Colloquium: Criticality and dynamical scaling in living systems

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A celebrated and controversial hypothesis suggests that some biological systems—parts, aspects, or groups of them—may extract important functional benefits from operating at the edge of instability, halfway between order and disorder, i.e., in the vicinity of the critical point of a phase transition. Criticality has been argued to provide biological systems with an optimal balance between robustness against perturbations and flexibility to adapt to changing conditions as well as to confer on them optimal computational capabilities, large dynamical repertoires, unparalleled sensitivity to stimuli, etc. Criticality, with its concomitant scale invariance, can be conjectured to emerge in living systems as the result of adaptive and evolutionary processes that, for reasons to be fully elucidated, select for it as a template upon which further layers of complexity can rest. This hypothesis is suggestive as it proposes that criticality could constitute a general and common organizing strategy in biology stemming from the physics of phase transitions. However, despite its implications, this is still in its infancy state as a well-founded theory and, as such, it has elicited some skepticism. From the experimental side, the advent of high-throughput technologies has created new prospects in the exploration of biological systems, and empirical evidence in favor of criticality has proliferated, with examples ranging from endogenous brain activity and gene-expression patterns to flocks of birds and insect-colony foraging, to name but a few. Some pieces of evidence are quite remarkable, while in some other cases empirical data are limited, incomplete, or not fully convincing. More stringent experimental setups and theoretical analyses are certainly needed to fully clarify the picture. In any case, the time seems ripe for bridging the gap between this theoretical conjecture and its empirical validation. Given the profound implications of shedding light on this issue, it is both pertinent and timely to review the state of the art and to discuss future strategies and perspectives.

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I. INTRODUCTION: STATISTICAL PHYSICS OF BIOLOGICAL SYSTEMS

One of the greatest challenges of science is to shed light on the essence of the phenomenon that we call "life," with all its astonishing diversity and complexity. Cells, the basic building

blocks of life, are intricate dynamical systems consisting of thousands of types of interacting molecules, being created, used, and destroyed every minute; multicellular organisms rely on the perfectly orchestrated motion of up to trillions of interacting cells, and communities assemble dozens of individuals, interacting in countless ways, forming entangled ecosystems, and giving rise to a hierarchy of *complexity*.

The standard viewpoint in biology, stemming from the reductionist tradition, is that each molecular component (protein, nucleic acid, metabolite, etc.) is specific and requires individualized scrutiny. This one-at-a-time approach has successfully identified and quantified most of the components and many of the basic interactions of life as we know it as stressed by the rapid advance of the "omics" sciences (genomics, proteomics, metabolomics, etc.). Still, unfortunately, it offers no convincing explanation of how systemic properties emerge (Sauer, Heinemann, and Zamboni, 2007). Questions such as "how are those myriads of elements and interactions coordinated together in complex living creatures?" or "how does coherent behavior emerge out of such a soup of highly heterogeneous components?" (Schrödinger, 1967) remain largely unanswered.

A complementary strategy consists of looking at complex biological problems from a global perspective, shifting the focus from specific details of the molecular machinery to integral aspects (Hartwell *et al.*, 1999; Alon, 2006; Kaneko, 2006; Sauer, Heinemann, and Zamboni, 2007; Goldenfeld and Woese, 2011; Bialek, 2012). System approaches to biology rely on the evidence that some of the most fascinating phenomena of living systems, such as memory and the ability to solve problems, are collective ones, stemming from the interactions of many basic units and might not be reducible to the understanding of elementary components on an individual basis (Bialek, 2018). Theoreticians have long struggled to elucidate whether simple and general principles, such as those in physics, could be of any help in tackling biological complexity. More specifically, they have long been seduced by the idea of adapting concepts and methods from statistical mechanics to shed light onto the large-scale organization of biological systems[1] (Schrödinger, 1967; Anderson *et al.*, 1972; Hopfield, 1982; Kelso, 1984; Haken, Kelso, and Bunz, 1985; Amit, 1992; Parisi, 1993; Alon, 2006; Bialek, 2012; Sneppen, 2014).

One of the most striking consequences of interactions among elementary constituents of matter (atoms, molecules, electrons, etc.) is the emergence of diverse *phases* whose behavior bears little resemblance to that of their basic components or small groups of them (Anderson *et al.*, 1972; Stanley, 1987; Chaikin and Lubensky, 2000). Systems consisting of very many (microscopic) components may exhibit rather diverse types of (macroscopic) collective behavior, i.e., phases, with different levels of internal order. Moreover, slight changes in external conditions (e.g., temperature, pression, etc.) or in the strength of interactions may induce dramatic structural rearrangements, i.e., *phase transitions*.

It is thus tempting to hypothesize that biological states might be manifestations of similar collective phases and that shifts between them could correspond to phase transitions (Anderson *et al.*, 1972; Hopfield, 1994). As a matter of fact, phase transitions are a common theme in biology (Pollack and Chin, 2008; Solé, 2011), as illustrated by the following nonexhaustive list of examples: (i) synchronization phase transitions in collective biological oscillators such as circadian clocks (Garcia-Ojalvo, Elowitz, and Strogatz, 2004), (ii) percolation transitions of fibers in connective tissues such as collagen (Forgacs *et al.*, 1991; Newman *et al.*, 2004; Alvarado *et al.*, 2013), (iii) melting phase transition in DNA strands (Poland and Scheraga, 1970; Li and Retzloff, 2006), and (iv) transitions between different dynamical regimes (oscillations, bursting, etc.) in neuronal networks (Kelso, 1984; Freeman and Holmes, 2005; Rabinovich *et al.*, 2006; Werner, 2007; Freeman, 2013; Haken, 2013).

Life, guided by evolution, has found its way to exploit very diverse types of order: crystalline structures (seashells, skeletons, etc.), liquid states (blood, lymph, sap, etc.), gels (vitreous humor, cell cytoplasm), etc. However, some aspects of biological systems (e.g., of neural networks or flocks of birds) exhibit intermediate levels of organization, halfway between order and disorder, and less regular than perfect crystals but more structured than random gases. Remarkably, it was conjectured that, under some circumstances, living systems, i.e., parts, aspects, or groups of them, could draw important functional advantages from operating right at the borderline between ordered and disordered phases, i.e., at the edge of a continuous phase transition or critical point[2] (Kauffman, 1993; Bak, 1996; Beggs, 2008; Chialvo, Balenzuela, and Fraiman, 2008; Chialvo, 2010; Plenz, 2013; Plenz and Niebur, 2014). For instance, rather generically, living systems need to achieve a trade-off between robustness (resilience of the system state to external perturbations, which is a property of ordered phase) and flexibility (responsiveness to environmental stimuli, which is a feature of disordered phases). An optimal balance between these two conflicting tendencies can be accomplished by keeping the system dynamical state at the borderline of an order-disorder phase transition, i.e., at criticality. Signatures of criticality, such as the spontaneous emergence of long-range spatiotemporal correlations and the exquisite sensitivity to stimuli, are also susceptible to be exploited for functional purposes, e.g., to create coordinated global behavior, as we shall discuss in what follows. The idea that, in some special circumstances, evolution might have favored states close to the edge of a phase transition is certainly tantalizing as it suggests that operating near criticality could be an overarching strategy in

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[1]The possibility that biological problems may stretch the frontiers of physics by uncovering phenomena and mechanisms unknown in purely physical systems is also inspiring (Goldenfeld and Woese, 2011; Frauenfelder, 2014).

[2]Phase transitions may occur in either a discontinuous or abrupt fashion (Binney *et al.*, 1993), with associate bistability of the two different phases and an abrupt or discontinuous jump at the transition point, or in a continuous or progressive way with an associated critical point. Our main focus here is on continuous ones, but we also encounter discontinuous transitions, which may also play a relevant role in biology.

biological organization (Kauffman, 1993; Bak, 1996; Beggs, 2008; Chialvo, 2010; Mora and Bialek, 2011; Plenz, 2013; Plenz and Niebur, 2014).

Critical points have long been appreciated to exhibit striking features. Still, given the need of careful fine-tuning for them to be observed, they were long treated as rarities. The development of some of the most remarkable intellectual achievements of the second half of the 20th century, such as the scaling hypothesis and the renormalization group theory (Fisher, 1974; Wilson and Kogut, 1974), changed this view and led to an elegant and precise theory of criticality, with unsuspected implications in many fields, from particle physics to polymer science.[3] The chief conclusion is that many features at critical points are quite robust and largely independent of small-scale details, giving rise to *universality* in the large-scale behavior. This has important consequences for studies in biology, as criticality and its concomitant scale invariance can be understood through simple stylized models, neglecting many irrelevant details of individual components and putting the emphasis on how they interact, paving the road to the understanding of collective aspects of living systems in relatively simple terms.

From the experimental side, the advent of high-throughput techniques and big-data analyses have created new prospects in the exploration of biological systems. This is true, for example, in neuroscience, where it is now possible to record activity from individual spiking neurons to entire brains with previously unthinkable resolution (Sejnowski, Churchland, and Movshon, 2014) and, similarly, in genomics (Lesk, 2017) or in collective motion analyses (Cavagna *et al.*, 2008). As a result, recent years have witnessed an upsurge of empirical works reporting on putative scale invariance and/or criticality in diverse biological systems, supporting these theoretical speculations. In some cases the evidence appears to be robust, while in others it is marginal, incomplete, or, to say the least, doubtful. In any case, the time seems to be ripe for bridging the gap between the theoretical hypothesis and its empirical validation.

The purpose of this Colloquium is to briefly review the main ideas and motivation behind the criticality hypothesis as a possible guiding principle in the collective organization of living systems and to scrutinize and discuss in a critical way the existing empirical evidence and prospects. It also aims at providing a self-consistent view of what is criticality and what is not, as well as an overview of the literature on this active and fascinating research field with countless ramifications.

Excellent articles exist reviewing some of these topics to different extents; the list includes the influential paper by Mora and Bialek (2011) which popularized the subject, and others focused on neural dynamics (Beggs, 2008; Chialvo, Balenzuela, and Fraiman, 2008; Chialvo, 2010; Shew and Plenz, 2013; Hesse and Gross, 2014; Plenz and Niebur, 2014; Massobrio *et al.*, 2015; Cocchi *et al.*, 2017), gene networks (Roli *et al.*, 2015), and collective motion (Vicsek and Zafeiris, 2012). This Colloquium aims at overviewing and complementing them, putting the emphasis on dynamical aspects and discussing together empirical evidence and theoretical approaches.

II. CRITICALITY AND SCALE INVARIANCE

Many discussions about "criticality" are semantic ones. Depending on authors and fields rather diverse contents are assigned to terms such as "critical," "quasicritical," "dynamically critical," "generically critical," or "self-organized critical." Given the broad audience this Colloquium is aimed at, we esteem that a section devoted to a synthetic overview of basic concepts and to fix ideas and notation is necessary.[4]

A. Scale invariance and power laws

In a seminal paper entitled "Problems in Physics with many scales of length" Wilson (1979) emphasized that "one of the more conspicuous properties of nature is the great diversity of size or length scales," and cited oceans as an example where phenomena at vastly disparate wavelengths coexist. Different scales are usually decoupled and the "physics" at each one can be separately studied. However, there are situations, known as scale invariant or scale free, where broadly diverse scales make contributions of equal importance. A remarkable instance of this, but just an example, are the critical points of continuous phase transitions where the microscopic, mesoscopic, and macroscopic scales are all alike.

Power-law (or Pareto) distributions such as $P(x) = Ax^{-\alpha}$, where α is a positive real number and A is a normalization constant, are the statistical trademark of *scale invariance* or *scaling*.[5] Actually, they are the only probability distribution functions for which a change of scale from x to Λx, for some constant Λ, leaves the functional form of $P(x)$ unaltered, i.e., $P(\Lambda x) = A(\Lambda x)^{\alpha} = A\Lambda^{\alpha}x^{\alpha} = \Lambda^{\alpha}P(x)$, in such a way that the ratio $P(\Lambda x)/P(x) = \Lambda^{-\alpha}$ does not depend on the variable x, i.e., it is scale invariant (Newman, 2005; Sornette, 2006). As opposed to exponential distributions, power laws lack a relevant characteristic scale, besides natural cutoffs.

Distributions with power-law tails appear in countless scenarios, including the statistics of earthquakes, solar flares, epidemic outbreaks, etc. (Mandelbrot, 1983; Newman, 2005; Sornette, 2006; West, 2017). They are also a common theme in biology (Goldberger, 1992; Gisiger, 2001; Goldberger *et al.*, 2002; West, 2010; Hu *et al.*, 2012). For example, physiological and clinical time-series data typically have a spectrum that decays as a power of the frequency (Mandelbrot, 2002) and mobility patterns often exhibit scale-free features (Barabasi, 2005; Brockmann, Hufnagel, and Geisel, 2006; Proekt *et al.*, 2012). Moreover, a number of commonly observed statistical patterns of natural-world data,

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[3]See, e.g., De Gennes (1979), Stanley (1987), Binney *et al.* (1993), Sethna (2006), Henkel, Hinrichsen, and Lübeck (2008), Delamotte (2012), and Täuber (2017).

[4]For a more exhaustive introduction to critical phenomena see, e.g., Stanley (1987), Binney *et al.* (1993), Marro and Dickman (1999), Christensen and Moloney (2005), Sethna (2006), and Henkel, Hinrichsen, and Lübeck (2008).

[5]A well-known example is the Guttenberg-Richter equation for the probability distribution of observing an earthquake of dissipated energy E, $P(E) \propto E^{-\alpha}$ (Corral, 2004).

such as Zipf's law,[6,7] (Marsili and Zhang, 1998; Sornette, 2006; Baek, Bernhardsson, and Minnhagen, 2011; Mora and Bialek, 2011; Visser, 2013), Benford's law (Benford, 1938; Pietronero *et al.*, 2001), and Taylor's law (Taylor, 1961; Cohen, Xu, and Schuster, 2012; Giometto *et al.*, 2015), stem from underlying power-law distributions.

Disputes on the validity and possible significance of power laws have a long history in diverse research fields. For some they reveal fundamental mechanisms, while some others perceive them as largely uninformative (Kello *et al.*, 2010; Stumpf and Porter, 2012) or even "more-normal-than-normal" distributions (Willinger *et al.*, 2004). Still, in some cases, there is robust evidence of scale invariance and it certainly provides valuable insight.[8]

The detection and statistical characterization of power-law distributions in real-world data is often hindered by sampling problems since very rare but large events control the statistics. Accordingly, the quality of power-law fits to empirical data was recently scrutinized showing that many claims of scale invariance actually lack statistical significance and presently more stringent statistical tests have become a must (Clauset, Shalizi, and Newman, 2009).

From the mathematical side, diverse explanatory mechanisms for the emergence of scaling in empirical data have come to light (Mitzenmacher, 2004; Newman, 2005; Sornette, 2009; Simkin and Roychowdhury, 2011; Marković and Gros, 2014). For example, random walks give rise to power laws in the distribution of return times and "avalanche" sizes as illustrated in Fig. 1. Other examples are as follows: (i) underlying multiplicative processes (Sornette and Cont, 1997; Sornette, 1998; Richmond and Solomon, 2001; Reed and Hughes, 2002), (ii) preferential attachment processes (Yule, 1925; Simon, 1955; Barabási and Albert, 1999), and (iii) optimization and constrained optimization (Carlson and Doyle, 2000; Seoane and Solé, 2015).

Even if, as the previous enumeration illustrates, empirical power-law distributions can in principle be ascribed to a handful of possible different generative mechanisms, in the

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[6]This states that the frequency with which a given pattern is observed declines as a negative power law of its *rank*, i.e., its position in the list of possible patterns ordered from the most frequent to the rarest one (Zipf, 1949).

[7]An elegant and illuminating approach allowed Mora and Bialek (2011) to map Zipf's law to underlying statistical criticality in a precise way. Within this setting, it was observed, however, that Zipf's law (and its concomitant statistical criticality) may emerge rather generically if there is a fluctuating unobserved (hidden) variable that affects the system such as a common input, even in systems not tuned to criticality (Schwab, Nemenman, and Mehta, 2014; Aitchison, Corradi, and Latham, 2016); see also Tkačik *et al.* (2015) for a discussion of these issues and how they can influence the conclusions about statistical criticality of empirical data.

[8]An important example is allometric scaling laws, which are power-law relationships between different measures of anatomy and physiology (Kleiber, 1932; West, Brown, and Enquist, 1997; Banavar *et al.*, 2010, 2014). These have been shown to stem from the constraint that living systems have an underlying optimal (e.g., nutrient) transportation network (Banavar, Maritan, and Rinaldo, 1999; Simini *et al.*, 2010).

FIG. 1. Random walks, such as the one illustrated in the left panel, lack a characteristic scale. As a consequence, the distribution of return times to the origin T of the one-dimensional (unbiased) random walk obeys $P(T) \sim T^{-\alpha}$ with $\alpha = 3/2$ and the areas and sizes S covered by their excursions before returning to the origin (i.e., "avalanches") obey $P(S) \sim S^{-\tau}$ with $\tau = 4/3$ (right panels) (symbols stand for computational results, while straight lines are theoretical fits) (Redner, 2001; di Santo *et al.*, 2017). Some biological systems exhibit scaling as a consequence of an underlying random-walk process; see, e.g., Gerstein and Mandelbrot (1964) and Berg (1993).

forthcoming sections we discuss the most prominent and general mechanism able to account for scale invariance in both space and time in a rather robust, powerful, and universal way: criticality.

B. Criticality in equilibrium systems and beyond

The concept of criticality was born in the context of systems at thermodynamic equilibrium. A paradigmatic example is ferromagnets. These exhibit a continuous or second-order phase transition at a critical temperature T_c below which the orientational symmetry of spins is spontaneously broken, i.e., a preferred direction emerges, and progressively more ordered and magnetized states emerge as the temperature is lowered. On the other hand, above T_c thermal fluctuations dominate and the system remains disordered. This change in the collective state is usually encoded in an order parameter (e.g., the overall magnetization) which measures the degree of order as the phase transition proceeds.

The described symmetry breaking is a collective phenomenon that requires a system-wide coordination for the global reorganization to emerge. This implies that the correlation length among individual components needs to span the whole system at criticality. Similarly, when the system is becoming incipiently ordered, it is highly fluctuating in the orientation to be chosen. For example, the classical experiment with liquid-gas transitions (e.g., with CO_2) shows that, right at criticality, light of many different wavelengths scatters with internal structures of the mixture (i.e., there are density fluctuations of all possible length scales), causing the normally transparent liquid to appear cloudy in a phenomenon called critical opalescence (Stanley, 1987; Binney *et al.*, 1993).

Importantly, the concepts and methods developed in the context of equilibrium systems were soon extended to time-dependent and nonequilibrium problems (Hohenberg and Halperin, 1977; Marro and Dickman, 1999; Hinrichsen, 2000; Henkel, Hinrichsen, and Lübeck, 2008; Kamenev,

2011; Täuber, 2014, 2017). Throughout this Colloquium, we adopt a view of criticality and phase transitions focused mostly on dynamical and nonequilibrium aspects. This seems to be the most natural choice to analyze living systems, which are dynamical entities kept away from thermal equilibrium by permanently exchanging energy and matter with their surroundings. It is important to underline the fact that there exists an alternative "statistical-criticality" approach to the analysis of biological data. It focuses on the statistics of existing configurations (without regard to the temporal order in which they appear, much as in equilibrium statistical mechanics) rather than on possible underlying dynamical processes, and it is only briefly discussed here where we choose to focus on dynamical aspects.

