RESEARCH ARTICLES

Paradox entails new kinds of medical knowledge

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Abstract

This essay concerns the inevitability of contradiction and the resulting paradox that occurs in the modeling of complex phenomena in general and within medicine in particular. We address how encountering a logical impasse in the interpretation of experimental data using simple models, forces the development of next generation mega models, or theory, in order to resolve an empirical paradox. The challenge to overcome such a data-based complexity barrier was met in physics with the development of quantum mechanics at the beginning of the twentieth century in order to resolve the paradoxical properties light, resulting in a revolutionary new way to understand the physical universe. A no-less transformational understanding of the complex way the human body combats illness occurred in medicine somewhat earlier when Jenner determined that the way to protect against a life-threatening disease was to expose a patient to that very disease. What could be more paradoxical than a vaccine? This was the beginning of a science revolution in medicine, requiring the synthesis of multiple disciplines to understand what was demonstrably true about vaccinations. New theory entailed by the resolution of empirical paradox invariably leads to new kinds of knowledge that is incompatible with prior understanding and this was certainly the case in medicine. Herein it is argued that the source of complexity is criticality, which is the emergent collective behavior of natural systems, and it is the cooperative behavior of critical dynamics that ultimately resolves empirical paradox. Understanding how to systematically resolve such internal contradictions is a necessity if the progress of medical understanding is to outpace the technology on which much of today's understanding is based.

1. Introduction

This is an essay on complexity and how that complexity is revealed through the emergence of paradox. In and of itself the study of such things might not seem to be worth your time, unless you are a student of conflict, but what is interesting about paradox is that its resolution not only generates new knowledge, but quite often it generates a new kind of knowledge. The argument is in some sense universal, which is to say that it does not depend on the discipline in which it is developed. But setting that aside I will confine the bulk of my remarks to the science of medicine.

However let me begin slowly and prepare the way, because as with other exercises the muscle may resist activity after such a long period of neglect. It seems to me that nothing better represents the universal importance of complexity resulting in paradox than the remarkable insight shown by Dickens in his opening sentence of the *Tale of Two Cities* [i]:

> It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope, it was the winter of despair, we had everything before us, we had nothing before us, we were all going directly to Heaven, we were all going direct the other way. [i]

These observations force the reader to acknowledge the paradoxical nature of European society at the time of the French Revolution and has been so often repeated that the attribution is superfluous. Each oxymoron in the opening sentence, in their turn, captures another aspect of society that is self-contradictory and displays another aspect of social complexity. Or from another perspective Dickens might have been introducing the state of the individual, who could at times be a wise man and at other times be a simpleton, naively accepting the world as it is, while cynically rejecting it. With a little reflection one can apply his reasoning to most if not all the affairs of humanity, including medicine.

But no matter how strongly the words of the poet and author resonate with our experience, as scientists we require a different standard a truth. Our intuitive brain embraces these words and we understand them to convey a deep truth; a deep truth being a statement that along with its mirror image is true. At the same time our cognitive brain realizes that a statement and its negation cannot both be true and wants to reject the oxymoron out of hand, but we do not. The implications of this ongoing conflict between the intuitive and cognitive brains in scientific research help focus these remarks and eventually lead to the understanding of how science resolves paradox, or at least paradox resulting from data and its interpretation.

Scientists measure things. They examine the data from experiments and search for patterns. These motifs are identified as information about the phenomenon being measured. When intuitive understanding of these patterns reach a given level, cognitive models are constructed that can reproduce the individual motifs observed in the data. At this cognitive level the various models of phenomena thought to be connected to one another define what is loosely called a discipline. The models that make up a discipline are then joined into a megamodel known as a theory. It is from such theory that knowledge flows and refinement of the underlying theory provides new knowledge.

