, scale-free biological phenomena cannot be explained mechanistically.

Marom (2010) presents such an argument and serves as one of Bechtel's targets. Marom argues that there is empirical evidence suggesting that neuronal activity is scale-free and, thus, is just the type of biological phenomenon that cannot be explained mechanistically. Marom's argument includes discussion of the Hodgkin-Huxley model, which leads him to conclude:

> Indeed, the lesson from our journey across levels of organization, from behavior through neural assemblies to single neurons and proteins, suggests that dreams on all-encompassing microscopic timescale-based descriptions, aimed at explaining the temporal richness of macroscopic levels, should be abandoned. Other approaches are called for. (2010, p. 23)

In short, Marom claims that there are no uniquely defined timescales that could justify defining action potentials as events that have a lower boundary of 10 ms. Consequently, macroscale neuronal activity that appear scale-free are not merely the result of additive or linear combinations of microscale contributions. Instead, they are truly scale-free: the micro timescales contribute to and constrain the macro timescales, but so too does the macro contribute to and constrain the micro, such that no single scale serves a more fundamental explanatory role than the others.

Bechtel's reply to Marom is that scale-free phenomena can still be explained mechanistically. But to do so requires that we appreciate the role of

mechanisms in scientific practice. According to Bechtel, scientists often posit "bounded mechanisms" for the purposes of testing hypotheses (2015, pp. 84-85). A scientist can understand that a phenomenon is interconnected (e.g., networks) and still pursue a mechanistic account of that phenomenon by drawing boundaries around that organism. Those bounded mechanisms are not abstractions, however. "Abstractions," according to Bechtel, leave information out. Instead, those bounded mechanisms are idealizations. Idealizations, according to Bechtel, are models with *simplifying* falsehoods (2015, p. 85). For example, if phenomenon X is understood to be highly interconnected, an explanation of X that assumes that it is not affected by all of those connections would be an abstraction. But to localize X to, for example, its nearest neighbors, is to provide a "*first approximation*" (2015, p. 85; italics in original) that appreciates the practical challenges of accounting for all the actual connections. Such an explanation would be both an idealization and a mechanism.

Although he accepts that neuronal dynamics can be scale-free, Bechtel remains committed to providing mechanistic explanations of those dynamics. Accordingly, Bechtel remains committed to mechanisms being bounded, on the further stipulation that such bounded mechanisms are idealizations and not abstractions. For example, the action potential is a "bounded mechanism" that occurs within 10 ms windows. Such an idealization is acceptable because it makes the timescales of that phenomenon tractable to investigators' cognitive limitations (2015, p. 92). Thus, the Hodgkin-Huxley model can be understood as an idealization of action potentials, with the 10 ms feature being a simplifying

falsehood—though not an abstraction that leaves out relevant features. This is a very streamlined presentation of Bechtel's argument, for example, he makes a further claim that such idealized mechanisms can point out areas for further investigation in a mechanistic explanation. What matters for my current purposes, is Bechtel's attempt to make room within mechanistic accounts to explain scale-free activity.

There is a lot in Bechtel's reply to Marom to agree with, for example, the fact that scientists are epistemically-limited creatures who need to simplify some phenomena in order to get an intellectual grip on them. However, I think Bechtel's reply overlooks a central issue raised by Marom. If mechanisms are, by definition, *bounded*, then scale-free phenomena (e.g., scale-invariant, fractal, flicker noise, power laws, etc.; Gisiger, 2001) are, by definition, not mechanisms. In the case of action potentials, the canonical Hodgkin-Huxley model sets a lower boundary on the phenomenon at 10 ms. In other words, it treats action potentials as starting and finishing within windows of time of at least 10 ms (Figure 1c). As discussed above, such a claim was justified as being consistent with the best science of the time (e.g., Adrian & Zotterman, 1926). With that said, it was constrained by technological (voltage clamp) and mathematical (the type of calculations that could be conducted on a Brunsviga 20 calculator; Figure 2) limitations. Technological advancements have certainly played a role in revealing scale-free dynamics (e.g., multielectrode arrays; Gross, 2011). However, data from advanced equipment alone has not justified the existence of scale-free dynamics in neuronal systems. The other part needed for the right account—

remember, “it takes two to make a thing go right”—is the pairing of data from suitable technology with the appropriate mathematical tools.