C. Nonequilibrium phase transitions: An example

In order to present a more formal approach, we describe in detail, as a guiding example, one of the simplest possible dynamical models exhibiting a nonequilibrium phase transition. The contact process is a prototypical toy model used to study the dynamics of propagation of some type of activity (as, e.g., infections in epidemic spreading); see Fig. 2 (Marro and Dickman, 1999; Hinrichsen, 2000; Harris, 2002; Henkel, Hinrichsen, and Lübeck, 2008). At any given time, each of the nodes $i = 1, 2, …, N$ of a given network (which, in particular, can be a lattice, a fully connected network, or one with a more complex architecture describing the pattern of connections among units or nodes) is in a state s_i that can be either occupied or active ($s_i = 1$) or empty or quiescent ($s_i = 0$). Occupied sites are emptied at the rate $\mu = 1$ and new active nodes are created at (empty) randomly selected nearest neighbors of active ones at the rate λ. Considering, for simplicity, a fully connected network with N nodes and performing a large-N expansion of the corresponding master equation (Van Kampen, 1992), one readily obtains the following "mean field" or deterministic equation:

$$\dot{\rho}(t) = \lambda\rho(t)[1 - \rho(t)] - \rho(t) = (\lambda - 1)\rho(t) - \lambda\rho^2(t), \quad (1)$$

where the dot stands for the time derivative of the activity density $\rho = \sum_{i=1}^{N} s_i / N$. This simple one-variable approximation already illustrates some of the essential features of criticality. Equation (1) reveals the presence of a bifurcation at a value $\lambda_c = 1$, separating a subcritical (also called "absorbing" or "quiescent") phase ($\lambda < 1$) in which transient activity decays to the only possible steady state $\rho_{st} = 0$ from a supercritical (or "active") one ($\lambda > 1$) with a sustained activity $\rho_{st} = 1 - 1/\lambda$ (see Fig. 2). Thus, defining $\delta = |\lambda - 1|$ as the distance to criticality, $\rho_{st} \sim \delta$ for small δ. In the quiescent (or absorbing) phase,[9] an initial density decays exponentially, $\rho(t) = \rho(0)\exp(-\delta t)$, implying that there is a characteristic time scale proportional to δ^{-1}. Note that such time diverges at criticality, i.e., it takes a long time for the system to "forget" its initial state, reflecting a generic feature of criticality: the so-called "critical slowing down." Indeed, right at the critical point, the activity decays asymptotically as a power law $\rho(t) \sim t^{-1}$.

[9]A similar argument holds in the active phase.
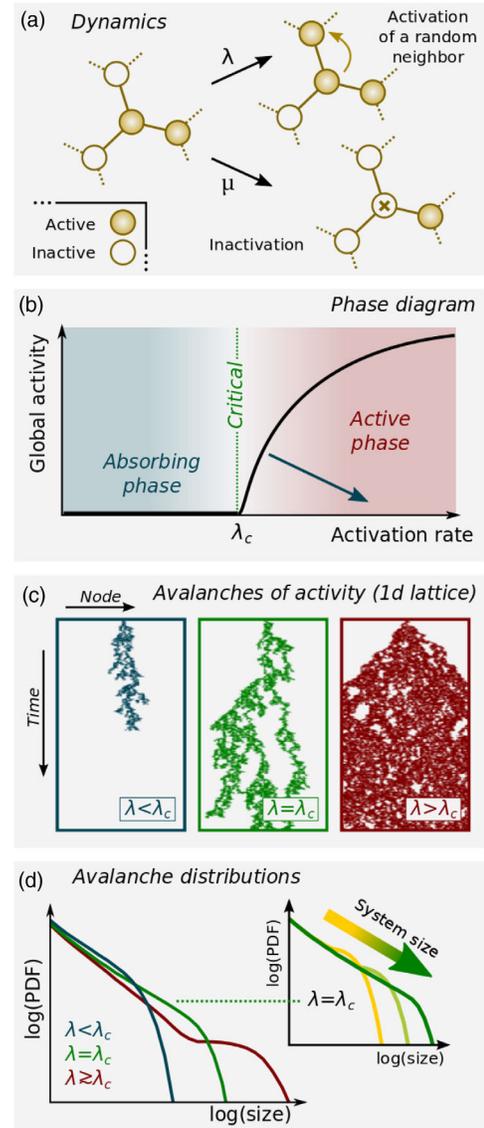
FIG. 2. Sketch of the main aspects of the contact process. (a) Dynamical rules. (b) Phase diagram, including a critical point. (c) Temporal raster plots of activity (avalanches) in the different regimes illustrating the complex patterns emerging at criticality $\lambda = \lambda_c$ (central panel), involving many different scales. (d) Avalanche size distributions in the different phases (main) and, right at the critical point for different system sizes (inset), illustrating finite-size scaling, i.e., the emergence at criticality, of a straight line in a double-logarithmic plot, as corresponds to scale invariance (see also Fig. 3).

Introducing an external field that creates activity at empty sites at rate h, the overall response or "susceptibility," defined as $\Xi = \partial\rho_{st}/\partial h|_{h\to 0}$, is $\Xi \propto \delta^{-1}$ that again diverges right at $\delta = 0$ (i.e., $\lambda = 1$), illustrating the diverging response to infinitesimal perturbations, another important generic feature of criticality.

A useful tool to analyze this type of transition consists of performing "spreading experiments" in which the evolution of a single localized seed of activity in an otherwise absorbing or quiescent state is monitored [see Fig. 2(c)]. In this case, given the small number of active sites, the dynamics is chiefly driven by fluctuations and cannot be analyzed within the deterministic

approximation. Stochastic cascades of spatiotemporal activity or avalanches of variable sizes and durations can be generated from the initial seed before the system returns to the quiescent state (extinction). In this framework the critical point separates a regime of sure extinction (absorbing phase) from one of nonsure extinction (active phase). Right at the critical point, the sizes and durations of avalanches are distributed as power laws with anomalously large (formally infinite) variance [Fig. 2(c)].[10] To understand this mathematically, one needs the next-to-leading correction to Eq. (1) in the large-N expansion to include the effect of "demographic" fluctuations. This leads to an additional term $+\sqrt{\rho}\eta(t)$, where $\eta(t)$ is a Gaussian white noise of variance $\sigma^2 = (\lambda + 1)/N$.[11]

A simple analysis of the resulting stochastic equation[12] shows that right at the critical point the time required to return to the quiescent state, i.e., the avalanche durations T, are distributed as power laws $F(T) \sim T^{-\alpha}$ with $\alpha = 2$; similarly, avalanche sizes s obey $P(S) \sim S^{-\tau}$, with $\tau = 3/2$. These mean-field exponents coincide with those of the Galton-Watson unbiased branching process (Watson and Galton, 1875; Harris, 2002; Liggett, 2004), introduced to describe the statistics of family names and often employed to illustrate the statistics of critical avalanches. Away from criticality, as well as in finite systems, cutoffs appear in the avalanche distributions (see Fig. 2). In particular, as a reflection of the underlying scale invariance at criticality, the finite-size cutoffs obey scaling laws such as

$$P(S, N) \sim S^{-\tau}\mathcal{G}(S/N), \qquad (2)$$

where the power law $S^{-\tau}$ is cut off by an unspecified function $\mathcal{G}$ at an N-dependent scale (Binder, 1981; Stanley, 1987; Binney *et al.*, 1993). This enforces that plotting $P(S, N)S^{\tau}$ as a function of the rescaled variable S/N should give a unique curve into which all individual curves for different sizes N collapse. This *finite-size scaling* method constitutes an important tool for analyzing critical phenomena (both in computer simulations and in experiments) as perfect power laws and divergences can appear only in the infinite-size limit, not reachable in biological problems. Indeed, while in finite systems true criticality does not exist, still these may exhibit a progressive transition between order and disorder. This can be characterized by the existence of a peak in some quantity such as the susceptibility or the correlation length that usually diverges at (true) criticality; this is used as a proxy for approximate criticality in finite systems.[13]

As a result of universality, all models exhibiting a phase transition to an absorbing or quiescent phase (without any additional symmetry or conservation law) share the same set of critical exponents and scaling functions, i.e., the same type of scale-invariant organization, with the contact process (Henkel, Hinrichsen, and Lübeck, 2008).[14]

Even if the simple propagation model discussed is not intended as a faithful description of the actual dynamics of any specific biological system, in some cases, such as neural and gene regulatory networks, it can constitute an adequate effective representation of "damage spreading" experiments, in which two identical replicas of the same system are considered; a localized perturbation in the state of one unit or node is introduced in one of the two, and the difference between both replicas is monitored as a function of time (Derrida and Pomeau, 1986). Depending on the system dynamical state, such perturbations may grow (active phase), shrink (quiescent phase), or fluctuate marginally (critical point), providing a practical tool to gauge the level of internal order.[15] Even if the actual dynamics might be much more complicated, the resulting damage spreading process is susceptible to be described in simple terms if local effective error "propagation" and error "healing" rates can be estimated.

D. Self-organization to criticality

As we have seen criticality requires of parameter fine-tuning to a precise point to be observed. How is it possible that natural systems (such as earthquakes, Barkhaussen noise, etc.) exhibit signatures of criticality, but without any apparent need for parameter tuning to settle them in at the edge of a phase transition? To answer this question P. Bak and collaborators introduced the important concept of self-organized criticality (SOC) through a series of archetypical models (Bak and Tang, 1989; Bak, Chen, and Tang, 1990; Drossel and Schwabl, 1992; Olami, Feder, and Christensen, 1992; Corral *et al.*, 1995; Bak, 1996; Frette *et al.*, 1996; Dhar, 1999), including its most famous representative: the *sandpile* model (Bak, Tang, and Wiesenfeld, 1987).

In the sandpile model a type of stress or energy (sand grains) accumulates at a slow time scale at the sites of a (two-dimensional) lattice, and when the accumulated stress overcomes a local instability threshold, it is instantaneously redistributed among nearest neighbor sites, and possibly released or dissipated at the system boundaries. This can create a cascade or avalanche of further instabilities. Remarkably, the durations and sizes of such avalanches turn out to be distributed as power laws, i.e., the system becomes critical without any apparent need for fine-tuning[16] (Bak, Tang, and Wiesenfeld, 1987; Bak, 1996; Jensen, 1998; Turcotte, 1999; Dickman *et al.*, 2000; Christensen and

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[10]The large variability of possible patterns is a generic key feature of criticality. In particular, in systems at equilibrium, the divergence at criticality of the specific heat reflects the large variability of possible internal states (Binney *et al.*, 1993).

[11]The square-root noise stems from the central limit theorem (Van Kampen, 1992).

[12]See di Santo *et al.* (2017) for a pedagogical derivation of this.

[13]Similarly, systems in the presence of an external driving force are not truly critical; in these cases, the Widom line, signaling the position of maximal susceptibility or correlation, can be taken as a surrogate of criticality (Williams-García *et al.*, 2014).

[14]To study spatial effects one needs to replace $\rho(t)$ in Eq. (1) by a field $\rho(x, t)$ and to introduce a diffusive coupling term (Hinrichsen, 2000; Henkel, Hinrichsen, and Lübeck, 2008; Ódor, 2008).

[15]The precise relationship between the damage spreading threshold and the system's actual critical point is an important and subtle issue (Coniglio *et al.*, 1989; Grassberger, 1995; Hinrichsen and Domany, 1997).

[16]Stochastic variants of the original (deterministic) sandpile model (Manna, 1991; Christensen *et al.*, 1996) show much cleaner scaling behavior than it (Ktitarev *et al.*, 2000; Bagnoli *et al.*, 2003).
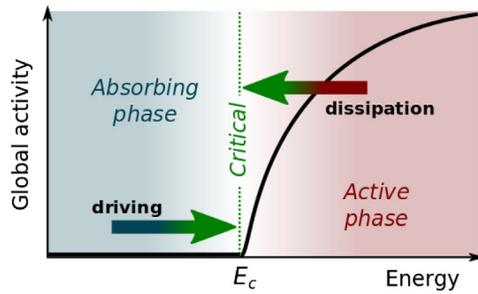
FIG. 3. The self-organization-to-criticality (SOC) mechanism works by establishing a feedback loop between the dynamics of the activity and that of the control parameter (total accumulated energy, stress, or sand grains) at separated time scales. In particular, the control parameter itself becomes a dynamical variable that operates in opposite ways depending on the system's state: *fast dissipation* (negative force) dominates while the control parameter lies within the active phase and by *slow driving* dynamics (positive force) dominates in the absorbing or quiescent phase. This feedback self-organizes the system to the critical point of its second-order phase transition if the separation between slow and fast time scales is infinitely large and the dynamics is conservative (Zapperi, Lauritsen, and Stanley, 1995; Vespignani *et al.*, 1998, 2000; Dickman *et al.*, 2000; Bonachela and Muñoz, 2009). Otherwise, the system is just self-organized to the neighborhood of the critical point with excursions around it, i.e., self-organized quasicriticality (Bonachela and Muñoz, 2009; Dickman *et al.*, 2000).

Moloney, 2005; Pruessner, 2012; Watkins *et al.*, 2015). The mechanism for self-organization to criticality in sandpile models is described in Fig. 3. It can be seen that it is characterized by a dynamical feedback that acts differentially depending on the actual system state. This is just an example of a broader class that has been extensively analyzed in the context of control theory (Sornette, 1994; Moreau and Sontag, 2003; Magnasco, Piro, and Cecchi, 2009; di Santo *et al.*, 2016), which is likely to emerge in biological systems as we shall discuss. Two important variants of this mechanism are as follows:

(a) Self-organized quasicriticality is analogous to SOC but occurs when the dynamics is nonconservative and/or when the separation of time scales is not perfect (relevant for biological problems). This self-organization mechanism drags the system back and forth around the critical point without sitting exactly at it and is able to generate effective scale invariance across quite a few scales (Bonachela and Muñoz, 2009; Kinouchi *et al.*, 2018).

(b) Adaptive criticality is a variant of SOC from a network perspective in which connections among nodes in a network are susceptible to be added, removed, or rewired depending on the system's dynamical state, creating a feedback loop between network architecture and dynamics in a sort of coadaptive process.[17] This mechanism can drive the dynamics

to criticality (Bianconi and Marsili, 2004; Liu and Bassler, 2006; Dorogovtsev, Goltsev, and Mendes, 2008) and in parallel the network architecture develops a highly nonrandom structure, thus capturing the feedback between dynamics and architecture in actual biological networks.

E. Classes of criticality

Not all dynamical phase transitions of relevance in biology occur between quiescent and active phases, nor can they be described by an associated activity-propagation process, such as the contact process. Other important classes of phase transitions discussed in this Colloquium are (i) synchronization transitions, at which coherent behavior of oscillators emerges, as described by the prototypical Kuramoto model (Kuramoto, 1975; Pikovsky, Rosenblum, and Kurths, 2003; Acebrón *et al.*, 2005); (ii) transitions to collective ordered motion, as represented for instance by the Vicsek model (Vicsek *et al.*, 1995; Vicsek and Zafeiris, 2012) and its variants; (iii) percolation transitions (Christensen and Moloney, 2005), and (iv) even thermodynamic transitions such as that of the Ising model (Binney *et al.*, 1993), to name but a few. Each of these classes has its own type of emerging ordering and its own scaling features. However, all of them share the basic features that constitute the fingerprints of criticality, such as diverging correlations and response, large variability, scale invariance, etc.

F. Criticality on complex networks

Thus far we discussed criticality in homogeneous systems. However, in many biological problems the substrates on top of which dynamical processes run are highly heterogeneous (Albert and Barabási, 2002; Newman, 2003, 2010; Caldarelli, 2007). In particular, complex systems, including biological ones, can be described as networks, where nodes represent units (neurons, genes, proteins, etc.) and links stand for allowed pairwise interactions among them. Such complex networks have been found to exhibit one or more of the following important architectural features: (i) large heterogeneity with a few highly connected nodes and many loosely connected ones, actually the distribution of connection can be scale free (Barabási and Albert, 1999); (ii) the small-world property (Watts and Strogatz, 1998); (iii) modular organization[18]; (iv) hierarchical organization, etc. (Corominas-Murtra *et al.*, 2013). These structural features usually entail profound implications on the dynamics of processes running on top of them (Boccaletti *et al.*, 2006; Barrat, Barthelemy, and Vespignani, 2008; Dorogovtsev, Goltsev, and Mendes, 2008; Pastor-Satorras *et al.*, 2015). For instance, synchronization transitions proceed in a stepped way on modular networks (Arenas *et al.*, 2008), and broad critical-like phases can emerge in hierarchical modular networks [as discussed by Muñoz *et al.* (2010) and Moretti and Muñoz (2013), Appendix A].

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[17]Different variants of this idea have been proposed in the literature (Bornholdt and Rohlf, 2000; Dorogovtsev and Mendes, 2002; Solé *et al.*, 2002; Gros, 2008; Gross and Blasius, 2008; Rohlf, 2008; Meisel and Gross, 2009; Perotti *et al.*, 2009; MacArthur, Sánchez-García, and Maayan, 2010; Kuehn, 2012; Droste, Do, and Gross, 2013; Saito and Kikuchi, 2013; Rybarsch and Bornholdt, 2014).

[18]Biology is "modular" in many aspects (Ravasz *et al.*, 2002; Alon, 2006), meaning that some components in biological networks (nodes) are connected among themselves more often or more strongly than they do with others (Alon, 2003).

G. Generic scale invariance

We have discussed the paradigm of a critical point, with its concomitant spatiotemporal scale invariance, separating two alternative phases. However, in some systems with peculiar symmetries, conservation laws, or structural disorder, critical-like features may appear in extended regions in the phase space and not just at a critical point. This is called *generic scale invariance* (Grinstein, 1991) and can account for empirically reported scale invariance in some biological problems without the need to invoke precise tuning to criticality. Mechanisms for the emergence of generic scale invariance are discussed in Appendix A.

H. Statistical criticality

We now briefly discuss an already mentioned alternative perspective to criticality, particularly useful to analyze the wealth of high-quality data now available for living systems (Mora and Bialek, 2011). It relies on the idea that some fundamental questions in biology can be tackled within a probabilistic setting (for instance, analyzing the statistics of spiking patterns may help deciphering the way in which neurons encode information) (Rieke, Bodnar, and Bialek, 1995). Bialek and co-workers developed a data-driven maximum-entropy (statistical physics) approach to biological problems that consists of approximating the probability distribution of different patterns in a given data set by a probabilistic model that consistently reproduces its main statistical features (e.g., mean values and pairwise correlations, see Appendix B). The resulting models are akin to the Ising models.[19] Rather remarkably, Bialek and collaborators observed that the emerging probabilistic models for a number of high-dimensional problems, including biological ones from retinal neural populations (Schneidman *et al.*, 2006; Tkačik *et al.*, 2013, 2014, 2015) to flocks of birds (Bialek *et al.*, 2012) and the immune system (Mora *et al.*, 2010), for which excellent empirical data sets are available, have parameter values sitting close to the edge of a phase transition, i.e., the emerging probabilistic models seem to be critical in a very precise sense (Mora and Bialek, 2011); see Appendix B.