In a nascent discipline such theory is often not far removed from the poet's writings. Consider the captivating literary style of Sigmund Freud, who introduced psychoanalysis to the world, and opened the unconscious mind to the scrutiny of scientific study. Unfortunately, because of the elegantly compelling nature of his scientific discourse, he simultaneously erected the barrier to be overcome in advancing the new science he had fathered. It was not until quantification and reproducibility was accepted by this community, through experimental psychology, neuroscience, etc. that the study of the brain took its rightful place among the other scientific disciplines.

More mature disciplines are circumscribed by theory that is well grounded in experiment, having been developed to explain this or that data set. This is where the notion of reductionism enters the picture. Every newly observed behavior within a discipline is only considered to be understood when the source of the behavior can be traced back to a more 'fundamental', previously understood, behavior. For example, the background noise heard when entering a party typically disappears once you have settled in and begin chatting with friends; the strong aroma of cheeses can be overpowering when opening the door of a deli and the smell of fresh bread in a bakery, all vanish even before you have had time to place your order. These are examples of the phenomenon of habituation in which sensory information that does not have survival value, once evaluated and determined to be benign, is no longer transmitted to the brain for executive action.[ii]

We formally implement reductionist thinking, such as in identifying habituation, when we retrace the transmission of information in data from the macroscopic back to the mesoscopic, and from there to the microscopic and thereby establish causal links from what is observed to what we know to be true about the smallest component of the system. Of course, in a generic sense we use the nomenclature microvariable to denote the most fundamental variable in the discipline of interest. Reductionist reasoning assumes that the macrobehavior is a direct consequence of the microdynamics of the system. The deterministic dynamical laws of physics, describing the orbiting planets, are the paradigm for this type of reasoning.

However, it is known that "more is different" [iii], which is to say, as the size of a naturally occurring network grows, so does its complexity and its fundamental character changes. Macroscopic properties emerge that cannot be traced back to the microdynamics, or at least could not have been traced back prior to their emergence. An emergent macroproperty cannot be described in terms of the micromodels that determine the microdynamics, but requires an entirely new view of how that part of the world works, a view that runs counter to reductionist thinking.

The limitations of reductionist thinking in medicine is a consequence of the undeniable complexity of medicine when the individual is considered as a whole [iv], rather than as an aggregation of healthy or diseased parts (organs, tissues, cells, or molecules). The biosocial understanding of disease advocated by these authors relies on the infrastructure provided by network science in the formulation of network medicine [v]. A new measure that has been introduced that is based on the complexity of living systems are 'tipping points' in which complex systems can unexpectedly switch from one critical state to another [vi]. The theory of critical states suggests that the relaxation rate of a perturbation approaches zero as a tipping point is approached, this is the phenomenon of 'critical slowing down' and is associated with the divergence of the observed relaxation time. The critical slowing down of mood dynamics has been used to predict future transitions to a state of major depression. As van de Leemput et al. [vii] observe, the mood system may have crucial points wherein positive feedbacks among a network of symptoms can propagate a person into major depression.

It is the loss of reductionism due to the complexity of medicine that most interests us here, since this is what engenders empirical paradox. The nomenclature empirical paradox (EP) is used to distinguish the kind of contradiction (paradox) that is entailed by complexity in the phenomenon being observed [viii]. Thus, EP is different from the more familiar form of say, a logical paradox, such as the sentence: "I always lie." In logic this is known as an antinomy and may require a revision in some "trusted patterns of reasoning" for its resolution [ix]. On the other hand, an EP arises in our understanding of real world data and that makes all the difference.

2. Empirical Paradox

In broad outline every discipline begins with elementary experiments, whose results are explained by simple models from which that discipline's basic concepts are extracted. As the scientific discipline matures the experiments become more sophisticated and these basic models are interwoven into ever more elaborate theories. Finally, a point is reached where experiments probe the true complexity of a discipline's underlying character and in order to explain the data there arises logical contradictions between two or more of the basic models. This is where the notion of EP enters the discussion, because nature presents us with something that logic tells us cannot exist, but there it is. Therefore the scientific discipline must reinvent itself, in whole or in part, to explain the contradictions implied by the new data and it does so by changing how we think about the phenomenon, using unexpected extensions of theory, if not the complete rejection of existing theory, in order to resolve the EP [viii].