In the case of single-neuron activity, the right mathematical tools are those from nonlinear dynamical systems theory (NDST; e.g., Izhikevich, 2007; Liebovitch & Toth, 1990). NDST methods are crucial to assessing scale-free structure, and can contribute to establishing whether a phenomenon is truly scale-free or not and, if so, what kind of scale-free characteristics it has. What’s more, applying NDST methods to complex and nonlinear phenomena typically requires powerful computers. For example, generating phase portraits of relatively simple two-dimensional dynamical systems was often not practical before computers. Hodgkin and Huxley’s “Brains of Steel” mechanical calculator was certainly not up to the task. Thus, the Izhikevich model of single-neuron activity required both the appropriate processing power (i.e., modern computers) *and* data analysis methods (i.e., NDST) in order to provide qualitative and quantitative accounts of that phenomenon’s nonlinear dynamics.

As mentioned above, nonlinear dynamics are not central to my current aims; but scale-free dynamics are. Scale-free properties are a particularly unique set of phenomena in regard to the need for coevolved technological and mathematical tools. Many aspects of mammalian biological phenomena alone exhibit scale-free structures, such as, bronchial tube branching, eye saccades, heart beats, neuronal networks, and postural sway. Accordingly, different mathematical tools are needed to properly determine the ways they are scale-free. For example, detrended fluctuation analysis (Peng et al., 1994) can assess

structural self-similarity in a signal, but will not necessarily make clear if the structure results from linear or nonlinear processes (Bryce & Sprague, 2012). In the case of appropriate mathematical methods for assessing the scale-free dynamics of action potentials, if such activity is, for example, fractal, then it would not have been possible to accurately analyze such data, regardless of technological advancements, until the 1980s. The reason is because the concept "fractals" was not introduced to the broader scientific community until then (Mandelbrot, 1983).

In order to identify fractal scale-free structures, whether resulting from linear or nonlinear processes, the concept "fractals" and their measurement must be part of an investigators toolbox. Fractals, such as the Koch triangle (Figure 4) are paradigm examples of scale invariance: the overall structure of the system is maintained at each level of observation. Such phenomena are thus not appropriately explained in terms that, for example, treat them as having an average value. Instead, as Mandelbrot pointed out, such phenomena are appropriately characterized via a fractal dimension. The fractal dimension provides a quantitative means of characterizing a scale-free phenomenon that accounts for all of its scales. The equation for calculating the fractal dimension is:

$$n = {}^{1}/_{S^{d}}$$

Let's go back to the Koch triangle. For demonstration purposes, we will look at a four-lined Koch triangle (Figure 4). Here *n* is the number of line segments at a particular scale of observation; in this case, it is 4. Next, *S* is the scale factor, or the size reduction at each iteration; here it is 1/3. Our equation is

now: $4 = 1/(1/3)^d$, or $4 = 3^d$. We want to figure out d, or the fractal dimension. To do so, we take the log of both sides: $d = \log 4/\log 3$, which gives us a fractal dimension $d = 1.26$. In English, this means that the fractal dimension of the Koch triangle is 1.26, which means it is not a straight line (1) or a square (2), but closer to being a straight line than a square (1.26). There are various other methods for mathematically assessing fractals and multifractals (Lopes & Betrouni, 2009).

The point of this example is to demonstrate that before Mandelbrot's invention (discover?) of fractal geometry, it was not possible to accurately account for such phenomena, for example, collapsing scale-invariant structures into single values (e.g., arithmetic mean). The consequence for neuronal activity is that it was not until the 1990s (e.g., Liebovitch & Toth, 1990) that scale-free dynamics could be properly identified. Before then, such properties were misidentified via other statistical methods. Since scale-free structures have no primary scale or average scale, they have no specific window to identify as the start and finish boundary. Such a view of neuronal activity is further evidenced by other NDST-based work, such as the Izhikevich model (2007; Figure 3b), which treats action potentials as continuous cycles and not "all-or-none" (cf. Figure 1c). If true, that is, if action potentials are not bounded within discrete windows of time, then action potentials cannot be accounted for mechanistically.

In concluding this section, an important clarification needs to be made in order to address a significant critique of the current line of thought. The critique centers on the notion of "bounded" in regard to natural phenomena. As discussed above, the currently-relevant aspect of the Bechtel/Marom debate centers on the