III. FUNCTIONAL ADVANTAGES OF CRITICALITY

Having discussed basic aspects of criticality and scale invariance, we move on to ask what are the potential virtues of them susceptible to be exploited by living systems to enhance their functionality? To shed light on this, we first describe a well-understood case in which both theoretical and empirical evidence match, and where the essential and beneficial role played by criticality in a biological system is clear and illuminating. Later on we discuss a set of possible functional advantages of criticality from a general perspective.

A. Criticality in the auditory and other sensory systems

The inner ear of vertebrates is able to detect acoustic stimuli with extraordinary sensitivity and exquisite frequency selectivity across many scales (Hudspeth, 2014). At the basis of these exceptional features there are *hair cells*, the ear's sensory receptors, which oscillate spontaneously even in the absence of stimuli being able to resonate with acoustic inputs (Gold, 1948; Choe, Magnasco, and Hudspeth, 1998; Martin, Hudspeth, and Jülicher, 2001). Intrinsic oscillations are either damped or self-sustained depending on the concentration of calcium ions, with a Hopf bifurcation separating these two regimes. Empirical evidence reveals that the ion concentration is regulated in such a way that hair cells operate in a regime very close to the Hopf bifurcation (Camalet *et al.*, 2000; Ospeck, Eguíluz, and Magnasco, 2001). This has been argued to entail important consequences for signal processing (Choe, Magnasco, and Hudspeth, 1998; Eguíluz *et al.*, 2000; Martin, Hudspeth, and Jülicher, 2001; Hudspeth, Jülicher, and Martin, 2010), as we discuss now.

In the simplest possible setting, a hair cell can be effectively described as a Hopf oscillator (Strogatz, 2014):

$$\dot{\phi}(t) = (a + i\tilde{\omega})\phi(t) - |\phi|^2\phi(t), \tag{3}$$

where ϕ is a complex number, $\tilde{\omega}$ is the resonance frequency, and a is the control parameter (ion concentration) setting the dynamical regime. Equation (3) exhibits self-sustained oscillations of the form $\phi(t) = \sqrt{a}e^{i\tilde{\omega}t}$ if $a > 0$, while if $a < 0$ oscillations are damped.[20] Introducing stimuli of the characteristic frequency $\omega = \tilde{\omega}$ and small amplitude F [i.e., adding $+Fe^{i\tilde{\omega}t}$ to Eq. (3)], and writing $\phi(t) = R(t)e^{i\omega t}$, one finds

$$\dot{R}(t) = R(t)[a - R^2(t)] + F. \tag{4}$$

In the oscillatory regime $a > 0$, the response R is proportional to the input amplitude F. However, at the bifurcation (or critical) point, $a = 0$, the response R is strongly nonlinear as $R = F^{1/3}$ and, consequently, the response-to-signal ratio $R/F = F^{-2/3}$ diverges at $F \to 0$, leading to a large response to small signals of the characteristic frequency. On the other hand, if the input has some other frequency $\omega \neq \tilde{\omega}$ the response is much smaller. This entails an extremely efficient frequency selection and amplification mechanism, vividly illustrating the advantage of working close to the instability point.

The described phenomenon involves a single hair cell with a specific intrinsic frequency and it is thus not a collective critical phenomenon. However, the cochlea is arranged in such a way that it involves an almost unidimensional array of diverse and coupled hair cells. Coupling many different Hopf oscillators results in the emergence of a true phase transition, i.e., a critical point with scale-free avalanches, entailing sharpened frequency response (Duke and Jülicher, 2003; Magnasco, 2003) and enhanced input sensitivity (Kern and Stoop, 2003; Gomez, Lorimer, and Stoop, 2015; Stoop and Gomez, 2016).

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[19]And since the inferred interactions among "spins" have both signs, they are a sort of spin glasses (Tkačik *et al.*, 2009, 2013).

[20]See Kern and Stoop (2003) from where this discussion is adapted.
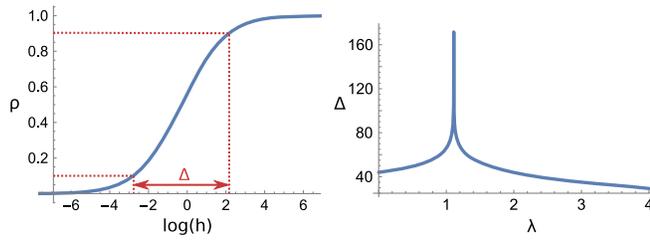
FIG. 4. The behavior of the dynamic range defined as near a critical point. (Left) Steady state density ρ as a function of the driving force h (in log scale) for a given value of the control parameter λ; the dynamic range Δ defined as $\Delta = 10 \log[h(\rho = 0.9)/h(\rho = 0.1)]$ signals the interval where distinguishable responses (i.e., values of ρ) can be measured. (Right) Δ exhibits a pronounced peak at criticality.

Summing up, working at criticality has been shown to be essential to generate the extraordinary features of vertebrate hearing, even the most intricate ones (Stoop and Gomez, 2016). Similar virtues of criticality have been explored in the olfactory system (Bushdid *et al.*, 2014) and the visual cortex (Shew *et al.*, 2015) [see also Chialvo (2006) and Friston, Breakspear, and Deco (2012)].

B. Exploiting criticality

1. Maximal sensitivity and dynamic range

As previously discussed, an important trademark of critical points is the divergence of the response (or susceptibility) which is likely to be exploited in biological sensing systems, needing to optimize their response to environmental cues. To better quantify this, a related quantity called a *dynamic range*, was introduced by Kinouchi and Copelli (2006). Consider a model for activity propagation (similar to the contact process) with a critical point ($\lambda_c = 1$) running on a random network under the action of an external stimulus h able to create activity at empty nodes. The dynamic range Δ (see Fig. 4) gauges the range of diverse stimuli intensities where variations in input h can be robustly coded by variations in the response, discarding stimuli that give almost indistinguishable outputs. Δ turns out to exhibit a marked peak at $\lambda_c = 1$, indicating that at criticality discriminative outputs can be associated with a very large variety of inputs, with functional advantages for signal detection and processing.

2. Large correlations

The emergence of arbitrarily large correlation lengths at criticality is an important feature susceptible to be exploited by living systems in order to induce coordinated behavior of individual units across space and time. This can be relevant for coordination purposes in neural systems where coherent behavior across extended areas is observed (Tagliazucchi *et al.*, 2012) in flocks of birds (Cavagna *et al.*, 2010) and in micro-organism colonies (De Palo, Yi, and Endres, 2017). Similarly, the emergence of very large correlation times and a critical slowing down may provide biological systems with a useful mechanism for the generation of long-lasting and/or slow-decaying memories at multiple time scales (Deco and Jirsa, 2012).

3. Statistical complexity and large repertoires

The variability of possible spatiotemporal patterns is maximal at criticality (as illustrated in Fig. 2); this may allow biological systems to exhibit a wide spectrum of possible responses, sometimes called "dynamical repertoire" (Rämö, Kesseli, and Yli-Harja, 2006; Rämö *et al.*, 2007; Yang *et al.*, 2012). This is consistent with the finding that models for brain activity reach the highest signal complexity, with a variety of attractors and multistability when operating near criticality (Deco and Jirsa, 2012; Haimovici *et al.*, 2013). Similarly, (i) the number of metastable states (Haldeman and Beggs, 2005), (ii) the variability of attractors to support memories (Krawitz and Shmulevich, 2007; de Arcangelis and Herrmann, 2010), and (ii) the diversity in structure-dynamics relationships (Nykter, Price, Larjo *et al.*, 2008) have been predicted to be maximized at criticality. All this suggests that in order to spontaneously generate complex patterns, required to store highly diverse tokens of information, operating near criticality can be an excellent solution for living systems. As a consequence, the capacity to store and process information is optimal at criticality, as we discuss in more depth in what follows.

4. Computation exploiting criticality

It was long ago conjectured that the extraordinary "computational power" of living systems could be the result of collective behavior, emerging out of a large number of simple components (Amari, 1972; Grossberg, 1982; Hopfield, 1982; Carpenter and Grossberg, 2016). By "computation" it is usually meant an algorithm or system that, with the aim of performing some task, assigns outputs to inputs following some internal logic. Thus, the computational power of a given device is quantified by estimating the amount and diversity of associations of inputs to outputs that it can support. As first suggested by Turing (1950) and Ashby (1960) and much further developed in the context of machine learning (Crutchfield and Young, 1988; Packard, 1988; Langton, 1990; Li, Packard, and Langton, 1990) networked systems operating at criticality can have exceptionally high computational capabilities. In particular, Langton formulated the question: "under what conditions will physical systems support the basic operations of information transmission, storage, and modification, required to support computation?" His answer was that systems[21] operating at the "edge of chaos" are especially suitable to perform complex computations.[22] The edge of chaos or critical point (as called here) is the borderline between two distinct phases or regimes: the chaotic or disordered one in which perturbations and noise propagate unboundedly (thereby corrupting information storage) and the frozen or ordered phase whereas changes are rapidly erased (hindering the capacity to react and transmit information). Therefore, the critical point confers on computing devices composed of equivalent units an optimal trade-off between information storage and information transmission,

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[21]Cellular automata in this case (Wolfram, 2002).
[22]This proposal triggered a heated debate; see, e.g., Crutchfield and Young (1988), Melanie, Crutchfield, and Hraber (1993), and Crutchfield (2012).

two of the key ingredients proposed by Turing as indispensable for universal computing machines (Turing, 1950).

In artificial intelligence, criticality is exploited in so-called "reservoir computing" (Lukoševičius, Jaeger, and Schrauwen, 2012) that was developed independently in the fields of machine learning ["echo state networks" in Jaeger (2007)] and computational neuroscience ["liquid state machine" in Maass, Natschlager, and Markram (2002)]. These machines consist of a network of nodes and links, "the reservoir," where each node represents an abstract "neuron" and links between them mimic the connectivity of actual biological circuits. A series of seminal works showed that such machines can perform real-time computations, responding rapidly to time varying input signals, in a coherent yet flexible way if they operate near a critical point (Maass, Natschlager, and Markram, 2002; Bertschinger and Natschlager, 2004; Legenstein, 2005; Legenstein and Maass, 2007; Boedecker *et al.*, 2012).

These ideas are corroborated by information-theoretic analyses (Cover and Thomas, 1991), which have unveiled the fact that the overall transmission of information between units in a network, as measured by diverse indicators,[23] is maximal if the underlying dynamical process is critical.[24]

Let us also mention that (i) state-of-the-art deep learning machines (LeCun, Bengio, and Hinton, 2015) may rely on some form of intrinsic scale invariance or even criticality (Mehta and Schwab, 2014; Lin and Tegmark, 2017; Oprisa and Toth, 2017a, 2017b; Song, Marsili, and Jo, 2017; Ringel and de Bem, 2018), opening exciting research avenues to understand how artificial-intelligence machines achieve their extraordinary performance, and (ii) from the empirical side, recent work has revealed that a mechanism akin to reservoir computing enables neuronal networks of the cerebellum to perform highly complex tasks in an efficient way by operating at criticality (Rössert, Dean, and Porrill, 2015).

IV. ALLEGED CRITICALITY AND SCALING IN BIOLOGICAL SYSTEMS

Having discussed putative virtues of critical dynamics, susceptible in principle to be exploited by biological systems, we now start with some of the most remarkable existing empirical evidence revealing signatures of criticality in such systems. We warn the reader that, even if the aim is to present a collection as extensive and exhaustive as possible, the selection of topics as well as the extent in which they are discussed might be biased by our own experience. Also, importantly, even if some of the experiments and findings to

be discussed are appealing, evidence in many cases is not complete and conclusions should always be taken with caution. Indeed, for many of the forthcoming examples, we also discuss existing criticisms and potential technical or interpretative problems.

A. Neural activity and brain networks

1. Spontaneous cortical activity

The cerebral cortex of mammalians is never silent, not even under resting conditions nor in the absence of stimuli; instead, it exhibits a state of ceaseless spontaneous electrochemical activity with very high variability and sensitivity (Arieli *et al.*, 1996; Yuste *et al.*, 2005; Fox and Raichle, 2007; Raichle, 2011). Understanding the genesis and functionality of spontaneous cortical activity, which accounts for about 20% of the total oxygen consumption of a person at rest, is key to shedding light onto how the cortex processes information and computes (Arieli *et al.*, 1996; Deco, Jirsa, and McIntosh, 2011, 2013; He, 2014). Criticality might play a key role to generate such a variable and sensitive activity as diverse empirical results suggest.

An adult human brain consists of almost 10^{11} neurons and up to 10^{15} synaptic connections among them, forming an amazingly complex network through which electric signals propagate (Keenan *et al.*, 2007). Neurons integrate presynaptic excitatory and inhibitory inputs from other neurons and fire an action potential when a given threshold is overcome, stimulating further activity. This generates irregular cascades or outbursts of activity interspersed by quiescent periods, as empirically observed both *in vitro* (Sanchez-Vives and McCormick, 2000; Segev and Ben-Jacob, 2001; Segev *et al.*, 2001; Tabak and Latham, 2003; Eytan and Marom, 2006) and *in vivo* (Meister *et al.*, 1991; Steriade, Nunez, and Amzica, 1993); see Fig. 5. Is this activity related to inherent critical behavior? In what follows we discuss empirical pieces of evidence suggesting diverse possible connections with different types of phase transitions.

2. The edge of activity propagation: Avalanches

In a remarkable breakthrough, Beggs and Plenz (2003) succeeded at resolving the internal spatiotemporal organization of the outbursts of neuronal activity. They analyzed mature cultures as well as acute slices of rat cortex and recorded spontaneous local field potentials (LFPs), which provide coarse-grained measurements of electrochemical activity, at different locations and times. Local events of activity are defined as (negative) peaks of the LFP signals, which are indicative of local population spikes (Beggs and Plenz, 2003). As illustrated in Fig. 5, events at different sites have a tendency to cluster in time, producing network spikes of activity. Each of these outbursts of activity when temporally resolved consists of a cascade of successive local events, organized as neuronal avalanches interspersed by periods of quiescence (Beggs and Plenz, 2003, 2004). The avalanche sizes (i.e., number of local events each one includes) and durations were found to be distributed as power laws with exponents $\tau \approx 3/2$ and $\alpha \approx 2$, respectively, with cutoffs that increase with system size in a scale-invariant way [i.e., the

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[23]Such as the transfer entropy (Solé and Miramontes, 1995; Lizier, Prokopenko, and Zomaya, 2008b; Shriki and Yellin, 2016), Fisher information (Wang, Lizier, and Prokopenko, 2011), and more in general statistical complexity (as previously discussed) (Krawitz and Shmulevich, 2007; Rämö *et al.*, 2007; Lizier, Prokopenko, and Zomaya, 2008a).

[24]See Li, Packard, and Langton (1990), Beggs (2008), Ribeiro *et al.* (2008), Toyoizumi and Abbott (2011), Barnett *et al.* (2013), and Prokopenko (2013) for a discrepant view.

FIG. 5. Illustration of how neuronal avalanches are measured from local field potential (LFP). (Top) LFPs are measured at different locations; negative peaks of the time series correlate with large population spikes of the underlying neurons within each local region. (Middle) Raster plot illustrating the times at which peaks of the LPF occurs for different sites, revealing a high degree of temporal clustering. (Bottom) Enhancing the temporal resolution, it is possible to resolve the spatiotemporal organization within apparently coherent large-scale events occurring in the form of "neuronal avalanches" (shaded columns) interspersed by periods of quiescence (white columns).

distributions obey finite-size scaling[25]; see Beggs and Plenz (2003), Mazzoni *et al.* (2007), and Petermann *et al.* (2009)]. The observed exponents coincide with those of the mean-field critical contact and branching processes as described and, thus, seem to describe a marginal activity-propagation process. Moreover, the mean temporal profile of neuronal avalanches of widely varying durations is quantitatively described by a single universal scaling function (Sethna, Dahmen, and Myers, 2001; Friedman *et al.*, 2012), and scaling relationships between the measured exponents are fulfilled (Friedman *et al.*, 2012). Similar avalanches have been observed *in vitro* (Mazzoni *et al.*, 2007; Pasquale *et al.*, 2008) and *in vivo* for different species (Gireesh and Plenz, 2008; Petermann *et al.*, 2009; Hahn *et al.*, 2010; Ribeiro *et al.*, 2010; Yu *et al.*,

2011) and across resolution scales, from single neuron spikes to rather coarse-grained measurements.[26] The fact that at quite different resolution scales similar results are reported is, by itself, strongly supportive of the existence of underlying scale-invariant dynamical processes.[27]

All this evidence regarding neuronal avalanches seems to make a strong case in favor of criticality. However, some caveats need to be made.

(i) Thresholding: A source of ambiguities in extracting (discrete) events from (continuous) time-series analyses comes from thresholding; i.e., signals at any given spatio-temporal location need to overcome some threshold to be declared an "event" of activity. Petermann *et al.* (2009) compared results for different thresholds in LFPs time series and found that exponent values remain unchanged, suggesting the existence of a truly scale-invariant organization of events. However, a word of caution is still required as recent works have underlined the "perils" associated with thresholding, which in some controlled cases has been shown to generate spurious effects such as effective exponent values and corre-lations in the timings of consecutive avalanches (; Laurson, Illa, and Alava, 2009; Font-Clos *et al.*, 2015; Janićević *et al.*, 2016). Further clarifying this issue is key to making solid progress in the empirical analysis of avalanching systems.

(ii) Time binning: Avalanches can be defined only by employing a criterion to establish when an avalanche starts and when it ends. This requires setting a discrete time binning to be applied to the data: an avalanche starts when a time bin with some activity within it follows a series of preceding consecutive quiescent ones and ends when a new quiescent time bin appears (Beggs and Plenz, 2003); see Fig. 5. This introduces some ambiguity, and the measured avalanche exponents have been shown to be sensitive to the choice of the time bin. However, taking the time bin to coincide with the mean inter-event interval, the mean-field branching process exponents seem to be systematically recovered (Beggs and Plenz, 2003; Petermann *et al.*, 2009; Tagliazucchi *et al.*, 2012; Haimovici *et al.*, 2013). Further work is needed to math-ematically clarify this important issue.

(iii) Subsampling: A related problem is that of subsampling as a result of observational and resolution limitations. Owing to these factors the statistic is not complete, and this might affect the shape of the observed distributions. Priesemann, Munk, and Wibral (2009) and Priesemann *et al.* (2013, 2014) argued that, taking into consideration subsampling effects, empirical data are best characterized by a slightly subcritical dynamics (additionally driven my external forces) rather than by a critical one.

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[25]Instead, if data are temporally reshuffled the distributions become exponential ones, meaning that large coherent events disappear (Beggs and Plenz, 2003; Plenz and Thiagarajan, 2007).

[26]This includes single unit recordings (Bellay *et al.*, 2015), LFPs (Beggs and Plenz, 2003; Petermann *et al.*, 2009), electroencepha-lography (EEG) (Freeman *et al.*, 2003; Allegrini *et al.*, 2010; Meisel *et al.*, 2013), electrocorticography (ECoG) (Solovey *et al.*, 2012), magnetoencephalography (MEG) (Novikov *et al.*, 1997; Poil *et al.*, 2012; Palva *et al.*, 2013; Shriki *et al.*, 2013), and functional magnetic resonance imaging (fMRI) (Tagliazucchi *et al.*, 2012; Haimovici *et al.*, 2013).

[27]Some studies suggest that even single neurons can be intrinsi-cally critical to optimize their inherent excitability (Gal and Marom, 2013; Gollo, Kinouchi, and Copelli, 2013).