The overhauling of theory to resolve contradiction occurs far more often in science than one might think. For example, contradiction resolution occupied most of the European scientific talent in physics during the second decade of the twentieth century, who pooled their collective intellect to answer the question: "Does light consist of waves, or does it consist of particles?" The answer should have been simple to obtain. Since physics is ostensibly an experimental science, the procedure to obtain the answer should have been to examine the data and that should tell us if light is localized in space like a particle, or is spatially distributed like a wave. The problem was that the data gave unambiguous patterns, some of which supported one interpretation and some supported the other, depending on the measurement made. Consequently, the option of selecting one interpretation over the other was ruled out, since it would be necessary to discard half the data in making such a selection and that would be bad science.

With *either/or* taken off the table, there only remained one option that was consistent with data-based science, the *both/and* choice. Consequently, the final resolution of the nature of the light paradox was accepting the notion of wave-particle duality, which abandons the mutually exclusive concepts of particles and waves and accepts the empirical reality that light is both. This hypothesis required accepting the quantum as a physical parcel of light and exploring the implications of that hypothesis for other physical phenomena. Thus, quantum mechanics was born, and with it a complete change in the scientific view of the physical universe.

As interesting as this is, this historic side trip into physics is just one example of the many conflicts that arise in complex phenomena; conflicts that force the generation of not just new knowledge, but new kinds of knowledge. The new kind of knowledge invalidates how we had previously understood a phenomenon and disrupts the existing order. In science the resolution of such empirical paradox appear as signposts marking the fact that things at this point changed and are forever different moving forward.

Medicine is filled with such EPs. A particularly outstanding one is the notion that in order to protect a person from a particular life threatening contagious disease one ought to expose that person to the disease in as direct a way as possible. To the non-medical eye this certainly has the appearance of an empirical paradox, as I am sure it was to the colleagues of Jenner in the final quarter of the eighteenth century, when he did experiments on human subjects to 'prove' that immunity to smallpox could be induced within a patient by inoculation with cowpox. This EP is over 250 years old and its resolution did not require a knowledge of chemistry, biology and physiology, but to understand the resolution certainly did.

However, this is not the place to regurgitate what we understand about why and how vaccines work. What is important to note for the argument presented here is that the theory developed to understand this EP required the introduction of multiple disciplines from outside of medicine and led to new kinds of knowledge, such as the notion that microorganisms cause disease, which was finally proven by Pasteur in the latter half of the nineteenth century. The need is the same as it is today, that being to understand the complexity of physiological systems, their interactions, and the role that complexity plays in an organism being able to successfully carry out its function.

Let us make the point as clearly as possible. As systems become increasingly complex, as measured by more refined experiments, through increasing spatial and temporal resolution in physical experiments, or the increase in population size of urban areas, or the weight of animals in ecosystems, in each case the once adequate micromodels are no longer sufficient to explain the observed macrobehavior of the system. Measures of complexity increase with increasing system size, as do the number of contradictions among the micromodels. This explains, in part, the empathetic response of readers to Dickens' extensive use of oxymorons to convey the social atmosphere between the two centers of Europe, London and Paris, in the late eighteenth century.

2.1 Feedback

Once an EP has been resolved and integrated into the culture of a scientific community it is often difficult to understand what the difficulty was prior to its resolution. Consider homeostasis, thought by many to be fundamental to our understanding of the macrobehavior of organisms and indispensable for establishing the proper protocol for healing [x]:

> Claude Bernard pointed out that the blood and lymph that bathe the cells of organisms constitute the milieu interne, or internal environment. This internal environment, a product of the organism and controlled by it, was termed the fluid-matrix by Walter Cannon, who expressed the belief that the organism's freedom from disturbance "in spite of the extensive changes in the outer world, has been brought about by mechanisms, which maintain uniformity of the fluid-matrix." This concept of the steady states maintained in the internal environment, or fluid matrix, and of the importance of the constancy of this matrix for continuous efficient action of the organism, ultimately became known as Cannon's doctrine of homeostasis. [x]