idea that mechanistic explanations treat targets of investigation as bounded, namely, as having delineated borders, which can be spatial or temporal. The Hodgkin-Huxley model of action potentials and its 10 ms event window were presented as an example of such a bounded mechanism. Scale-free neuronal dynamics was presented as an unbounded phenomenon, which means it is not a phenomenon accessible to mechanistic explanation (i.e., if "mechanistic explanations" include the stipulation of boundedness; see Bechtel, 2015 and Marom, 2010). The critique of this line of thought centers on the point that even scale-free neuronal dynamics are "bounded" in a number of ways, for example, there *is* a window of time in which they occur (e.g., they do not last for months, years, or centuries) and they *are* spatially confined (e.g., they occur in an area of the brain, and not across the whole brain, let alone body). This is a compelling critique. However, it does not address the way in which scale-free dynamics are "unbounded." The way in which scale-free dynamics are unbounded concerns the inability of single, bounded values to *characterize* the phenomenon. A time series (Figure 5) need not be infinite nor recorded from an event that has no spatial location in order to be scale free. A scale-free time series exhibits the same pattern among windows of various lengths of time. For example, if a heartbeat shows a pattern of activity over 60 minutes, then, to be considered scale-free, that same pattern should be shown in each of two 30 minute windows of time, at each of four 15 minute windows, and so on. In that way, the time series is not properly understood as "bounded" in that there is no single length of time that characterizes the entire signal. That is to say, it is not correct to treat the event as a

bounded 60 minute event, or a 30 minute event, and so on; but in terms of the structure of the patterns across various scales. It is in that sense that Marom argues that neuronal dynamics do not have timescales, and it is in that sense that they are unbounded, and, thus, not properly explained mechanistically.

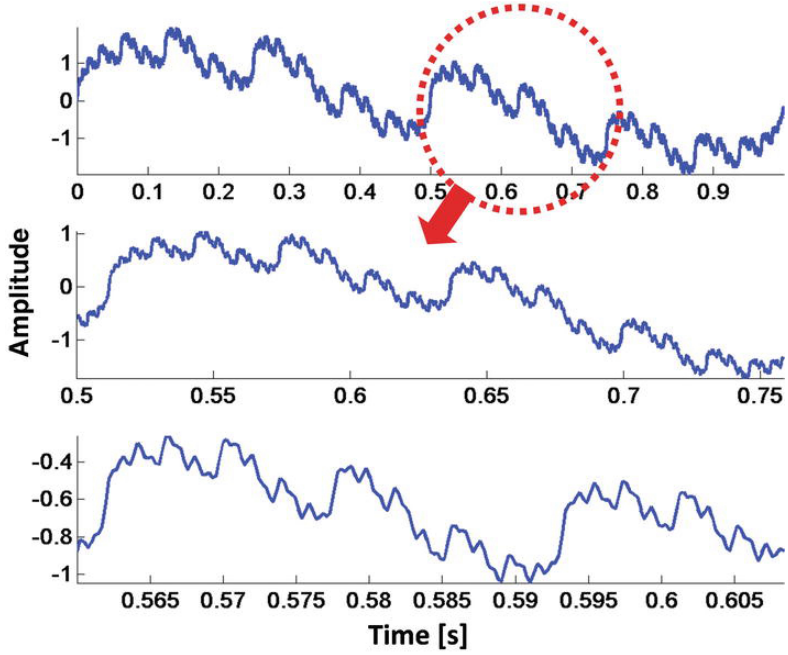

Figure 5. Fractal time series exhibiting scale-free structure at various windows of time. (Reproduced with permission from Armentano et al., 2017. CC BY 3.0.)

4. Conclusion

It is highly unlikely to find disagreement among the scientific research community at large that technological advancements have paved the way for some of the greatest advances and discoveries. What is less often acknowledged—especially in neuroscience—is the necessity of coevolving our mathematical tools with technological advances, and vice versa. Consequently, technological advancements that produce more detailed and accurate data

recording will not alone necessarily provide proper explanations of biological phenomena. Mathematical tools like those provided by NDST are needed as well in order to properly characterize data. The Hodgkin-Huxley model was informed and constrained by the available technological (i.e., voltage clamp) and mathematical (i.e., Brunsviga 20 calculator) tools of the time. Since then, more advanced technology (e.g., multielectrode arrays) and mathematics (e.g., fractal analysis) have highlighted some of the shortcoming of the Hodgkin-Huxley model as a comprehensive model of action potentials across temporal scales. Scale-free neuronal activity provides a rich example of this. In order to identify scale-free activity, researchers needed more accurate measurements, data analyses, and—in this case—new concepts altogether. In order to properly account for scale-free activity, a new concept—namely, fractals and the fractal dimension—was needed, as was accompanying innovative mathematical analyses. One consequence of the existence of scale-free neuronal activity discussed here involves the limitations of mechanistic explanations to account for phenomena that are without discrete temporal boundaries. In sum, an attempt has been made here to demonstrate that it takes two to make progress in neuroscience, namely, both technological and mathematical advancements.

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