(iv) Limited scales: In general, no more than 2, at most 3, orders of magnitude in avalanche statistics have been reported which is somehow unsatisfactory. Obtaining much broader regimes of scale invariance is technically challenging, but would make a stronger case for actual scale invariance (Yu *et al.*, 2014).

(v) Some support different interpretations of the observed power laws, which are unrelated to criticality (Bédard, Kröger, and Destexhe, 2006; Destexhe, 2009; Touboul and Destexhe, 2010, 2017).

This series of observations, taken together, seem to shed some doubts on evidence in favor of criticality relying on avalanches. To further strengthen it, we now discuss other complementary experimental signatures of criticality from different perspectives.

3. The edge of neural synchronization

Much attention has been historically devoted to brain rhythms observed in EEG, MEG, and LFP measurements (Buzsaki, 2009). Such rhythms emerge owing to the transient synchronization between different neural regions and circuits, and they play a key role in neural function (Steriade, Amzica, and Contreras, 1996). Clusters of neurons with coherent neural activity have a much stronger coordinated effect on other neuronal assemblies than asynchronous neurons do (Kelso, Scholz, and Schöner, 1986; Scholz, Kelso, and Schöner, 1987; Brunel and Hakim, 2008). Thus, phase synchrony is essential for large-scale integration of information (Varela *et al.*, 2001), and abnormalities in the level of synchronization, either by excess or by defect, are a signature of pathologies such as epilepsy, Parkinson's disease, schizophrenia, or autism (Yang *et al.*, 2012). Empirically, the measured level of synchronization across resting brain regions and across time has been found to be highly variable and with strong long-range correlations. Such spatiotemporal variability can be interpreted as a template to codify vastly different tasks and to allow for a large dynamical repertoire (Arieli *et al.*, 1996) and has been observed to diminish when the subject is engaged in a specific task (Tinker and Velazquez, 2014).

The role that criticality might play in keeping intermediate and variable levels of synchrony, which could, for example, be essential to achieve a good balance between integration and segregation (Tononi, Sporns, and Edelman, 1994), has been empirically analyzed as we discuss now. Analyzing spontaneous bursts of coordinated activity (as in Fig. 5) (Segev and Ben-Jacob, 2001; Segev *et al.*, 2001), the overall level of phase synchrony between different electrodes has been recorded under different pharmacological conditions, ranging from excitation-dominated to inhibition-dominated regimes. It was observed that this is a critical point at which excitation and inhibition balance (Yang *et al.*, 2012). At such a point, i.e., at "the edge of synchrony" (Brunel, 2000; Deco *et al.*, 2014; Palmigiano *et al.*, 2017), the level of synchronization variability is maximal and scale-free avalanches of activity can be concomitantly observed (Gireesh and Plenz, 2008; Yang *et al.*, 2012). Actually, a recent theoretical work emphasized that if the cortex operates at a critical point, it should be a synchronization critical point, where marginal

synchronization and scale-free avalanches emerge together (di Santo *et al.*, 2018a). Last but not least, the detailed computational model built within the large-scale collaborative Blue brain project (Markram, 2006) also suggests that the cortical dynamics operates at the edge of a synchronization phase transition (Markram *et al.*, 2015).

4. The edge of global stability

High temporal-resolution electrocorticography data from humans reveal time-varying levels of activity across different spatial locations (Magnasco, Piro, and Cecchi, 2009; Solovey *et al.*, 2012). Representing the system's state at a given time as a vector, its time evolution can be approximated as a series of linear (matricial) transformations between successive time-discrete vector states (Akaike, 1969). By employing an eigenvector decomposition of each of such matrices, it is possible to monitor the temporal dynamics of the leading eigenvalues (Lyapunov exponents). In awake individuals, the leading eigenvalue turns out to oscillate closely around the threshold of instability, indicating that the dynamics is self-regulated at the edge of a phase transition between stable and unstable regimes. Quite remarkably, in anesthetized subjects eigenvalues become much more stabilized, suggesting that operating at the edge of stability is a property of a functional brain and that deviations from such point can be used as a measure of loss of consciousness (Alonso *et al.*, 2014).

5. The edge of percolation

Cortical dynamics can be viewed as a sort of percolation phenomenon. Tagliazucchi *et al.* (2012) analyzed a functional magnetic resonance imaging (fMRI) time series at different regions of resting humans. By thresholding them they obtained discrete spatiotemporal maps of activity (much as in Fig. 5). They found that using the density of active sites at a given time as a control parameter, and the size of the largest connected cluster at each time as a percolation order parameter, there is a value of the control parameter nearby where the dynamics spends most of the time and, remarkably, it corresponds to the value for which the total number of different connected clusters as well as their size variability are maximal as happens at the threshold of percolation transitions. These empirical data reveal that the dynamics is close to the critical percolation density value, but with broad excursions to both subcritical and supercritical phases, suggesting that regulatory mechanisms keep the system hovering around a percolation transition (much as suggested by the mechanism of self-organized quasicriticality discussed in Sec. I). In other words, the resting brain spends most of its time near the point of marginal percolation of activity, neither too inactive nor exceedingly active.

6. The edge of a thermodynamic transition

The state of a neural network at a given small time window can be represented by a binary vector encoding whether each individual neuron has spiked or remained silent within it (Tkačik *et al.*, 2013). Questions of interest are how often does a given simultaneous (i.e., within a given time bin) spike pattern appear? What is the simplest probabilistic model

(in the sense of equilibrium statistical mechanics) able to reproduce such statistical patterns?

Pioneering empirical studies obtained data from large-scale multielectrode array recordings to determine the statistics of patterns of neural activity in large populations of retinal (ganglion) cells of a salamander (Marre *et al.*, 2012). Employing such high-resolution data and inferring from them maximum-entropy probabilistic (Ising-like) models (as described in Appendix B), Tkačik *et al.* (2013) observed that the associated specific heat diverges as a function of sample size as occurs in thermodynamic critical points. Furthermore, introducing an effective temperature they observed that empirical data are poised near the critical point of the temperature-dependent generalized model suggesting that the visual cortex might operate in a close-to-critical regime (Mora and Bialek, 2011; Tkačik *et al.*, 2014, 2015; Mora, Deny, and Marre, 2015).

A possible interpretation of these results, backed by recent empirical evidence (Gautam *et al.*, 2015; Shew *et al.*, 2015), is that adaptation to sensory inputs has tuned the visual cortex to statistical criticality, thus optimizing its performance. A competing view is that the observed signatures of criticality could reflect an effective averaging over unobserved variables (such as common external inputs in the case of retinal populations), lacking thus any relationship with possible functional advantages (Aitchison, Corradi, and Latham, 2016; Nonnenmacher *et al.*, 2017); see Appendix B. We refer to Tkačik *et al.* (2015) and Nonnenmacher *et al.* (2017) for more thorough discussions on these alternative viewpoints.

7. Large-scale cortical dynamics

Large research initiatives have allowed for the measurement of network of physical (neuro-anatomical) connections between different regions of the human brain, i.e., the "human connectome network."[28]

On the other hand, fMRI studies performed in the resting state, i.e., while the subject is awake not performing any specific task, reveal the emergence of spatiotemporal patterns of strongly coherent fluctuations at the level of activity at the large scale. This allows for the determination of so-called "resting state networks," encoding pairwise correlations between different brain regions, or in other words brain regions that become active or inactive together and that are consistently found in healthy individuals.[29]

Diverse studies of simple dynamical models running on top of the empirically determined human connectome network revealed that spatiotemporal correlations similar to those of the empirically measured resting state are reproduced only if the models operate close to criticality (Fraiman *et al.*, 2009; Cabral *et al.*, 2011; Haimovici *et al.*, 2013; Plenz, 2013),

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[28]The resulting human connectome turns out to be a network organized in a hierarchical modular way (Sporns *et al.*, 2004; Sporns, Tononi, and Kötter, 2005; Hagmann *et al.*, 2008; Meunier, Lambiotte, and Bullmore, 2010; Sporns, 2010; Kaiser, 2011; Betzel *et al.*, 2013; Breakspear, 2017).

[29]See the vast literature on this, e.g., Biswal *et al.* (1995), Raichle *et al.* (2001), Greicius *et al.* (2003), Beckmann *et al.* (2005), Deco, Jirsa, and McIntosh (2011, 2013), and Diez *et al.* (2015).

suggesting that resting state spatiotemporal patterns of activity emerge from the interplay between critical dynamics and the large-scale underlying architecture of the brain. Thus, resting state networks reflect structured and critical fluctuations among a set of possible attractors suggestive of a state of alertness facilitating rapid task-dependent shifts (Ghosh *et al.*, 2008; Deco and Jirsa, 2012; Deco *et al.*, 2013).

On the other hand, one could expect that scale invariance emerges in broad regions of parameter space and not just at critical points (see Appendix A), owing to the modular and highly heterogeneous architecture of structural brain networks. This has indeed been verified to be true for models of neural activity propagation (Moretti and Muñoz, 2013) as well as for synchronization dynamics (Shanahan, 2010; Villegas, Moretti, and Muñoz, 2014; Sadilek and Thurner, 2015) and implies that cortical dynamics might not be required to be exactly critical to reproduce empirical findings, but just to be located in a broad region in parameter space exhibiting generic scale invariance (e.g., in a Griffiths phase, see Appendix A).

8. Disruptions of criticality in pathological conditions

Important pieces of evidence that scale invariance and criticality might be specific of awake and healthy brain activity emerges from experimental analyses of neural activity under pathology or modified physiological conditions. For example, signatures of criticality have been reported to fade away during epileptic seizures (Hobbs, Smith, and Beggs, 2010; Meisel *et al.*, 2012) as well as during anomalously large periods of wakefulness (Meisel *et al.*, 2013) or while performing simple tasks (Tomen, Rotermund, and Ernst, 2014; Hahn *et al.*, 2017). Also, long-range temporal correlations, characteristic of the awake state (Expert *et al.*, 2011; He, 2011), break down during anesthesia (Ribeiro *et al.*, 2010; Bellay *et al.*, 2015), unconsciousness (Tagliazucchi *et al.*, 2016), or under deep sleep (Tagliazucchi *et al.*, 2013), suggesting that critical dynamics is specific to the state of wakefulness. Interestingly, sleep has been interpreted as a mechanism to restore the overall dynamics to a critical state (Pearlmutter and Houghton, 2009).

By pharmacologically altering the ratio of excitation to inhibition, i.e., breaking the balance condition that characterizes functional neural networks (van Vreeswijk and Sompolinsky, 1996; Rosenbaum and Doiron, 2014; Barral and Reyes, 2016), induces a tendency to supercritical propagation of activity, including many large system-spanning avalanches, clearly disrupting scale-invariant behavior (Beggs and Plenz, 2003; Mazzoni *et al.*, 2007). Similarly, only during naturally balanced conditions the dynamic range (as defined) is empirically observed to be maximal (Shew *et al.*, 2009; Gautam *et al.*, 2015).

There is also experimental evidence supporting the idea that developing cortical networks go through different stages in the process of maturating: they shift from being supercritical to subcritical and then finally converge toward criticality only when they become mature (Stewart and Plenz, 2008; Tetzlaff *et al.*, 2010).

Taken together, these observations suggest that criticality is the baseline state of mature, healthy, and awake neural

networks and that deviations from criticality have profound functional consequences (Massobrio *et al.*, 2015).

9. Mathematical models of neurocriticality

Since the idea that the computational power of the brain could emerge out of collective properties of neuronal assemblies (Hopfield, 1982; Hertz, Krogh, and Palmer, 1991), a large and disparate number of modeling approaches have been proposed to scrutinize neural dynamics (Amit, 1992; Amit and Brunel, 1997; Kandel, Schwartz, and Jessel, 2000; Izhikevich, 2004; Dayan and Abbott, 2006; Izhikevich, 2007; Mattia and Sanchez-Vives, 2012). These models uncovered a large variety of phases and possible dynamical regimes such as up and down states (Holcman and Tsodyks, 2006; Parga and Abbott, 2007; Mejias, Kappen, and Torres, 2010; Hidalgo *et al.*, 2012; Mattia and Sanchez-Vives, 2012), synchronous and asynchronous phases (Abbott and van Vreeswijk, 1993; Brunel, 2000; Brunel and Hakim, 2008), as well as phase transitions separating them. Our aim here is not to review them exhaustively but rather to discuss those aimed at justifying the possible emergence of criticality in actual neural networks.

P. Bak and collaborators are to be acknowledged for first proposing that concepts of self-organization to criticality could play a role in neural dynamics.[30] Herz and Hopfield (1995) realized that stylized integrate-and-fire models of neuronal networks were mathematically equivalent to SOC archetypes.

Short-time synaptic depression (Markram and Tsodyks, 1996; Tsodyks and Markram, 1997; Sussillo, Toyoizumi, and Maass, 2007) was introduced in SOC-like neural-network models (in which some form of neural stress is accumulated and then released to connected units in a conserved way) as a regulatory mechanism able to auto-organize them to the edge of a phase transition (de Arcangelis, Perrone-Capano, and Herrmann, 2006; Levina, Herrmann, and Geisel, 2007, 2009; Gómez *et al.*, 2009)[31]; synaptic resources become depleted owing to network activity and remain so for a characteristic recovery period, while they slowly recover to their baseline level. The alternation of these activity-dependent mechanisms (i.e., slow charging and fast dissipation) generates a feedback loop that allegedly guides the networks to criticality, much as in SOC (Fig. 3).

Alternative regulatory (*homeostatic*) mechanisms such as spike-timing dependent plasticity (Shin and Kim, 2006; Meisel and Gross, 2009; Rubinov *et al.*, 2011; Effenberger, Jost, and Levina, 2015), retrosynaptic signals (Hernandez-Urbina and Herrmann, 2017), and Hebbian plasticity (de Arcangelis and Herrmann, 2010; Uhlig *et al.*, 2013) have been

proposed to explain self-organization to criticality (Bienenstock and Lehmann, 1998).

However, these SOC-like approaches might not be biologically plausible, as they rely on conservative or almost conservative dynamics (while neurons and synapses are leaky) and even more importantly they require an unrealistically large (infinite) separation of time scales between dissipation and recovering to actually self-tune the dynamics to a critical state (Bonachela *et al.*, 2010; de Andrade Costa, Copelli, and Kinouchi, 2015). If the separation of time scales in these models is fixed to moderate (finite) values, critical self-organization is not achieved; instead, the system hovers around the critical point with excursions to both sides of it, as in the previously discussed self-organized quasicriticality (Bonachela and Muñoz, 2009; Kinouchi *et al.*, 2018), or may become not critical at all (Bonachela *et al.*, 2010).

To overcome these difficulties an influential model was proposed to explain self-organized criticality without assuming conservative dynamics nor an infinite separation of time scales (Millman *et al.*, 2010). This model (consisting of a network of leaky integrate-and-fire neurons with synaptic plasticity) exhibits a discontinuous phase transition, rather than a continuous one with a critical point, between states of high and low activity, respectively. This is neurobiologically sound as similar "up" and "down" states are empirically known to emerge under deep sleep or anesthesia (Steriade, Nunez, and Amzica, 1993; Holcman and Tsodyks, 2006). Remarkably, the model was also found to display scale-free avalanches all across its active phase. This is puzzling from the viewpoint of models of activity propagation, which generate scale-free avalanches only at criticality.

This apparent paradox was recently solved: avalanches in the model of Millman *et al.* are not the result of criticality; they appear owing to the existence of generic scale invariance, which is a consequence of an underlying neutral dynamics (see Appendix A). Importantly, such neutral avalanches are detected in computational models by employing information about causal relationships on which the neuron triggers the firing of each other (Martinello *et al.*, 2017), and this type of information is usually not accessible in experiments.[32] Furthermore, if avalanches in the model of Millman *et al.* are measured as in experiments (employing a time binning) they are not scale free (Martinello *et al.*, 2017). Thus, this model, as well as some other similar ones (Stepp, Plenz, and Srinivasa, 2015), does not describe empirical temporally defined scale-free avalanches. More generally, these results reveal a gap in the literature between time-binned defined avalanches (in experiments) and causally defined avalanches (in models).

What all of these approaches have in common is that they identify neural criticality with the edge of an activity-propagation phase transition. Recently, some other theoretical models provided theoretical evidence that neural dynamics should exhibit a synchronization phase transition, at which neuronal avalanches and incipient oscillations coexist (Gireesh and Plenz, 2008; Poil *et al.*, 2012; Yang *et al.*, 2012; di Santo *et al.*, 2018a). However, these models provide

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[30]See, e.g., Stassinopoulos and Bak (1995), Bak (1996), Chialvo and Bak (1999), Bak and Chialvo (2001), and Chialvo (2004). Also, early work by Haken, Kelso, and co-workers brought about the role that critical fluctuations and critical slowing down might play in neural dynamics (Haken, 1977; Kelso, Scholz, and Schöner, 1986; Scholz, Kelso, and Schöner, 1987; Haken, 2013).

[31]This allowed studies of the interplay between critical dynamics, memory, and learning (de Arcangelis and Herrmann, 2010, 2012; de Arcangelis, Lombardi, and Herrmann, 2014; de Arcangelis, 2011, 2012).

[32]See, however, Williams-Garcia, Beggs, and Ortiz (2017).

no explanation other than a possible fine-tuning of why the dynamics should operate precisely at the edge synchronization.

Last but not least, the detailed computational model built within the large-scale collaborative Blue brain project (Markram, 2006) suggests that the cortical dynamics operates at the edge of a phase transition between an asynchronous phase and a synchronous one with emerging oscillations (Markram *et al.*, 2015). The regulation of calcium dynamics has been cited as a possible responsible mechanism for keeping the system close to such a critical state, operating at a point at which a whole set of empirical results can be quantitatively explained by the model (Markram *et al.*, 2015).

Finally, let us comment on two theoretical approaches, not relying on criticality, proposed to account for scale-free neuronal avalanches. The first one is a mechanism called "stochastic amplification of fluctuations" which is able to produce highly variable avalanches with an approximate but not perfect or critical balance between excitatory and inhibitory couplings together with inherent stochasticity (Murphy and Miller, 2009; Benayoun *et al.*, 2010). However, this mechanism is not able to reproduce the empirically observed exponent values (di Santo *et al.*, 2018b).

The second is a recent work by Touboul and Destexhe (2017), where it was proposed that scale-free avalanches can naturally emerge in networks of neurons [described as a balanced network with excitation and inhibition (Brunel, 2000), or even as simple Poissonian point processes] operating in synchronous irregular regimes away from criticality. In our opinion, further work needs to be done to understand how and under which circumstances this is true, and what are the corresponding values of the resulting avalanche exponents. Summing up, appealing empirical evidence as well as sound dynamical models supporting the idea of criticality in the brain exists; however, in many cases empirical results are not fully convincing and alternative theoretical interpretations are still under debate. Fully clarifying the nature of the overall cortical dynamical state remains an open challenge.

B. Gene regulatory networks

Setting aside neural networks, we move on to another type of biological information-processing networks that also exhibit signatures of criticality: genetic networks.