It appears that homeostasis is the evolutionary strategy nature has selected which enables the human body to maintain an internal balance, although it is not always evident how a particular suppressing response is related to a specific antagonism. Evolution has, over unchartered history, reduced homeostatic networks to the bare minimum, so that in the spirit of parsimony, every internal mechanism of a physiological network either maintains the structural or functional integrity of the organism. Nature's choices have to do with the fact that no physiologic network is isolated, but is made up of a mind-numbing number of subnetworks, the cells (microvariables). The task of a cell is simple and repetitive, but that of an organ (macrovariables) is not. Therefore a complex network like the cardiovascular is made up of a variety of cell types, each type performing a given different function. If responses to challenges from the external environment were at the cellular level, physiology would be much more complicated than it is already, if it could exist at all.

West [xi] argued that if the immediate environment of the cells is kept within certain narrowly defined limits, then the cells can continue to perform their specific tasks and no others, even while organs respond to sometimes extravagant external disturbances. As long as the internal environment stays within a certain operational range the cells continue to function without change. Thus, homeostasis is the presumed strategy that nature has devised to keep the internal state of the body under control and to maintain steady levels of temperature and other vital conditions such as the water, salt, sugar, protein, fat, calcium and oxygen contents of the blood [xii].

A century before homeostasis was identified in medicine the idea of a feedback control mechanisms was brought to light with the centrifugal fly-ball governor (1788) constructed by J. Watt for regulating the speed of the rotary steam engine. This artificial control mechanism heralded the onset of the Industrial Revolution. The first mathematical description and consequent understanding of Watt's governor was constructed by the English physicist J. C. Maxwell in 1868, about the same time that Bernard was reasoning about the fluid-matrix. Maxwell linearized the differential equations describing the governor's dynamics, whose solutions are stable when the eigenvalues have negative real parts (stabilizing feedback). In this way the language for the control of dynamical networks was introduced.

The homeostatic control of physiologic networks classifies the dynamics as negative feedback, because such homeostatic networks respond in ways to dampen environmental disturbances including fluctuations. However the control of certain networks has the opposite behavior, that is, they have a positive feedback, because the networks respond in ways to amplify perturbations. Of course, such responses lead to unstable behavior in general, but such instability is sometimes useful, as in child birth [xiii]. Consequently feedback can either amplify or suppress disturbances depending on the network's dynamics.

All this and more is entailed by the deceptively simple definition of homeostasis. The mathematics on which homeostasis rests was brought to maturity in *Cybernetics* [xiv], a discipline synthesizing much of the unclassified war research into the communications between humans and machines, by the mathematician Norbert Wiener. The mathematics of negative feedback is a balance between a number of forces and factors, that has evolved from the cybernetic idea of requisite variability, in which a control signal must match the variability of the organism being controlled [xv], into the more modern complexity management effect (CME) [xvi], as explained by Mahmoodi et al. [xvii].

One of the things that becomes clear by incorporating other disciplines into medical science is that the engineering notion of separating time series into signal plus noise is untenable, in part, because the high frequency fluctuations usually identified as noise, often contain important information about physiological processes. Traditional statistical processing techniques proved inadequate for tracking behavior in which the time scales are interdependent, what is now know as fractal scaling. West et al. [xvi], among many others, noted that the signature of complexity is often the power spectrum $S_p(f)$ taking on an inverse power-law (IPL) shape: $S_p(f) \propto 1/f^{\alpha}$,with the IPL index α in the interval $0.5 \le \alpha \le 1.5$. In fact, this 1/f- variability appears in a vast array of phenomena including the human brain [xviii], body movements [xix], music [xx,xxi,xxii], physiology [xiv], and genomics [xxiii], to name a few applications.

West et al. [xvi] used the IPL index as a measure of a network's complexity and reviewed the literature arguing that two interacting complex networks exchange information most efficiently when the IPL indices of the two networks match. One example of this variable coupling of complex networks is given by meditation, where from a physiological perspective meditation constitutes a coupling of the functionality of the heart with that of the brain. Tuladhar et al. [xxiv] provide a measure of reduction in the level of stress provided by meditation, quantified through the statistical analysis of heart rate variability (HRV) time series before and during meditation.

The term CME has been widely used recently to include such information exchange activities as side-by-side walking [xxv], ergometer rowing [xxvi], syncopated finger tapping [xxvii], dyadic conversation [xxviii], and interpersonal coordination [xxix,xxx].

3. Criticality and Complexity

One of the more elegant exemplars of emergent properties of complex systems and certainly one of the most familiar is the change of state of water. We see it in the radiating lines of frost on the window when the outside temperature dips below freezing, we feel it in the cooling effect of sweat evaporating from our skin after exercise, and in the condensation of the water vapor visible on the bathroom mirror when we step out of the morning shower. Criticality is one of the physical mechanisms that the body uses in the homeostatic regulation of its temperature, along with blood flow near the surface of the skin, among others. The physical mechanisms controlling the transformation from one phase of water to another was not understood until the second half of the twentieth century. It was, of course, clear that the phase transitions are dependent on the temperature of the surroundings and on the transfer of heat, but the secret of how differing macroproperties of the gas, fluid and solid phases emerged from the microdynamics required a new way of understanding the transition into and out of criticality.

Subsequently, phase transitions were recognized to give rise to a kind of universal behavior that is independent of the microdynamics. For example, when a liquid is boiled it becomes a gas and the corresponding volume increases discontinuously as a manifestation of critical behavior. This universal behavior is manifest in the scaling of certain system parameters called critical exponents, of which there is now a vast literature. One critical exponent of water is the correlation length, which diverges as the temperature approaches its critical value from above. It is the divergence of the macroscopic correlation length that unambiguously describes the phase transition.

These changes in macroscopic behavior during a phase transition eventually found their way into the social, biological and medical sciences, initiating new ways of thinking about the behavior of collectives, whether they were collections of neurons in the brain, cells in a membrane, birds in a flock, humans in a demonstration, or warriors on a battlefield. Scientists began to ask questions such as: How do vast forms of fireflies synchronize their blinking behavior? [xxxi] Why do some peaceful demonstrations devolve into riots and others do not? How do the large number of pacemaker cells, each of which is a relatively unreliable time-piece, synchronize their firing to generate normal sinus rhythm? Do the properties of collectives depend on the microdynamics outside the physical domain, or do they only depend on the complexity of the system and have emergent macroproperties that do not depend on the discipline? In short do physiologic systems manifest universal behavior and if it does what are the implications for medicine?

3.1 Multiple forms of criticality

Is the critical behavior in complex systems discussed above unique? The answer is a resounding no. The first group, call it Type I, models phenomena that achieve criticality through the external tuning of a control parameter, such as the temperature. This critical behavior was first successfully described by renormalization group theory, see, e.g., the work of Wilson [xxxii], which established that the properties of a system near a phase transitions are universal, as expressed through scaling relations, that is, they have little, if anything, to do with the details of a system's microdynamics, only with its level of complexity. These scaling properties are observed in the control of the macrodynamics of complex networks [xxxiii].

The second group, call it Type II, models phenomena in which criticality emerges through internal dynamics, along with scaling behavior, with no externally controlled parameter. Type II criticality spontaneously drives the system to a critical state by its own internal dynamics and has acquired the name self-organized criticality (SOC) and is used to explain the observed distribution in the magnitudes of earthquakes, solar flares, starquakes, species extinction, stock market disruptions, and traffic jams, to name a few physical applications [xxxiv]. Here again the universality of criticality makes the macroproperties of the system independent of the detailed microdynamics. Bak [xxxv] observed in his book, tracing the history of the 'science' of SOC, that the complexity of a system is a consequence of criticality.