Living cells exhibit stable characteristic features which are robust even under highly variable conditions. In parallel, they also exhibit flexibility to adapt to environmental changes. These two aspects are compatible owing to the fact that a given set of genes ("genotype") can give rise to different cellular states ("phenotypes"), consisting of diverse gene-expression patterns in which some genes are differentially expressed or silenced. Since the pioneering work of Kauffman (1993), cellular states have been identified as attractors of the dynamics of gene regulatory networks, where the genes are the network nodes and their mutual regulatory (activation or repression) interactions are represented as directed links between them. Cells can be thought of as "machines" executing complex gene-expression programs that involve

the coordinated expression of thousands of genes[33] (Crick, 1970; Kitano *et al.*, 2001; Alon, 2006; Koonin, Wolf, and Karev, 2006; Buchanan, 2010; Koonin, 2011). Consequently, the study of information processing in cells shifted progressively from single genes to increasingly complex circuits and networks of genes and regulatory interactions, shedding light on collective cellular states (Hartwell *et al.*, 1999; Shmulevich and Dougherty, 2010; Garcia-Ojalvo, 2011). The development of powerful experimental high-throughput technologies in molecular biology paved the way to the experimental investigation of gene-expression patterns in large regulatory networks (Filkov, 2005) and, in particular, provided empirical evidence that sequences of cell states (apoptosis, proliferation, differentiation, etc.) can be viewed as programs encoded in the dynamical attractors of gene regulatory networks (Albert and Othmer, 2003; Espinosa-Soto, Padilla-Longoria, and Alvarez-Buylla, 2004; Li *et al.*, 2004; Huang *et al.*, 2005).

1. Models of genetic regulatory networks

Many genes are empirically observed to exhibit bistability, i.e., their gene-expression levels can be approximated as either "high" (on) or very "low" (off) depending on conditions. Such binary states are believed to be the building blocks of genetic logical circuits (Tyson, Chen, and Novak, 2003). Thus, genetic regulatory networks have been traditionally modeled as binary information-processing systems in which the expression level of each gene is represented by a Boolean (on/off) variable and their interactions are modeled as Boolean functions whose inputs are the states of other genes (see Fig. 6) (Kauffman, 1993; Shmulevich and Dougherty, 2010).[34] Boolean descriptions constitute the most basic and crudest approach to gene regulatory networks; still, they are particularly adequate to analyze large networks as they reduce the overwhelming complexity of the real problem to a logical one, and they have been shown to successfully explain cell cycles (Kauffman, 1993, 1996; De Jong, 2002; Aldana, 2003; Bornholdt, 2005, 2008; Serra *et al.*, 2007; Drossel, 2008; Gros, 2008).

In the simplest setup, the network architecture is described as a random directed network[35] and regulatory interactions are described as random Boolean functions (Kauffman, 1969, 1993; De Jong, 2002; Albert, 2004; Alon, 2006; Gros, 2008); see Fig. 6. So defined random Boolean networks (RBNs) can operate in different regimes, depending on their averaged connectivity. The ordered (low connectivity) is characterized

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[33]Individual genes are the basic information units of the genetic code and occupy a central role in biological inheritance and evolution. Gene information is *transcribed* into RNA molecules and from them *translated* into proteins (i.e., "expressed") which are the final result of gene expression and the building blocks of functionality (Crick, 1970).

[34]Alternatively, it is also standard to use continuous approaches, based on reaction-kinetics differential equations (Kaneko and Ikegami, 1992; Furusawa and Kaneko, 2012b). See De Jong (2002) for a review.

[35]More realistic network architectures including node heterogeneity and modularity have also been considered (Aldana, 2003; Poblanno-Balp and Gershenson, 2011).
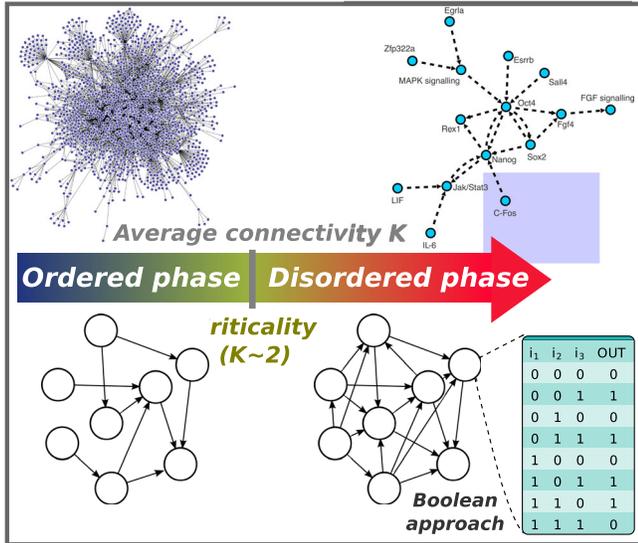
FIG. 6. The upper panel represents two gene regulatory networks: (left) a large-scale one [for *E. Coli* (Gama-Castro *et al.*, 2015)] and (right) a small-scale one [mouse embryonic stem-cell subnetwork (Parfitt and Shen, 2014)]. In both cases, nodes stand for genes and links between them for regulatory interactions (see main text). The lower panel shows a sketch of random Boolean networks as simple models of gene regulation. For low (high) average connectivities they lie in the ordered (disordered) phase, with a critical point occurring close to $K = 2$. The table illustrates a set of logical operations (associating an output to a set of three different inputs) for a given node in a Boolean setting.

by a small set of stable attractors which are largely robust to perturbations, while in the disordered phase (large connectivity) perturbations rapidly propagate and proliferate hindering the existence of truly stable states. Separating these two phases there is a critical point at which perturbations propagate marginally (Derrida and Pomeau, 1986). More complex models, with stochasticity and/or continuous levels of activity, also exhibit such two alternative phases (Rohlf and Bornholdt, 2002).

Kauffman (1993, 1996) conjectured that models operating at their critical point might provide the best possible representation of real gene regulatory networks, and that this might entail a large variety of essential functional advantages (Kauffman *et al.*, 2003; Aldana *et al.*, 2007; Krawitz and Shmulevich, 2007; Nykter, Price, Larjo *et al.*, 2008; Ribeiro *et al.*, 2008; Torres-Sosa, Huang, and Aldana, 2012). In the ordered regime, convergence in state space implies that distinctions between different inputs are readily erased, precluding reliable discrimination of them. In the disordered phase, even small perturbations lead to a very large divergence of trajectories in state space precluding reliable action (Kauffman *et al.*, 2003). Hence, criticality might confer on such networks an optimal trade-off between the robustness and accuracy that biological machinery demands and responsiveness to environmental clues (Kauffman *et al.*, 2003). At larger evolutionary scales, criticality might provide networks with an optimal balance between robustness and evolvability under changing conditions (Wagner, 2005; Aldana *et al.*, 2007; Gershenson, 2012; Kaneko, 2012; Torres-Sosa, Huang, and Aldana, 2012).

It remains to be clarified how could adaptive (Gell-Mann, 1994; Gros, 2008) and/or evolutionary (Nowak, 2006) mechanisms, specific of living systems,[36] lead biological networks to operate close to criticality. Theoretical approaches tackling this question are discussed in Appendix C.

2. Gene knockout and damage spreading

DNA microarrays or "DNA chips" are devices allowing one to measure the expression levels of large numbers of genes within a cell as well as to quantify the differences in expression levels between two cells (Brown and Botstein, 1999). Also, novel technologies made it possible to perform gene knockout experiments in which individual genes are silenced. Combining these two techniques it became possible to perform damage-spreading experiments (Derrida and Pomeau, 1986; Rohlf, Gulbahce, and Teuscher, 2007) in which the difference in gene-expression levels between perturbed and unperturbed cells in quantitatively monitored. The statistics of the sizes of avalanches caused by single-gene knockout experiments has been analyzed using empirical gene-expression data from the yeast (*Saccharomyces cerevisae*) (Hughes *et al.*, 2000), with the conclusion that the best correspondence between empirical results and (RBN) model predictions is obtained for the model operating close to its critical point (Serra, Villani, and Semeria, 2004; Rämö, Kesseli, and Yli-Harja, 2006; Serra *et al.*, 2007). However, as a word of caution, let us stress that given that expression levels are noisy it is necessary to introduce a threshold expression level to declare when a gene is differentially expressed in the two cells. A caveat is that it is not clear what the influence of thresholding is on the definition of avalanches and on their associated (size and duration) probabilities. Thus, even if results are promising, more precise analyses are still much needed.

3. Networks from DNA-microarray data

In a parallel endeavor, empirical analyses of hundreds of DNA-microarray experiments allowed researchers to infer the whole network of regulatory interactions among genes, i.e., who regulates whom in a given cell (Filkov, 2005). It has been consistently found that the in-degree distribution of such regulatory networks is Poissonian, while the out-degree distribution is scale free (Aldana, 2003; Drossel and Greil, 2009). Performing damage-spreading computational analyses of dynamical RBN models running on top of such networks, with the empirically determined architecture of diverse organisms such as *S. cerevisiae* and *E. coli* (Albert and Othmer, 2003), it was concluded that they all are indeed very close to criticality in the sense of marginal propagation of perturbations (Aldana *et al.*, 2007; Balleza *et al.*, 2008; Darabos *et al.*, 2009; Chowdhury *et al.*, 2010).

Alternatively to inferring the architecture of the underlying network of interactions, which is a difficult problem (Filkov, 2005), algorithmic information theory has also been employed to asses the dynamical state directly from empirical

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[36]This is, beyond purely self-organization mechanisms, such as SOC, also exhibited by inanimate systems (Halley and Winkler, 2008).

measurements from DNA-microarray data in a model-free way (Kauffman *et al.*, 2003; Shmulevich, Kauffman, and Aldana, 2005).[37] Analyses of empirical data (e.g., for the macrophage) following these protocols produced results compatible with marginality in the information flow, i.e., with critical dynamics (Nykter, Price, Aldana *et al.*, 2008).[38]

4. Zipf's law in gene-expression data

Inspection of gene-expression databases of diverse unicellular organisms (such as yeast) reveals that the continuous-valued abundance of expressed genes is distributed as a power law with exponent close to -1, obeying Zipf's law (Furusawa and Kaneko, 2003).[39] Furusawa and Kaneko (2012a) analyzed an abstract dynamical (not Boolean) model describing a cellular network (the network formed by the set of molecules which interact with others to give products within the cell) with nutrient uptake, and showed that Zipf's law is a universal feature of self-regulated cells optimizing their growth rate in nutrient-rich environments. In this setting, cells seem to adapt to criticality to achieve the maximal capacity to assimilate and use nutrients for recursive formation of other products (Kaneko, 2006; Stokić, Hanel, and Thurner, 2008; Hanel, Pöchacker, and Thurner, 2010; Furusawa and Kaneko, 2012a; Erez *et al.*, 2017).

C. Collective behavior of cells

We have discussed the possibility of criticality within the internal networks of individual cells. But, also ensembles of cells, both in social unicellular organisms and in multicellular ones, may exhibit signatures of scale invariance and criticality in their collective behavior (Nadell *et al.*, 2013). For instance, in aggregates of the unicellular amoeba Dictyostelium discoideum (the "slime mold"), local cell-cell coupling via secreted chemicals may be tuned to a critical value (De Palo, Yi, and Endres, 2017), resulting in emergent long-range communication and enhanced sensitivity. In the following we discuss some other examples in multicellular organisms.

1. Stem-cell pluripotency

Large diversity in gene-expression levels has been observed in multipotent stem-cell populations of multicellular organisms (Goodell, Nguyen, and Shroyer, 2015). Multipotent (hematopoietic) stem cells can differentiate onto either erythroid or myeloid blood cells, with rather different functionalities,

depending on the expression level of a gene called *Sca1* (Ridden *et al.*, 2015). The empirically measured distribution of expression levels of *Sca1* within a population of stem cells turns out to be very broad and with various local maxima. This has been modeled as a stochastic process, and it has been found that the model can exhibit two different regimes: either a stable low-*Sca1* or a stable high-*Sca1* regime. Separating these phases there is a line of discontinuous transitions (with bistability) finishing at a critical point. Remarkably, the best fit to gene-expression empirical data is obtained fixing model parameters close to criticality, where maximal variability of the two possible phenotypes is obtained. Thus, it seems that by adjusting near to criticality, the stem-cell population is prompt to react and produce either erythroid or myeloid cells in response to changing demands in an optimal way (Ridden *et al.*, 2015). Similar ideas have been discussed in the more general context of collective cell decision making (Halley, Burden, and Winkler, 2009; Lopez-Garcia *et al.*, 2010; Garcia-Ojalvo and Arias, 2012; Yamaguchi, Kawaguchi, and Sagawa, 2017), as well as in cancer progression (Tsuchiya *et al.*, 2015, 2016).

2. Morphogenesis I: Hydra regeneration

Morphogenesis is the biological process at the basis of the development of multicellular organisms. It is achieved by a precise control of cell growth, proliferation, and differentiation. As first suggested in the seminal work of Turing (1952), morphogenesis involves the creation of self-organized patterns and shapes in the embryo. A prototypical organism studied in this context is the Hydra polyp, which has a remarkable regeneration power, as an entire new individual can be spontaneously reassembled even from dissociated cells from an adult individual (Bosch, 2007). Along such a regeneration process, first a cell bilayer is formed with a spherical (hollow) shape. How does the spherical symmetry break down to form a well-defined foot-head axis in adults? During this process, there is a gene called *ks1* that becomes progressively expressed and that can be transferred to neighboring cells. It was empirically found that right at the time when the spherical symmetry is broken, the size distribution of *ks1*-rich domains of cells across the sphere becomes scale free and that a spanning cluster emerges, much as in a percolation phase transition (Soriano, Colombo, and Ott, 2006; Gamba *et al.*, 2012). Thus a critical percolationlike state with collective fluctuations of gene-expression levels is exploited to break the symmetry, defining a head-tail axis (Soriano, Colombo, and Ott, 2006; Soriano *et al.*, 2009).

3. Morphogenesis II: Gap genes in Drosophila

A set of so-called "gap" genes is responsible for the emergence of spatial patterns of gene expression that are at the origin of the formation of different segments along the head-tail axis in the development of the fruit-fly (Drosophila) embryo. Empirical scrutiny of the expression levels of gap genes along the head-tail axis revealed a number of remarkable features that include the following: slow dynamics, correlations of expression-level fluctuations over large distances, non-Gaussianity in the distribution of such fluctuations, etc. Krotov *et al.* (2014) proposed a simple dynamical model in which the process is controlled by only two mutually

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[37]For example, one such method relies on computing estimators of the Kolmogorov complexity (Ming and Vitányi, 1990) of sets of gene-expression time series in diverse microarrays, and computing how the difference between the information content of any two system states (Benedetto, Caglioti, and Loreto, 2002) changes over time.

[38]Similar analyses for Eukaryotic cells gave results compatible with the dynamics being either ordered or critical but not disordered (Shmulevich, Kauffman, and Aldana, 2005).

[39]Indeed, clonal populations of unicellular organisms such as viruses or bacteria often exhibit phenotypic diversity, which constitutes a sort of "bet-hedging" strategy to cope with unpredictable environmental changes (Kussell and Leibler, 2005; Wolf, Vazirani, and Arkin, 2005; Veening, Smits, and Kuipers, 2008).

repressing gap genes. Assuming that a fixed point exists, and performing a linear stability analysis to describe the fate of fluctuations, one readily finds that there is an instability point as the interaction strength between the two genes is varied. Krotov *et al.* (2014) argued that if the dynamics of the coupled system is tuned to operate at such an instability point, then it constitutes an excellent qualitative description of all these empirical findings, implying that the gene dynamics operates at criticality. This suggests that criticality helps defining patterns without a characteristic scale, as required for expanding and developing systems [see Pal, Ghosh, and Bose (2014) and Bose and Pal (2017) for a pedagogical discussion of these ideas in the general context of cell differentiation].

D. Collective motion

Collective motion of large groups of individuals is a phenomenon observed in a variety of social organisms such as flocks of birds, fish schools, insect swarms, herds of mammals, human crowds (Bonabeau, Dorigo, and Theraulaz, 1999; Krause and Ruxton, 2002; Couzin and Krause, 2003; Sumpter, 2010; Berdahl *et al.*, 2013) and also at smaller scales in bacterial colonies (Sokolov *et al.*, 2007; Ramaswamy, 2010; Peruani *et al.*, 2012; Nadell *et al.*, 2013), and groups of cells in general (Méhes and Vicsek, 2014). Flocking, schooling, swarming, milling, and herding constitute outstanding examples of collective phases where simple interactions between individuals give rise to fascinating emergent behavior at larger scales, even in the absence of central coordination. Flock of birds and fish schools behave as plastic entities able to exhibit coherent motion, including rapid escape maneuvers when attacked by predators, which confers obvious fitness advantages to the group as a whole (Couzin, 2007, 2009).

Such collective phenomena have attracted the attention of statistical physicists who have tackled the problem employing the following: (i) individual-based models of self-propelled particles such as the one in Vicsek *et al.* (1995) which models collective motion by assuming that an individual in a group essentially follows the trajectory of its neighbors, with some deviations treated as noise,[40] and (ii) continuum (hydrodynamic) theories, more amenable to theoretical analysis (Toner and Tu, 1995; Toner, Tu, and Ramaswamy, 2005). These approaches have in common the existence of phase transitions between phases of coherent and incoherent motion. For example, in the Vicsek model, a phase transition from an ordered "flocking phase" to a disordered "swarming phase" occurs when the density of individuals goes below a given threshold or, for a fixed density, when the level of stochasticity is large. This is consistent with experimental findings. Buhl *et al.* (2006) investigated the social behavior of locusts and reported on a density-driven phase transition from disordered movement of individuals to highly aligned collective motion as density is increased (Dyson *et al.*, 2015). At a conceptual level, marginally coordinated critical motion can be

hypothesized to constitute an optimal trade-off to deal with conflicting imperatives such as (i) the need to behave cohesively as a unique entity and (ii) being highly responsive to information from transitorily well-informed individuals (Couzin *et al.*, 2005, 2011; Vanni, Luković, and Grigolini, 2011; De Vincenzo *et al.*, 2017). Similar dichotomies exist in the empirical examples we discuss now.

1. Flocks of birds

On the empirical side, the pioneering work by Cavagna, Giardina, and collaborators (Ballerini *et al.*, 2008; Cavagna *et al.*, 2010) on starling flocks allowed one to record individual trajectories (with purposely devised tracking technology). By analyzing the fluctuations in individual velocity with respect to the average velocity of the group, these studies provided remarkable evidence that long-range scale-invariant correlations may be a general feature in systems exhibiting collective motion. In particular, experimentally measured correlations, both in orientation and in speed fluctuations, were found to grow with flock size in large flocks, suggesting that a correlation length much larger than the interaction range could be a common trait of self-organized groups needing to achieve large-scale coordination (Cavagna *et al.*, 2010). Let us note that the scale-free correlations in the orientation might be attributed to the broken continuous rotational symmetry, which as discussed in Appendix A leads to generic scale invariance. However, the presence of scale-free correlations in the scalar speed fluctuations cannot be explained in this way, suggesting that the flock might be tuned to a critical point with maximal susceptibility.[41] Furthermore, experiments on starling flocks also allow one to measure how the information of the turning of one individual propagates across the flock, revealing that this occurs in a very fast and efficient way, which can be taken as direct evidence of the existence of scale-free correlations in flocks (Attanasi *et al.*, 2014a).