The biological complexity of the brain has been argued to be a consequence of the same mechanism underlying physical complexity and that is criticality [xxxvi]. The experimental evidence for this is the existence of second-order phase transitions as indicated by the divergence of correlation lengths in fMRI data [xxxvii]; another is brain activity consisting of neuronal avalanches in neocortical circuits characterized by scale-free inverse power law distributions [xxxviii,xxxix]. In addition to the brain, other physiologic systems that provide direct evidence of criticality through self-regulation include spiral waves in astrocyte syncytia [xl], global gene expression [xli], and intracellular calcium signaling in cardiac myocytes [xlii], to name a few.

There is in addition a second kind of self-organizing criticality that has not yet seen its second birthday and which we refer to as Type III. Instead of focusing on the magnitude of the event being observed in Type II criticality, Type III records the time interval since a self-organized event of a given kind last occurred and determines the distribution of these time intervals. Consequently, Type III refers to self-organized temporal criticality (SOTC) and has been used to explain the resolution of EP in complex systems, such as the altruism paradox in macroevolution [viii,,xliii].

The time series for the inter-beat intervals of the heart, inter-breath intervals and inter-stride intervals have all been shown to be fractal and/or multifractal statistical phenomena having IPL distributions. Consequently, the fractal dimension, which is related to the IPL index, turns out to be a significantly better indicator of the quality of an organism's functions in health and disease than the traditional average measures, such as average heart rate, average breathing rate, and average stride interval.

Control of physiologic complexity is one of the goals of medicine, in particular, understanding and controlling physiological networks in order to ensure their proper operation. West [xii] emphasized the difference between homeostatic and allometric control mechanisms that arise in Type III networks. Homeostatic controls have a negative feedback character, which is both local and rapid. Allometric control, on the other hand, is a relatively new concept that takes into account long-time memory, correlations that are IPL in time, as well as long-range interactions in complex phenomena as manifest by IPL distributions in the network variable. He hypothesized that allometric control maintains the fractal character of erratic physiologic time series to enhance the robustness of physiological networks. Moreover, allometric control can often be described using the fractional calculus to capture the dynamics of complex physiologic networks.

4. Discussion and conclusions

The preliminary indications from theory are that EP invariably results from inconsistencies in the models of phenomena, as well as, behavior in complex systems. These contradictions between micromodel predictions of macroproperties and those properties observed in data necessitates the formulation of new theory in order to resolve the empirical paradox. The new theory generates a new kind of knowledge that emerges from the internal dynamic synthesis of both poles of the EP and in a medical context is a Type II or Type III model.

Complexity is a function of system size, both in the natural world and in the world of scientific modeling. It is in this latter world where knowledge is initiated and understanding begins. However, the formal cognitive tools available for generating new knowledge are the remnants of a simpler time. The complexity of modern society requires new ways of thinking, ways that are often counter-intuitive, requiring us to accept things which we 'know' are fundamentally incompatible. This understanding requires complexity thinking that enable the practitioner to resolve EPs and in that way generate new kinds of knowledge.

Let us close with an example of a presently unresolved EP, drawn from health care and the introduction of technology [xliv]. The purpose of technology is to make things easier and support the practitioner becoming a more autonomous individual, one that is less dependent on others. The result has been that the individual, whether physician or administrator, has become dependent on the technology, making it difficult, if not impossible in some cases, to do their work without it. This is almost the textbook definition of heteronomy the mirror image of autonomy and thus forming an EP.

The problem is that the health care system is still struggling with how to resolve this EP, but we know that it will not be an *either/or* resolution. We know this because humans are unwilling to give up their individual freedom in making medical decisions and they are equally unwilling to abandon their technology once they have experienced its utility. The SOTC theory [viii] suggests a *both/and* resolution to the autonomy/heteronomy-EP in which a dynamic balance is reached in which the information exchange in the human/machine interaction is maximally efficient. But the details, wherein the devil resides, need to be worked out.