Bialek *et al.* (2012) applied a maximum-entropy method to construct a statistical model consistent with the empirically measured correlations (see Appendix B). They concluded that the interaction strength and the number of interacting neighbors do not change with flock size in the probabilistic model; and, more importantly, the model was able to reproduce scale-free correlations in velocity fluctuations. It was observed (i.e., inferred from data) that this occurs as a result of the effective model's operating close to its critical point (Mora and Bialek, 2011; Bialek *et al.*, 2014; Mora *et al.*, 2016).

2. Insect swarms

Extensive field analyses of insect (midge) swarms, which unlike birds traveling in a flock hover around a spot on the ground, have also been performed (Attanasi *et al.*, 2014b). By employing finite-size analyses of the data, Attanasi *et al.* showed that both the correlation length and the susceptibility

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[40]See Grégoire and Chaté (2004), Chaté, Ginelli, Grégoire, Peruani, and Raynaud (2008), Chaté, Ginelli, Grégoire, and Raynaud 2008)), and Ginelli (2016) for detailed statistical-mechanics analyses of Vicsek models and variants of it.

[41]Similar results have been obtained for aggregates of a social amoeba (slime mold) (De Palo, Yi, and Endres, 2017), as well as for colonies of the bacteria *Bacillus subtilis* in the experimental setup of Chen *et al.* (2012) [but not in that of Sokolov *et al.* (2007), which reveals only short-range correlations].

grow with the swarm size, while the spacing between midges decreases. Moreover, such changes with swarm size occur as in the Vicsek model for finite-size systems sitting near the maximally correlated point of their transition region at each finite size.[42] Thus, midges obey spatiotemporal scaling and to achieve it they seem to regulate their average distance or density (which acts as a control parameter) so as to function close to criticality (Attanasi *et al.*, 2014b; Chaté and Muñoz, 2014; Cavagna *et al.*, 2017). On the contrary, laboratory experiments of small swarms do not indicate critical behavior, which may signal that it arises only in "natural conditions" or for larger sizes (Kelley and Ouellette, 2013; Puckett and Ouellette, 2014).

3. Mammal herds

Social herbivores (Merino sheep) have also been studied in well-controlled environments, revealing the existence of two conflicting needs: (i) the protection from predators offered by being part of a large cohesive group and (ii) the exploration of foraging space by wandering individuals. Sheep resolve this conflict by alternating a slow foraging phase, during which the group spreads out, with fast packing events triggered by individual behavioral shifts, leading to intermittent collective dynamics with packing events of all accessible scales, i.e., a "near critical" state (Ginelli *et al.*, 2015).

4. Social-insect foraging strategies

Studies of ant foraging strategies have been recently performed (Beekman, Sumpter, and Ratnieks, 2001; Loengarov and Tereshko, 2008; Solé, 2011; Bhattacharya and Vicsek, 2014; Li *et al.*, 2014; Gallotti and Chialvo, 2017). For ant colonies to achieve an efficient foraging strategy, a trade-off needs to be reached between exploratory behavior of some individuals and predominant compliance with the rules (Feinerman and Korman, 2017). It has been found by using a combination of experiments and theory that some ant groups optimize their overall performance by sitting at the edge of a phase transition between random exploration and gregarious strategies, thus resulting in effective criticality. This entails efficient group-level processing of information emerging out of an optimal amplification of transient individual information (Gelblum *et al.*, 2015). Similar ideas are presently being explored for the design of artificial systems, i.e., in *swarm robotics* (Beni, 2004; Erskine and Herrmann, 2014).

To further enrich this bird's-eye view over different aspects of criticality in biological systems, a miscellaneous collection of other examples from the literature is presented in Appendix C.

V. DISCUSSION

The hypothesis that living systems may operate in the vicinity of critical points, with concomitant scale invariance, has long inspired scientists. From a theoretical viewpoint this conjecture is certainly appealing, as it suggests an overarching

mechanism exploited by biological systems to derive important functional benefits essential in their strive to survive and proliferate. The list of possible critical features susceptible to be harnessed by living systems includes the unparalleled sensitivity to stimuli, the existence of large dynamical repertoires, maximal transmission and storage of information, as well as optimal computational capabilities, among others. When living systems are interpreted as information-processing devices, needing to operate robustly but at the same time having to cope with diverse environmental changes, the virtues of critical behavior are undeniable. Criticality represents a simple strategy to achieve a balance between robustness (order) and flexibility (disorder) needed to derive functionality. Similar trade-offs, as discussed (e.g., between stability and evolvability), underline the potential of operating at the edge between different types of order.

Throughout we focused dynamical aspects of criticality, meaning that in most of the discussed examples it is assumed, either directly or indirectly, that there is an underlying dynamical process at work, and that such a process, susceptible to be mathematically modeled, operates in the vicinity of a continuous phase transition at the borderline between two alternative regimes. Such a dynamical perspective is essentially different from the purely statistical (or *static*) one, as described in Mora and Bialek (2011). In this latter, the focus is on analyzing the statistics of existing patterns; it has the great advantage that it harnesses existing high-quality empirical data sets. On the other hand, it disregards the possible dynamical generative mechanisms behind them and focuses on an effective description (which can be very useful). Even if both approaches have deep interconnections, here we chose to focus mostly on the dynamical one.

Synthesizing (maybe oversynthesizing), one could argue that the ultimate reason why putative criticality appears so often in the scrutiny of complex biological systems is that it constitutes the simplest physical or dynamical mechanism generating complex spatiotemporal patterns spanning through many different scales that are all correlated, implying system-wide coherence and large responses to perturbations. From this perspective, critical-like behavior, and the nested hierarchy of spatiotemporal structures it spontaneously generates, can be identified as a scaffold upon which multiscale biological systems may build up further complexity.

Statistical physics teaches us that under some circumstances, including systems with some form of heterogeneity (relevant for the study of brain networks), or in systems with continuous symmetries (relevant in collective motion) the standard scenario of a unique critical point separating diverse phases needs to be replaced by that of extended critical-like regions (such as Griffiths phases discussed for the overall brain dynamics) where some form of scale invariance emerges in a generic way. In such cases, it might suffice for biological systems to operate in such phases without the need to invoke precise tuning to the edge of a phase transition to obtain functional benefits stemming from spatiotemporal scale invariance.

From the experimental viewpoint, we tried to summarize existing empirical pieces of evidence for each of the discussed examples, stressing possible drawbacks and interpretative problems, and underlining criticisms raised in the literature. Readers will extract their own conclusions on whether each of

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[42]The Vicsek model exhibits, at least for not-too-large sizes, a wide regime where correlations peak at the transition and finite-size scaling holds (Vicsek *et al.*, 1995; Grégoire and Chaté, 2004; Chaté, Ginelli, Grégoire, and Raynaud, 2008; Baglietto, Albano, and Candia, 2012).

the examples is sufficiently convincing or not. Our general impression is that, in most of the cases, larger systems, more accurate measurements, and less ambiguous analyses would be needed to further confirm or disprove the existence of an underlying dynamical critical process. For most of the leading examples (i.e., neural systems, genetic regulatory networks, and collective motion), our opinion is that as of today there is not a fully convincing proof, where experimental evidence and mathematical theory and modeling match perfectly; i.e., we still do not have a "smoking gun." Still, the existing collection of remarkable pieces of evidence is extremely appealing and hard to neglect.

Two important aspects should be considered in future empirical analyses to make solid progress. One is that, given that biological systems are finite, they cannot be truly critical in the precise sense of statistical physics; thus it is important to perform, whenever possible, finite-size analyses to prove the existence of scale invariance within the experimentally accessible ranges. A second aspect is that the two alternative phases that the alleged criticality separates should be clearly identified in each case. From this view, we find particularly appealing pieces of evidence (e.g., in neuroscience) in which, by experimentally inducing alterations to standard conditions, deviations from criticality are measured in otherwise critical-looking systems.

A general criticism can be raised to some of the analyses discussed along this work, specifically, to those in which the evidence relies on the existence of a theoretical model that provides, when tuned close to its critical point, the best possible fit to empirical observations. The criticism is that, if feature-rich empirical data with structures spanning over broadly diverse scales are considered, then it seems almost a tautology to conclude that the best possible representation of them is obtained by fitting the proposed dynamical model to operate close to its critical point, as this is typically the only region in parameter space where complex (feature-rich) patterns, with many scales, are generated. In contrast, from the opposite perspective, if actual biological data are structured across many scales, it does not seem too far fetched to assume, applying the Occam's razor, that a general common mechanism may underlie the emergence of such a hierarchy of scales, and the main candidate mechanism for this consists in operating at the edge of a continuous phase transition, i.e., being close to criticality. Thus, we are confronted with an epistemological dichotomy: Is the putative criticality of living systems just a reflection of the limitation of our models which can possibly resemble large levels of complexity only at criticality? Or, on the contrary, is criticality actually a common organizing principle at the roots of the generation of many levels of organization required for complex biological behavior to emerge? Providing a satisfactory answer to these questions is a problem of utmost importance to advance in the theoretical understanding and modeling of complex living systems.

Even if diverse biological systems were finally proved to be genuinely critical, some researchers might still retain this conclusion as largely uninformative or even irrelevant. It could be asked: "so what?" What practical implications could be derived from such knowledge? In our opinion, the design of strategies to control neural or genetic networks, especially those aiming at resolving pathologies, based on notions of criticality, the construction of algorithms of artificial intelligence exploiting scale invariance at different layers, or the application of ideas of collective motion or intelligence to the design of swarms of robots, could constitute important avenues to provide constructive answers to this question.

Novel advances, at both the experimental and theoretical sides, will help elucidating what is the actual role played by criticality and scale invariance in biological systems; meanwhile the mere possibility remains as inspiring as ever and, definitely, worth pursuing.

APPENDIX A: GENERIC SCALE INVARIANCE

There are situations in which spatiotemporal scaling may emerge without the need of parameter fine-tuning (Grinstein, 1991). (i) A well-known example is the breaking of a continuous symmetry in low-dimensional systems, as it happens in some models of magnetism in which each spin can point in any arbitrary direction in a plane (Binney *et al.*, 1993). These systems, instead of the usual ordered phase at low temperature, exhibit a broad "quasiordered" phase characterized by local order together with generic power-law decaying correlations (Grinstein, 1991). This type of ordering is relevant for bacterial-colony patterns (Ramos *et al.*, 2008) as well as in the analysis of collective motion (see Sec. IV.C).

(ii) Generic scale invariance can also emerge in the presence of structural disorder or heterogeneity. In statistical physics, one refers to "quenched disorder" as the form of spatial-dependent heterogeneity which is intrinsic to the microscopic components and remains frozen in time, reflecting structural heterogeneities. Quenched disorder can alter the nature of phase transitions (Vojta, 2006; Villa Martín, Bonachela, and Muñoz, 2014) and can also induce novel phases absent in homogeneous systems. For instance, in the contact process, quenched disorder can be implemented by considering a lattice with some missing links, a more complex disordered network of connections, and/or a node-dependent propagation rate λ. In all these cases, a novel phase called a *Griffiths phase*, characterized by critical-like features appearing all across the phase and not just at a unique point, emerges (Moreira and

Dickman, 1996; Cafiero, Gabrielli, and Muñoz, 1998; Vojta, 2006; Muñoz *et al.*, 2010).

(iii) Another mechanism that produces a type of generic scale invariance relevant in biological systems (see, e.g., Sec. IV.A.7) is "neutral dynamics." Neutral theories play a key role in population genetics (Kimura, 1984), population ecology (Hubbell, 2001; Azaele *et al.*, 2016), epidemics (Pinto and Munoz, 2011), etc. They have in common the fact that differences among possible coexisting "species" (let them be alleles of a gene, types of trees, bacterial strains, etc.) are neglected. In other words, all species are dynamically equivalent or *neutral* (Dornic *et al.*, 2001; Liggett, 2004; Blythe and McKane, 2007). It was recently shown that in a "multispecies" contact process that includes different types or species of activity, if a new species, neutral to the exiting ones, is introduced, it experiences a stochastic process in which its total population does not have a net tendency to either grow or shrink. This generates generically scale-free avalanches of the focal species unfolding in a sea of activity of the other species, without the need to invoke criticality (Martinello *et al.*, 2017).

APPENDIX B: PROBABILISTIC MODELS AND STATISTICAL CRITICALITY

Probabilistic models can be constructed such that they match the statistics of observed empirical data (Rieke, Bodnar, and Bialek, 1995). Without loss of generality, an empirically observed pattern at a given time window can be codified as a sequence of binary variables of length N: $s_i = 0, 1$ for $i = 1, 2, …, N$. Denoting $P(\mathbf{s})$ the unknown probability of finding the system in the state $\mathbf{s} = (s_1, s_2, …, s_N)$ it is possible to approximate it by a distribution function with the constraint that it reproduces the empirically measured mean values $\langle s_i \rangle$ for all i, as well as the covariances $\langle s_i s_j \rangle$ for all i and j. Imposing a maximum entropy principle (i.e., selecting the model with the smallest number of assumptions[43]) it is straightforward to derive the explicit form of the optimal model

$$P(\mathbf{s}) = \frac{1}{Z} \exp \left[\sum_{i<j} J_{ij} s_i s_j + \sum_i h_i s_i \right], \qquad (B1)$$

where Z ensures normalization and which coincides with the Boltzmann equilibrium distribution of the Ising-like model, and where the free parameters h_i and J_{ij} need to be fitted so that the imposed constraints are satisfied (Ackley, Hinton, and Sejnowski, 1985).[44]

Bialek and co-workers introduced an effective parameter β, much as an inverse temperature in equilibrium statistical mechanics, multiplying each estimated parameter in the inferred model equation (B1). Clearly, by varying β a relative change of

the weights assigned to different configurations is produced. In this way one generates a family of β-dependent probability distributions $P(\mathbf{s}|\beta g)$ interpolating between the low and high temperature phases.[45] At some intermediate value β_c there is a critical point (as identified by a peak in the susceptibility or the specific heat). It was found that diverse inference problems [from retinal populations (Schneidman *et al.*, 2006; Tkačik *et al.*, 2013, 2014, 2015) to flocks of birds (Bialek *et al.*, 2012), and the immune system (Mora *et al.*, 2010)] produce models in which $\beta_c \approx 1$, or converges to 1 as the system size is enlarged, i.e., that inferred models appear to be close to the very critical point of the underlying Ising-like problem [see Mora and Bialek (2011) for a clear and pedagogical discussion of these issues].

Let us also mention that there is an ongoing debate on the interpretation of these results. In particular, it was shown that signatures of criticality may emerge naturally in inferred models if there is a marginalization over nonobserved variables, such as correlated external inputs, even without the need for direct interactions among units (Schwab, Nemenman, and Mehta, 2014; Aitchison, Corradi, and Latham, 2016). In general, Marsili and collaborators pointed out that the alleged criticality of such models can be a consequence of the inference procedure, meaning that inferred models fitting real-world ("feature-rich" or "informative") data do most likely look critical when an effective probabilistic model is constructed (Mastromatteo and Marsili, 2011; Marsili, Mastromatteo, and Roudi, 2013; Tyrcha *et al.*, 2013; Haimovici and Marsili, 2015). We will not delve further into the controversy about the meaning and significance of this type of purely statistical approaches to criticality (see also Sec. V).

APPENDIX C: ADAPTATION AND EVOLUTION TOWARD CRITICALITY

To shed light onto the general problem of how information-processing living systems tune themselves to operate near critical points, Goudarzi *et al.* (2012) considered an ensemble of individuals or "agents," each represented as an internal RBN, including some input nodes (able to read information from the environment) and some readout nodes (providing outputs and responses). Such agents evolve though a genetic algorithm (Goldberg and Holland, 1988) that allocates larger "fitness" values to agents that better perform a series of computational tasks (each one consisting of assigning a given output to each specific input), which are alternated in time. The conclusion is that agents converge to a state close to criticality; i.e., critical dynamics emerge as the optimal solution under the combined selective pressures of having to learn different tasks and being able to readily shift among them, following changes in the tasks. Instead, in the presence of noise, optimal agents tend to be slightly subcritical, rather than critical, thus compensating for extrinsic sources of variability (Villegas *et al.*, 2016). In a similar approach, Hidalgo *et al.* (2014) showed that communities of similar

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[43]In information theory, the entropy of a probability distribution quantifies the ignorance about the variable; thus, making no assumptions about the distribution is equivalent to maximizing the entropy (Cover and Thomas, 1991; Banavar, Maritan, and Volkov, 2010).

[44]Obtaining the optimal parameter set, i.e., inferring effective interactions from correlations, is a computationally costly task, usually referred to as an "inverse Ising problem" (Schneidman *et al.*, 2006; Cocco, Leibler, and Monasson, 2009; Aurell and Ekeberg, 2012).

[45]At $\beta = 0$ infinite temperature all configurations are equiprobable, while in the opposite limit all the weight concentrates on the most likely fully ordered configuration.

adaptive agents, whose task is to communicate with each other (inferring their respective internal states) in an efficient way, converge to quasicritical states. This result constitutes a possible parsimonious explanation for the emergence of critical-like behavior in groups of individuals coordinating themselves as a collective entity (Hidalgo *et al.*, 2016) [see also Iliopoulos, Hintze, and Adami (2010)].

APPENDIX D: OTHER PUTATIVELY CRITICAL LIVING SYSTEMS

Here we briefly discuss a sample of other biological systems for which empirical evidences of criticality exist.

Cell membranes: Cell membranes are not just rigid impenetrable walls separating the interior of cells from the outside environment; they regulate the kind, direction, and amount of substances that can pass across them. Cell membranes are permeable only at some locations and for this their local composition needs to be heterogeneous (Hyman and Simons, 2012; Cicuta, 2013; Lee *et al.*, 2013). There is compelling empirical evidence that the mixture of lipids that constitute the skeleton of cell membranes operates very close to the demixing phase transition at which their different components segregate (Veatch *et al.*, 2007, 2008; Honerkamp-Smith *et al.*, 2008; Ehrig, Petrov, and Schwille, 2011; Cicuta, 2013). In this way, composition fluctuations are extremely large, enabling very diverse structural domains to appear, thus providing the membrane with a large spectrum of possible local structures at which different processes may occur and entailing a rich repertoire of functionalities.

RNA viruses: RNA viruses are believed to replicate at the edge of an "error catastrophe." If the error rates for copying the viral genome were very small, RNA viruses would have little variability, hindering adaptation and evolution. Instead, if they were too large then the fidelity of the replication machinery would be compromised and it would not be possible to maintain important genetic elements nor the identity of the (quasi)species itself (Eigen and Schuster, 1979; Eigen, McCaskill, and Schuster, 1989). It was conjectured (Solé *et al.*, 1996, 1999; Drake and Holland, 1999; Eigen, 2002) and has been partially verified in recent experiments (Crotty, Cameron, and Andino, 2001; Hart and Ferguson, 2015) that RNA viruses might operate right at the edge of the catastrophe, providing them with maximal variability compatible with genotypic robustness.[46]

Physiological rhythms: The presence of temporal scale invariance in physiological rhythms of healthy subjects, as well as its breakdown in abnormal conditions, has long been explored (Bassingthwaighte, Liebovitch, and West, 1994; Losa, 1995; Goldberger *et al.*, 2002). In particular, to mention one example, a specific connection between the complex fluctuations of human heart-rate variability and criticality has been brought forward (Ivanov *et al.*, 1999; Kiyono *et al.*, 2004, 2005; Ivanov, 2007). In the related context of blood-pressure regulation, vaso-vagal syncopes have been identified

as large "avalanches" in a self-organized cardiovascular regulatory system poised at criticality (Fortrat and Gharib, 2016). In general, such a regulation to scale-free behavior seems to impart health advantages, including system integrity and adaptability (Goldberger *et al.*, 2002).