References

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[i] Dickens C., *A Tale of Two Cities*, Centennial Edition, Heron Books; the final chapter was published in Dickens' circular, All the Year Round (1859).

[ii] West BJ and Grigolini P, Habituation and 1/f-noise, *Physic A*. 2010; 389: 5706-15.

[iii] Anderson PW, More is different, *Science*. 1972; 177: 393-6.

[iv] Greene JA and Loscalzo J, Putting the Patient Back Together - Social Medicine, Network Medicine, and Limits of Reductionism, *N. Engl. J Med*. 2017; 377: 2493-2499.

[v] Loscalzo J, Barabasi A-L, and Silverman EK, Complex systems in human disease and therapeutics, pp.1-16, in *Network Medicine* 2017,Cambridge, MA, Harvard University Press.

[vi] Veraart A, Faassen EJ, Dakos V, van Nes EH, Lürling M and Scheffer M, Recovery rates reflect distance to a tipping point in a living system, *Nature Lett.* 2012; 481: 357-359.

[vii] van de Leemput I, Wichers M, Angélique S, et al., Critical slowing down as early warning of the onset and termination of depression, *PNAS.* 2014; 111: 87-92.

[viii] West B.J., Mahmoodi K and Grigolini P, *Empirical Paradox, Complexity Thinking and Generating New Kinds of Knowledge.* 2019; Cambridge Scholars, Cambridge, UK.

[ix] Quine W.V., Paradox, in *The Ways of Paradox and other essays*. 1966; Harvard University Press, Cambridge, MA.

[x] Patton H.D., Chapter 10, in *Physiology and Biophysics*. Ed. T.C. Ruch and H.D. Patton, W.B. Saunders Co., Philadelphia and London.

[xi] West B.J., Fractal Physiology and the Fractional Calculus: A Perspective, *Front. Physiol*. 2010; 1(12): 1-18.

[xii] Rodolfo K., What is Homeostasis?, *Scientific American.* 2016; 282:

[xiii] West, B.J., *Where Medicine Went Wrong*. 2006; World Scientific, New Jersey.

[xiv] Wiener N., *Cybernetics: Or Control and Communication in the Animal and the Machine*. 1948; MIT Press, Cambridge, MA. ISBN 978-0-262-73009-9.

[xv] Ashby WR, *An Introduction to Cybernetics*. 1957; Chapman & Hall LTD.

[xvi] West BJ, Geneston EL and Grigolini P, Maximizing information exchange between complex networks, *Phys. Rep*. 2008; 468: 1-99.

[xvii] Mahmoodi K, West BJ and Grigolini P, Complexity Matching and Requisite Variety, under review

[xviii] Kello CT, Beltz BC, Holden JG and Van Orden GC, The emergent coordination of cognitive function, *J. of Exp. Psych*. 2007; 136: 551-62.

[xix] Deligniéres D, Almurad ZMH, Roume C and Marmelat V, Multifractal signatures of complexity matching, *Exp. Brain Res*. 2016; 234- 2773-81.

[xx] Pease A, Mahmoodi K and West BJ, Complexity measures of music, *Chaos, Solitons and Fractals*. 2018; 108: 82-90.

[xxi] Su Z-Y and Wu T, Music walk, fractal geometry in music, *Physica A*. 2007;380: 418-25.

[xxii] Voss RF and Clarke J, 1/f noise in music and speech, *Nature (London)*. 1975; 258: 317-19.

[xxiii] Li W. and Holste D, Universal 1/f noise, crossovers of scaling exponents, and chromosome-specific patterns of guanine-cytosine content in DNA sequences of the human genome, *Phys. Rev. E*. 2005; 71: 041910-15.