Miscellanea: Criticality has also been claimed to play a relevant role in the immune system (Burgos and Moreno-Tovar, 1996; Mora *et al.*, 2010), cancer and carcenogenesis (Solé, 2003; Solé and Deisboeck, 2004; Davies, Demetrius, and Tuszynski, 2011; Rosenfeld, 2013), proteins (Phillips, 2009; Tang *et al.*, 2017), mitochondria (Aon, Cortassa, and O'Rourke, 2004; Zamponi *et al.*, 2018), etc. Also, quantum criticality and its relevance for the origin of life at the microscopic scale has been the subject of a recent proposal (Vattay *et al.*, 2015). Finally, let us mention that ecosystems as a whole have been studied, from a macroevolutionary viewpoint, as dynamical structures lying at the edge of instability (Bak and Sneppen, 1993; Adami, 1995; Sneppen *et al.*, 1995; Solé *et al.*, 1999; Solé, Alonso, and McKane, 2002; Suweis *et al.*, 2013; Biroli, Bunin, and Cammarota, 2017), illustrating that the ideas discussed here can be extended to larger scales in the hierarchy of biological complexity.

REFERENCES

Abbott, L., and C. van Vreeswijk, 1993, Phys. Rev. E **48**, 1483.

Acebrón, J. A., L. L. Bonilla, C. J. Pérez-Vicente, F. Ritort, and R. Spigler, 2005, Rev. Mod. Phys. **77**, 137.

Ackley, D., G. Hinton, and T. Sejnowski, 1985, Cogn. Sci. **9**, 147.

Adami, C., 1995, Phys. Lett. A **203**, 29.

Aitchison, L., N. Corradi, and P. Latham, 2016, PLoS Comput. Biol. **12**, e1005110.

Akaike, H., 1969, Ann. Inst. Stat. Math. **21**, 243.

Albert, R., 2004, in *Complex Networks* (Springer, New York), pp. 459–481.

Albert, R., and A.-L. Barabási, 2002, Rev. Mod. Phys. **74**, 47.

Albert, R., and H. Othmer, 2003, J. Theor. Biol. **223**, 1.

Aldana, M., 2003, Physica D (Amsterdam) **185**, 45.

Aldana, M., E. Balleza, S. Kauffman, and O. Resendiz, 2007, J. Theor. Biol. **245**, 433.

Allegrini, P., P. Paradisi, D. Menicucci, and A. Gemignani, 2010, Front. Physiol. **1**, 128.

Alon, U., 2003, Science **301**, 1866.

Alon, U., 2006, *An Introduction to Systems Biology: Design Principles of Biological Circuits* (CRC Press, London).

Alonso, L. M., A. Proekt, T. H. Schwartz, K. O. Pryor, G. A. Cecchi, and M. O. Magnasco, 2014, Front. Neural Circuits **8**, 20.

Alvarado, J., M. Sheinman, A. Sharma, F. C. MacKintosh, and G. H. Koenderink, 2013, Nat. Phys. **9**, 591.

Amari, S., 1972, IEEE Trans. Comput. **C-21**, 1197.

Amit, D., 1992, *Modeling Brain Function: The World of Attractor Neural Networks* (Cambridge University Press, Cambridge, England).

Amit, D., and N. Brunel, 1997, Cereb. Cortex **7**, 237.

Anderson, P. W., *et al.*, 1972, Science **177**, 393.

Aon, M. A., S. Cortassa, and B. O'Rourke, 2004, Proc. Natl. Acad. Sci. U.S.A. **101**, 4447.

Arenas, A., A. Díaz-Guilera, J. Kurths, Y. Moreno, and C. Zhou, 2008, Phys. Rep. **469**, 93.

Arieli, A., A. Sterkin, A. Grinvald, and A. Aertsen, 1996, Science **273**, 1868.

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[46]Error catastrophe has been considered for treatment of viral infections employing drugs that push the error rate beyond this threshold; see Summers and Litwin (2006) for a critical review.

Ashby, W., 1960, *Design for a Brain. The origin of adaptive behaviour* (Wiley, New York).

Attanasi, A., *et al.*, 2014a, Nat. Phys. **10**, 691.

Attanasi, A., *et al.*, 2014b, Phys. Rev. Lett. **113**, 238102.

Aurell, E., and M. Ekeberg, 2012, Phys. Rev. Lett. **108**, 090201.

Azaele, S., S. Suweis, J. Grilli, I. Volkov, J. R. Banavar, and A. Maritan, 2016, Rev. Mod. Phys. **88**, 035003.

Baek, S. K., S. Bernhardsson, and P. Minnhagen, 2011, New J. Phys. **13**, 043004.

Baglietto, G., E. V. Albano, and J. Candia, 2012, Interface Focus **2**, 708.

Bagnoli, F., F. Cecconi, A. Flammini, and A. Vespignani, 2003, Europhys. Lett. **63**, 512.

Bak, P., 1996, *How Nature Works: The Science of Self-Organized Criticality* (Copernicus, New York).

Bak, P., K. Chen, and C. Tang, 1990, Phys. Lett. A **147**, 297.

Bak, P., and D. R. Chialvo, 2001, Phys. Rev. E **63**, 031912.

Bak, P., and K. Sneppen, 1993, Phys. Rev. Lett. **71**, 4083.

Bak, P., and C. Tang, 1989, J. Geophys. Res. **94**, 15635.

Bak, P., C. Tang, and K. Wiesenfeld, 1987, Phys. Rev. Lett. **59**, 381.

Ballerini, M., *et al.*, 2008, Proc. Natl. Acad. Sci. U.S.A. **105**, 1232.

Balleza, E., E. R. Alvarez-Buylla, A. Chaos, S. Kauffman, I. Shmulevich, and M. Aldana, 2008, PLoS One **3**, e2456.

Banavar, J. R., T. J. Cooke, A. Rinaldo, and A. Maritan, 2014, Proc. Natl. Acad. Sci. U.S.A. **111**, 3332.

Banavar, J. R., A. Maritan, and A. Rinaldo, 1999, Nature (London) **399**, 130.

Banavar, J. R., A. Maritan, and I. Volkov, 2010, J. Phys. Condens. Matter **22**, 063101.

Banavar, J. R., M. E. Moses, J. H. Brown, J. Damuth, A. Rinaldo, R. M. Sibly, and A. Maritan, 2010, Proc. Natl. Acad. Sci. U.S.A. **107**, 15816.

Barabasi, A.-L., 2005, Nature (London) **435**, 207.

Barabási, A.-L., and R. Albert, 1999, Science **286**, 509.

Barnett, L., J. T. Lizier, M. Harré, A. K. Seth, and T. Bossomaier, 2013, Phys. Rev. Lett. **111**, 177203.

Barral, J., and A. D. Reyes, 2016, Nat. Neurosci. **19**, 1690.

Barrat, A., M. Barthelemy, and A. Vespignani, 2008, *Dynamical Processes on Complex Networks* (Cambridge University Press, Cambridge, England).

Bassingthwaighte, J. B., L. S. Liebovitch, and B. J. West, 1994, in *Fractal Physiology* (Springer, New York), pp. 11–44.

Beckmann, C. F., M. DeLuca, J. T. Devlin, and S. M. Smith, 2005, Phil. Trans. R. Soc. B **360**, 1001.

Bédard, C., H. Kröger, and A. Destexhe, 2006, Phys. Rev. Lett. **97**, 118102.

Beekman, M., D. J. Sumpter, and F. L. Ratnieks, 2001, Proc. Natl. Acad. Sci. U.S.A. **98**, 9703.

Beggs, J. M., 2008, Phil. Trans. R. Soc. A **366**, 329.

Beggs, J. M., and D. Plenz, 2003, J. Neurosci. **23**, 11167.

Beggs, J. M., and D. Plenz, 2004, J. Neurosci. **24**, 5216.

Bellay, T., A. Klaus, S. Seshadri, and D. Plenz, 2015, eLife **4**, e07224.

Benayoun, M., J. D. Cowan, W. Van Drongelen, and E. Wallace, 2010, PLoS Comput. Biol. **6**, e1000846.

Benedetto, D., E. Caglioti, and V. Loreto, 2002, Phys. Rev. Lett. **88**, 048702.

Benford, F., 1938, Proc. Am. Philos. Soc. **78**, 551.

Beni, G., 2004, in *International Workshop on Swarm Robotics* (Springer, New York), pp. 1–9.

Berdahl, A., C. J. Torney, C. C. Ioannou, J. J. Faria, and I. D. Couzin, 2013, Science **339**, 574.

Berg, H. C., 1993, *Random Walks in Biology* (Princeton University Press, Princeton, NJ).

Bertschinger, N., and T. Natschlager, 2004, Neural Comput. **16**, 1413.

Betzel, R. F., A. Griffa, A. Avena-Koenigsberger, J. Goñi, J.-P. Thiran, P. Hagmann, and O. Sporns, 2013, Network Sci. **1**, 353.

Bhattacharya, K., and T. Vicsek, 2014, J. R. Soc. Interface **11**, 20140674.

Bialek, W., 2012, *Biophysics: Searching for Principles* (Princeton University Press, Princeton, NJ).

Bialek, W., 2018, Rep. Prog. Phys. **81**, 012601.

Bialek, W., A. Cavagna, I. Giardina, T. Mora, O. Pohl, E. Silvestri, M. Viale, and A. M. Walczak, 2014, Proc. Natl. Acad. Sci. U.S.A. **111**, 7212.

Bialek, W., A. Cavagna, I. Giardina, T. Mora, E. Silvestri, M. Viale, and A. M. Walczak, 2012, Proc. Natl. Acad. Sci. U.S.A. **109**, 4786.

Bianconi, G., and M. Marsili, 2004, Phys. Rev. E **70**, 035105.

Bienenstock, E., and D. Lehmann, 1998, Adv. Complex Syst. **01**, 361.

Binder, K., 1981, Z. Phys. B **43**, 119.

Binney, J., N. Dowrick, A. Fisher, and M. Newman, 1993, *The Theory of Critical Phenomena* (Oxford University Press, Oxford).

Biroli, G., G. Bunin, and C. Cammarota, 2017, arXiv:1710.03606.

Biswal, B., F. Zerrin Yetkin, V. M. Haughton, and J. S. Hyde, 1995, Magn. Reson. Med. **34**, 537.

Blythe, R. A., and A. J. McKane, **2007**, J. Stat. Mech. 07, P07018 [http://stacks.iop.org/1742-5468/2007/i=07/a=P07018].

Boccaletti, S., V. Latora, Y. Moreno, M. Chavez, and D.-U. Hwang, 2006, Phys. Rep. **424**, 175.

Boedecker, J., O. Obst, J. T. Lizier, N. M. Mayer, and M. Asada, 2012, Theory Biosci. **131**, 205.

Bonabeau, E., M. Dorigo, and G. Theraulaz, 1999, *Swarm Intelligence: From Natural to Artificial Systems* (Oxford University Press, New York), p. 1.

Bonachela, J., S. de Franciscis, J. Torres, and M. A. Muñoz, **2010**, J. Stat. Mech. 02, P02015 [http://stacks.iop.org/1742-5468/2010/i=02/a=P02015].

Bonachela, J. A., and M. A. Muñoz, 2009, J. Stat. Mech. 09, P09009 [http://stacks.iop.org/1742-5468/2009/i=09/a=P09009].

Bornholdt, S., 2005, Science **310**, 449.

Bornholdt, S., 2008, J. R. Soc. Interface **5**, S85.

Bornholdt, S., and T. Rohlf, 2000, Phys. Rev. Lett. **84**, 6114.

Bosch, T., 2007, Dev. Biol. **303**, 421.

Bose, I., and M. Pal, 2017, J. Biosci. **42**, 683.

Breakspear, M., 2017, Nat. Neurosci. **20**, 340.

Brockmann, D., L. Hufnagel, and T. Geisel, 2006, Nature (London) **439**, 462.

Brown, P. O., and D. Botstein, 1999, Nat. Genet. **21**, 33.

Brunel, N., 2000, J. Comput. Neurosci. **8**, 183.

Brunel, N., and V. Hakim, 2008, Chaos **18**, 015113.

Buchanan, M., 2010, *Networks in Cell Biology* (Cambridge University Press, Cambridge, England).

Buhl, J., D. J. Sumpter, I. D. Couzin, J. J. Hale, E. Despland, E. Miller, and S. J. Simpson, 2006, Science **312**, 1402.

Burgos, J., and P. Moreno-Tovar, 1996, BioSystems **39**, 227.

Bushdid, C., M. O. Magnasco, L. B. Vosshall, and A. Keller, 2014, Science **343**, 1370.

Buzsaki, G., 2009, *Rhythms of the Brain* (Oxford University Press, New York).

Cabral, J., E. Hugues, O. Sporns, and G. Deco, 2011, NeuroImage **57**, 130.

Cafiero, R., A. Gabrielli, and M. A. Muñoz, 1998, Phys. Rev. E **57**, 5060.

Caldarelli, G., 2007, *Scale-free Networks: Complex Webs in Nature and Technology* (Oxford University Press, New York).

Camalet, S., T. Duke, F. Jülicher, and J. Prost, 2000, Proc. Natl. Acad. Sci. U.S.A. **97**, 3183.

Carlson, J. M., and J. Doyle, 2000, Phys. Rev. Lett. **84**, 2529.

Carpenter, G. A., and S. Grossberg, 2016, in *Encyclopedia of Machine Learning and Data Mining* (Springer, New York), pp. 1–17.

Cavagna, A., A. Cimarelli, I. Giardina, G. Parisi, R. Santagati, F. Stefanini, and M. Viale, 2010, Proc. Natl. Acad. Sci. U.S.A. **107**, 11865.

Cavagna, A., D. Conti, C. Creato, L. Del Castello, I. Giardina, T. S. Grigera, S. Melillo, L. Parisi, and M. Viale, 2017, Nat. Phys. **13**, 914.

Cavagna, A., I. Giardina, A. Orlandi, G. Parisi, A. Procaccini, M. Viale, and V. Zdravkovic, 2008, Animal Behaviour **76**, 217.

Chaikin, P. M., and T. C. Lubensky, 2000, *Principles of Condensed Matter Physics*, Vol. 1 (Cambridge University Press, Cambridge, England).

Chaté, H., F. Ginelli, G. Grégoire, F. Peruani, and F. Raynaud, 2008, Eur. Phys. J. B **64**, 451.

Chaté, H., F. Ginelli, G. Grégoire, and F. Raynaud, 2008, Phys. Rev. E **77**, 046113.

Chaté, H., and M. Muñoz, 2014, Physics **7**, 120.

Chen, X., X. Dong, A. Beer, H. Swinney, and H. Zhang, 2012, Phys. Rev. Lett. **108**, 148101.

Chialvo, D. R., 2004, Physica A (Amsterdam) **340**, 756.

Chialvo, D. R., 2006, Nat. Phys. **2**, 301.

Chialvo, D. R., 2010, Nat. Phys. **6**, 744.

Chialvo, D. R., and P. Bak, 1999, Neuroscience (N.Y.) **90**, 1137.

Chialvo, D. R., P. Balenzuela, and D. Fraiman, 2008, AIP Conf. Proc. **1028**, 28.

Choe, Y., M. O. Magnasco, and A. Hudspeth, 1998, Proc. Natl. Acad. Sci. U.S.A. **95**, 15321.

Chowdhury, S., J. Lloyd-Price, O.-P. Smolander, W. C. Baici, T. R. Hughes, O. Yli-Harja, G. Chua, and A. S. Ribeiro, 2010, BMC Syst. Biol. **4**, 143.

Christensen, K., Á. Corral, V. Frette, J. Feder, and T. Jøssang, 1996, Phys. Rev. Lett. **77**, 107.

Christensen, K., and N. Moloney, 2005, *Complexity and Criticality* (Imperial College Press, London).

Cicuta, P., 2013, in *Encyclopedia of Biophysics* (Springer, New York), pp. 387–390.

Clauset, A., C. R. Shalizi, and M. E. J. Newman, 2009, SIAM Rev. **51**, 661.

Cocchi, L., L. L. Gollo, A. Zalesky, and M. Breakspear, 2017, Prog. Neurobiol. **158**, 132.

Cocco, S., S. Leibler, and R. Monasson, 2009, Proc. Natl. Acad. Sci. U.S.A. **106**, 14058.

Cohen, J. E., M. Xu, and W. S. Schuster, 2012, Proc. Natl. Acad. Sci. U.S.A. **109**, 15829.

Coniglio, A., L. de Arcangelis, H. J. Herrmann, and N. Jan, 1989, Europhys. Lett. **8**, 315.

Corominas-Murtra, B., J. Goñi, R. V. Solé, and C. Rodríguez-Caso, 2013, Proc. Natl. Acad. Sci. U.S.A. **110**, 13316.

Corral, A., 2004, Phys. Rev. Lett. **92**, 108501.

Corral, A., C. J. Pérez, A. Díaz-Guilera, and A. Arenas, 1995, Phys. Rev. Lett. **74**, 118.

Couzin, I., 2007, Nature (London) **445**, 715.

Couzin, I. D., 2009, Trends Cognit. Sci. **13**, 36.

Couzin, I. D., C. C. Ioannou, G. Demirel, T. Gross, C. J. Torney, A. Hartnett, L. Conradt, S. A. Levin, and N. E. Leonard, 2011, Science **334**, 1578.

Couzin, I. D., and J. Krause, 2003, Adv. Study Behav. **32**, 1.

Couzin, I. D., J. Krause, N. R. Franks, and S. A. Levin, 2005, Nature (London) **433**, 513.

Cover, T. M., and J. Thomas, 1991, *Elements of Information Theory* (Wiley, New York).

Crick, F., 1970, Nature (London) **227**, 561.

Crotty, S., C. E. Cameron, and R. Andino, 2001, Proc. Natl. Acad. Sci. U.S.A. **98**, 6895.

Crutchfield, J. P., 2012, Nat. Phys. **8**, 17.

Crutchfield, J. P., and K. Young, 1988, in *Entropy, Complexity, and the Physics of Information*, edited by W. Zurek (Addison-Wesley, Reading).

Darabos, C., M. Giacobini, M. Tomassini, P. Provero, and F. Di Cunto, 2009, in *European Conference on Artificial Life* (Springer, New York), pp. 281–288.

Davies, P. C., L. Demetrius, and J. A. Tuszynski, 2011, Theor. Bio. Med. Modell. **8**, 30.

Dayan, P., and L. F. Abbott, 2006, *Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems* (MIT Press, Cambridge, MA).

de Andrade Costa, A., M. Copelli, and O. Kinouchi, **2015**, J. Stat. Mech. 06, P06004.

de Arcangelis, L., 2011, J. Phys. Conf. Ser. **297**, 012001.

de Arcangelis, L., 2012, Eur. Phys. J. Spec. Top. **205**, 243.

de Arcangelis, L., and H. J. Herrmann, 2010, Proc. Natl. Acad. Sci. U.S.A. **107**, 3977.

de Arcangelis, L., and H. J. Herrmann, 2012, Front. Physiol. **3**, 62.

de Arcangelis, L., F. Lombardi, and H. Herrmann, **2014**, J. Stat. Mech. 03, P03026.

de Arcangelis, L., C. Perrone-Capano, and H. J. Herrmann, 2006, Phys. Rev. Lett. **96**, 028107.