[xxiv] Tuladhar R, Bohara G, Grigolini P and West BJ, Meditation-Induced Coherence and Critical Events, *Front. Physiol*. 2018; 9: 626 -35. *doi: 10.3389/fphys.2018.00626*

[xxv] Almurad ZMH, Roume C and Deligniéres D, Complexity matching in side-by-side walking, *Human Movement Sc*. 2017; 54: .

[xxvi] Den Hartigh RJR, MarmelatV and Cox RFA, Multiscale coordination between athletes: Complexity matching in ergometer rowing, *Human Movement Sc*. 2018; 57: 434-43.

[xxvii] Coey CA, Washburn A, Hassebrock J and Richardson MJ, Complexity matching effects in bimanual and interpersonal syncopated finger tapping, *Neuroscience Letters*. 2016; 616: 204-11.

[xxviii] Abney DH, Paxton A, Dale R and Kello CT, Complexity matching in dyadic conversation, *J. Exp. Psych.: Gen*. 2014; 143: 2304-12.

[xxix] Fine JM, Likens AD, Amazeen EL and Amazeen PG, Emergent Complexity Matching in Interpersonal Coordination: Local Dynamics and Global Variability, *J. Exp. Psych.: Human Perc. and Perf*. 2015; 41: 723-42.

[xxx] Marmelat V and Deligniéres D, Strong anticipation: complexity matching in interpersonal coordination, *Exp. Brain. Res*. 2012; 222: 137-145.

[xxxi] Strogatz S, *Sync:The emerging science of spontaneous order*. 2003; Hyperion, NY.

[xxxii] Wilson KG, The renormalization group: critical phenomena and the Kondo problem, *Rev. Mod. Phys*. 1975; 47: 773-95.

[xxxiii] Turalska M, Lukovic M, West BJ and Grigolini P, Complexity and synchronization, *Phys. Rev. E*. 2009; 80: 021110-1.

[xxxiv] Watkins NW, Pruessner G, Chapman SC, Crosby NB and Jensen HJ, 25 years of self-organized criticality: concepts and controversies, *Space Sci. Rev*. 2015; 198: 3-44.

[xxxv] Bak P, *How nature works, the science of self-organized criticality*. 1996; Springer-Verlag, NY.

[xxxvi] Tagliazucchi E and Chialvo DR, Brain complexity born out of criticality, in *Physics, Computation, and the Mind - Advances and Challenges at Interfaces*. 2012; Eds. J. Marro, P. L. Garrido & J. J. Torres, American Institute of Physics, NY.

[xxxvii] Fraiman D and Chialvo DR, What kind of noise is brain noise: anomalous scaling behavior of the resting brain activity fluctuations, *Front. Physiol*. 2012; 3: 307-16.

[xxxviii] Beggs JM and Plenz D, Neuronal avalanches in neocortical circuits, *J. Neuroscience*. 2003; 23: 11167-77.

[xxxix] Lovecchio E, Allegrini P, Geneston E, West BJ and Grigolini P, From self-organized to extended criticality, *Front. Physiol*. 2012; 3: 1-13.

[xl] Jung P, Cornell-Bell A, Madden S and Moss F, Noise-Induced spiral waves in Astrocyte Syncytia show evidence of self-organized criticality, *Am. Physiol. Soc*. 1998; : 1098-105.

[xli] Tsuchiya M, Giuliani A, Hashimoto M, Erenpreisa J and Yoshikawa K, Self-organizing global gene expression regulated through criticality: mechanism of the cell-fate change, *PLOS ONE*. 2016*;* :

[xlii] Nivala M, Ko CY, Nivala M, Weiss JN and Qu Z, Criticality in intracellular calcium signaling in cardiac myocytes, *Biophys. J*. 2012; 102: 2433-42.

[xliii] Mahmoodi K, West BJ and Grigolini P, Self-organizing complex networks: individual versus global rules, *Frontiers in Physiology*. 2017; 8: 478-89.

[xliv] Hofmann B, The paradox of health care, *Health Care Analysis*. 2001; 9: 369-386.