Deco, G., and V. K. Jirsa, 2012, J. Neurosci. **32**, 3366.

Deco, G., V. K. Jirsa, and A. R. McIntosh, 2011, Nat. Rev. Neurosci. **12**, 43.

Deco, G., V. K. Jirsa, and A. R. McIntosh, 2013, Trends Neurosci. **36**, 268.

Deco, G., A. Ponce-Alvarez, P. Hagmann, G. L. Romani, D. Mantini, and M. Corbetta, 2014, J. Neurosci. **34**, 7886.

Deco, G., A. Ponce-Alvarez, D. Mantini, G. L. Romani, P. Hagmann, and M. Corbetta, 2013, J. Neurosci. **33**, 11239.

De Gennes, P.-G., 1979, *Scaling Concepts in Polymer Physics* (Cornell University Press, Ithaca).

De Jong, H., 2002, J. Comput. Biol. **9**, 67.

Delamotte, B., 2012, in *Renormalization Group and Effective Field Theory Approaches to Many-Body Systems* (Springer, New York), pp. 49–132.

De Palo, G., D. Yi, and R. G. Endres, 2017, PLoS Biol. **15**, e1002602.

Derrida, B., and Y. Pomeau, 1986, Europhys. Lett. **1**, 45.

Destexhe, A., 2009, J. Comput. Neurosci. **27**, 493.

De Vincenzo, I., I. Giannoccaro, G. Carbone, and P. Grigolini, 2017, Phys. Rev. E **96**, 022309.

Dhar, D., 1999, Physica A (Amsterdam) **263**, 4.

Dickman, R., M. A. Muñoz, A. Vespignani, and S. Zapperi, 2000, Braz. J. Phys. **30**, 27.

Diez, I., P. Bonifazi, I. Escudero, B. Mateos, M. A. Muñoz, S. Stramaglia, and J. M. Cortes, 2015, Sci. Rep. **5**, 10532.

di Santo, S., R. Burioni, A. Vezzani, and M. A. Muñoz, 2016, Phys. Rev. Lett. **116**, 240601.

di Santo, S., P. Villegas, R. Burioni, and M. A. Muñoz, 2017, Phys. Rev. E **95**, 032115.

di Santo, S., P. Villegas, R. Burioni, and M. A. Muñoz, 2018a, Proc. Natl. Acad. Sci. U.S.A. [http://www.pnas.org/content/early/2018/01/26/1712989115]

di Santo, S., P. Villegas, R. Burioni, and M. A. Muñoz, 2018b, arXiv:1803.07858.

Dornic, I., H. Chaté, J. Chave, and H. Hinrichsen, 2001, Phys. Rev. Lett. **87**, 045701.

Dorogovtsev, S. N., A. V. Goltsev, and J. F. Mendes, 2008, Rev. Mod. Phys. **80**, 1275.

Dorogovtsev, S. N., and J. F. Mendes, 2002, Adv. Phys. **51**, 1079.

Drake, J. W., and J. J. Holland, 1999, Proc. Natl. Acad. Sci. U.S.A. **96**, 13910.

Drossel, B., 2008, in *Reviews of Nonlinear Dynamics and Complexity*, Vol. 1, edited by H. G. Schuster (Wiley, New York), Chap. 3, pp. 69–110.

Drossel, B., and F. Greil, 2009, Phys. Rev. E **80**, 026102.

Drossel, B., and F. Schwabl, 1992, Phys. Rev. Lett. **69**, 1629.

Droste, F., A.-L. Do, and T. Gross, 2013, J. R. Soc. Interface **10**, 20120558.

Duke, T., and F. Jülicher, 2003, Phys. Rev. Lett. **90**, 158101.

Dyson, L., C. A. Yates, J. Buhl, and A. J. McKane, 2015, Phys. Rev. E **92**, 052708.

Effenberger, F., J. Jost, and A. Levina, 2015, PLoS Comput. Biol. **11**, e1004420.

Eguíluz, V. M., M. Ospeck, Y. Choe, A. Hudspeth, and M. O. Magnasco, 2000, Phys. Rev. Lett. **84**, 5232.

Ehrig, J., E. P. Petrov, and P. Schwille, 2011, Biophys. J. **100**, 80.

Eigen, M., 2002, Proc. Natl. Acad. Sci. U.S.A. **99**, 13374.

Eigen, M., J. McCaskill, and P. Schuster, 1989, *Advances in Chemical Physics* (Wiley Online Library, Hoboken, NJ), Vol. 75, p. 149.

Eigen, M., and P. Schuster, 1979, *The hypercycle: A principle of self-organization* (Springer-Verlag, Berlin/Heidelberg).

Erez, A., T. A. Byrd, R. M. Vogel, G. Altan-Bonnet, and A. Mugler, 2017, arXiv:1703.04194.

Erskine, A., and J. M. Herrmann, 2014, arXiv:1402.6888.

Espinosa-Soto, C., P. Padilla-Longoria, and E. R. Alvarez-Buylla, 2004, Plant Cell **16**, 2923.

Expert, P., R. Lambiotte, D. R. Chialvo, K. Christensen, H. J. Jensen, D. J. Sharp, and F. Turkheimer, 2011, J. R. Soc. Interface **8**, 472.

Eytan, D., and S. Marom, 2006, J. Neurosci. **26**, 8465.

Feinerman, O., and A. Korman, 2017, J. Exp. Biol. **220**, 73.

Filkov, V., 2005, *Handbook of Computational Molecular Biology* (Chapman & Hall, CRC Press), p. 27.

Fisher, M. E., 1974, Rev. Mod. Phys. **46**, 597.

Font-Clos, F., G. Pruessner, N. R. Moloney, and A. Deluca, 2015, New J. Phys. **17**, 043066.

Forgacs, G., S. A. Newman, S. P. Obukhov, and D. E. Birk, 1991, Phys. Rev. Lett. **67**, 2399.

Fortrat, J.-O., and C. Gharib, 2016, Front. Phys. **7**, 113.

Fox, M. D., and M. E. Raichle, 2007, Nat. Rev. Neurosci. **8**, 700.

Fraiman, D., P. Balenzuela, J. Jennifer, and D. R. Chialvo, 2009, Phys. Rev. E **79**, 061922.

Frauenfelder, H., 2014, Phys. Biol. **11**, 053004.

Freeman, W. J., 2013, in *Chaos, CNN, Memristors and Beyond: A Festschrift for L. Chua*, Vol. 1, edited by A. Adamatzky and G. Chen (World Scientific Publishing Co., Singapore), pp. 271–284.

Freeman, W. J., and M. D. Holmes, 2005, Neural Netw. **18**, 497.

Freeman, W. J., M. D. Holmes, B. C. Burke, and S. Vanhatalo, 2003, Clin. Neurophysiol. **114**, 1053.

Frette, V., K. Christensen, A. Malthe-Sørenssen, J. Feder, T. Jøssang, and P. Meakin, 1996, Nature (London) **379**, 49.

Friedman, N., S. Ito, B. A. W. Brinkman, M. Shimono, R. E. L. DeVille, K. A. Dahmen, J. M. Beggs, and T. C. Butler, 2012, Phys. Rev. Lett. **108**, 208102.

Friston, K., M. Breakspear, and G. Deco, 2012, Front. Comput. Neurosci. **6**, 44.

Furusawa, C., and K. Kaneko, 2003, Phys. Rev. Lett. **90**, 088102.

Furusawa, C., and K. Kaneko, 2012a, Phys. Rev. Lett. **108**, 208103.

Furusawa, C., and K. Kaneko, 2012b, Science **338**, 215.

Gal, A., and S. Marom, 2013, Phys. Rev. E **88**, 062717.

Gallotti, R., and D. R. Chialvo, 2017, arXiv:1707.07135.

Gama-Castro, S., *et al.*, 2015, Nucleic Acids Res. **44**, D133.

Gamba, A., M. Nicodemi, J. Soriano, and A. Ott, 2012, Phys. Rev. Lett. **108**, 158103.

Garcia-Ojalvo, J., 2011, Contemp. Phys. **52**, 439.

Garcia-Ojalvo, J., and A. M. Arias, 2012, Current opinion in genetics & development **22**, 619.

Garcia-Ojalvo, J., M. B. Elowitz, and S. H. Strogatz, 2004, Proc. Natl. Acad. Sci. U.S.A. **101**, 10955.

Gautam, S. H., T. T. Hoang, K. McClanahan, S. K. Grady, and W. L. Shew, 2015, PLoS Comput. Biol. **11**, e1004576.

Gelblum, A., I. Pinkoviezky, E. Fonio, A. Ghosh, N. Gov, and O. Feinerman, 2015, Nat. Commun. **6**, 7729.

Gell-Mann, M., 1994, *Complexity: Metaphors, Models, and Reality*, Santa Fe Institute Studies in the Sciences of Complexity, No. 19 (Addison-Wesley, Reading, MA), pp. 17–45.

Gershenson, C., 2012, Theory Biosci. **131**, 181.

Gerstein, G. L., and B. Mandelbrot, 1964, Biophys. J. **4**, 41.

Ghosh, A., Y. Rho, A. R. McIntosh, R. Kötter, and V. K. Jirsa, 2008, PLoS Comput. Biol. **4**, e1000196.

Ginelli, F., 2016, Eur. Phys. J. Spec. Top. **225**, 2099.

Ginelli, F., F. Peruani, M.-H. Pillot, H. Chaté, G. Theraulaz, and R. Bon, 2015, Proc. Natl. Acad. Sci. U.S.A. **112**, 12729.

Giometto, A., M. Formentin, A. Rinaldo, J. E. Cohen, and A. Maritan, 2015, Proc. Natl. Acad. Sci. U.S.A. **112**, 7755.

Gireesh, E. D., and D. Plenz, 2008, Proc. Natl. Acad. Sci. U.S.A. **105**, 7576.

Gisiger, T., 2001, Biol. Rev. Camb. Philos. Soc. **76**, 161.

Gold, T., 1948, Proc. R. Soc. B **135**, 492.

Goldberg, D. E., and J. H. Holland, 1988, Mach. Learn. **3**, 95.

Goldberger, A. L., 1992, IEEE Eng. Med. Biol. Mag. **11**, 47.

Goldberger, A. L., L. A. Amaral, J. M. Hausdorff, P. C. Ivanov, C.-K. Peng, and H. E. Stanley, 2002, Proc. Natl. Acad. Sci. U.S.A. **99**, 2466.

Goldenfeld, N., and C. Woese, 2011, Annu. Rev. Condens. Matter Phys. **2**, 375.

Gollo, L., O. Kinouchi, and M. Copelli, 2013, Sci. Rep. **3**, 3222.

Gomez, F., T. Lorimer, and R. Stoop, 2015, arXiv:1510.03241.

Gómez, V., A. Kaltenbrunner, V. López, and H. J. Kappen, 2009, *Advances in neural information processing systems*, pp. 513–520.

Goodell, M. A., H. Nguyen, and N. Shroyer, 2015, Nat. Rev. Mol. Cell Biol. **16**, 299.

Goudarzi, A., C. Teuscher, N. Gulbahce, and T. Rohlf, 2012, Phys. Rev. Lett. **108**, 128702.

Grassberger, P., 1995, J. Stat. Phys. **79**, 13.

Grégoire, G., and H. Chaté, 2004, Phys. Rev. Lett. **92**, 025702.

Greicius, M. D., B. Krasnow, A. L. Reiss, and V. Menon, 2003, Proc. Natl. Acad. Sci. U.S.A. **100**, 253.

Grinstein, G., 1991, J. Appl. Phys. **69**, 5441.

Gros, C., 2008, *Complex and Adaptive Dynamical Systems: A Primer* (Springer, New York).

Gross, T., and B. Blasius, 2008, J. R. Soc. Interface **5**, 259.

Grossberg, S., 1982, in *A Portrait of Twenty-five Years* (Springer, New York), pp. 257–276.

Hagmann, P., L. Cammoun, X. Gigandet, R. Meuli, C. J. Honey, V. J. Wedeen, and O. Sporns, 2008, PLoS Biol. **6**, e159.

Hahn, G., T. Petermann, M. N. Havenith, S. Yu, W. Singer, D. Plenz, and D. Nikolić, 2010, J. Neurophysiol. **104**, 3312.

Hahn, G., A. Ponce-Alvarez, C. Monier, G. Benvenuti, A. Kumar, F. Chavane, G. Deco, and Y. Frégnac, 2017, PLoS Comput. Biol. **13**, e1005543.

Haimovici, A., and M. Marsili, **2015**, J. Stat. Mech. 10, P10013.

Haimovici, A., E. Tagliazucchi, P. Balenzuela, and D. R. Chialvo, 2013, Phys. Rev. Lett. **110**, 178101.

Haken, H., 1977, Phys. Bull. **28**, 412.

Haken, H., 2013, *Principles of Brain Functioning: A Synergetic Approach to Brain Activity, Behavior and Cognition*, Springer Science & Business Media, Vol. 67.

Haken, H., J. S. Kelso, and H. Bunz, 1985, Biol. Cybern. **51**, 347.

Haldeman, C., and J. M. Beggs, 2005, Phys. Rev. Lett. **94**, 058101.

Halley, J. D., F. R. Burden, and D. A. Winkler, 2009, Stem Cell Res. **2**, 165.

Halley, J. D., and D. A. Winkler, 2008, BioSystems **92**, 148.

Hanel, R., M. Pöchacker, and S. Thurner, 2010, Phil. Trans. R. Soc. A **368**, 5583.

Harris, T. E., 2002, *The Theory of Branching Processes* (Courier Corporation, North Chelmsford, MA).

Hart, G. R., and A. L. Ferguson, 2015, Phys. Rev. E **91**, 032705.

Hartwell, L. H., J. J. Hopfield, S. Leibler, and A. W. Murray, 1999, Nature (London) **402**, C47.

He, B. J., 2011, J. Neurosci. **31**, 13786.

He, B. J., 2014, Trends Cognit. Sci. **18**, 480.

Henkel, M., H. Hinrichsen, and S. Lübeck, 2008, *Non-equilibrium Phase Transitions: Absorbing Phase Transitions*, Theor. and Math. Phys. (Springer London, Berlin).

Hernandez-Urbina, V., and J. M. Herrmann, 2017, Front. Phys. **4**, 54.

Hertz, J., A. Krogh, and R. G. Palmer, 1991, *Introduction to the Theory of Neural Computation*, Vol. 1 (Basic Books, New York).

Herz, A. V., and J. J. Hopfield, 1995, Phys. Rev. Lett. **75**, 1222.

Hesse, J., and T. Gross, 2014, Front. Syst. Neurosci. **8**.

Hidalgo, J., J. Grilli, S. Suweis, A. Maritan, and M. A. Muñoz, **2016**, J. Stat. Mech. 3, 033203.

Hidalgo, J., J. Grilli, S. Suweis, M. A. Muñoz, J. R. Banavar, and A. Maritan, 2014, Proc. Natl. Acad. Sci. U.S.A. **111**, 10095.

Hidalgo, J., L. Seoane, J. Cortés, and M. Muñoz, 2012, PLoS One **7**, e40710.

Hinrichsen, H., 2000, Adv. Phys. **49**, 815.

Hinrichsen, H., and E. Domany, 1997, Phys. Rev. E **56**, 94.

Hobbs, J. P., J. L. Smith, and J. M. Beggs, 2010, J. Clin. Neurophysiol. **27**, 380.

Hohenberg, P. C., and B. I. Halperin, 1977, Rev. Mod. Phys. **49**, 435.

Holcman, D., and M. Tsodyks, 2006, PLoS Comput. Biol. **2**, e23.

Honerkamp-Smith, A. R., P. Cicuta, M. D. Collins, S. L. Veatch, M. den Nijs, M. Schick, and S. L. Keller, 2008, Biophys. J. **95**, 236.

Hopfield, J., 1994, J. Theor. Biol. **171**, 53.

Hopfield, J. J., 1982, Proc. Natl. Acad. Sci. U.S.A. **79**, 2554.

Hu, K., J. H. Meijer, S. A. Shea, H. Tjebbe vanderLeest, B. Pittman-Polletta, T. Houben, F. van Oosterhout, T. Deboer, and F. A. Scheer, 2012, PLoS One **7**, e48927.

Huang, S., G. Eichler, Y. Bar-Yam, and D. E. Ingber, 2005, Phys. Rev. Lett. **94**, 128701.

Hubbell, S. P., 2001, *The Unified Neutral Theory of Biodiversity and Biogeography (MPB-32)*, Vol. 32 (Princeton University Press, Princeton, NJ).

Hudspeth, A., 2014, Nat. Rev. Neurosci. **15**, 600.

Hudspeth, A., F. Jülicher, and P. Martin, 2010, J. Neurophysiol. **104**, 1219.

Hughes, T. R., *et al.*, 2000, Cell **102**, 109.

Hyman, A. A., and K. Simons, 2012, Science **337**, 1047.

Iliopoulos, D., A. Hintze, and C. Adami, 2010, PLoS Comput. Biol. **6**, e1000948.

Ivanov, P., 2007, IEEE Eng. Med. Biol. Mag. **26**, 33.

Ivanov, P. C., L. A. N. Amaral, A. L. Goldberger, S. Havlin, M. G. Rosenblum, Z. R. Struzik, and H. E. Stanley, 1999, Nature (London) **399**, 461.

Izhikevich, E. M., 2004, IEEE Trans. Neural Networks **15**, 1063.

Izhikevich, E. M., 2007, *Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting* (MIT Press, Cambridge, MA).

Jaeger, H., 2007, Scholarpedia **2**, 2330.

Janićević, S., L. Laurson, K. J. Måløy, S. Santucci, and M. J. Alava, 2016, Phys. Rev. Lett. **117**, 230601.

Jensen, H. J., 1998, *Self-organized Criticality: Emergent Complex Behavior in Physical and Biological Systems* (Cambridge University Press, Cambridge, England).

Kaiser, M., 2011, NeuroImage **57**, 892.

Kamenev, A., 2011, *Field Theory of Non-equilibrium Systems* (Cambridge University Press, Cambridge, England).

Kandel, E., J. Schwartz, and T. Jessel, 2000, *Principles of Neural Science* (McGraw-Hill, New York).

Kaneko, K., 2006, *Life: An Introduction to Complex Systems Biology* (Springer, New York).

Kaneko, K., 2012, J. Stat. Phys. **148**, 687.

Kaneko, K., and T. Ikegami, 1992, Physica D (Amsterdam) **56**, 406.

Kauffman, S., 1969, J. Theor. Biol. **22**, 437.

Kauffman, S., 1996, *At Home in the Universe: The Search for the Laws of Self-Organization and Complexity* (Oxford University Press, New York).

Kauffman, S., C. Peterson, B. Samuelsson, and C. Troein, 2003, Proc. Natl. Acad. Sci. U.S.A. **100**, 14796.

Kauffman, S. A., 1993, *The Origins of Order: Self Organization and Selection in Evolution* (Oxford University Press, New York).

Keenan, J. P., A. L. Krill, S. M. Platek, and T. K. Shackelford, 2007, *Evolutionary Cognitive Neuroscience* (MIT Press, Cambridge, MA), p. 579.

Kelley, D. H., and N. T. Ouellette, 2013, Sci. Rep. **3**, 1073.

Kello, C. T., G. D. Brown, R. Ferrer-i Cancho, J. G. Holden, K. Linkenkaer-Hansen, T. Rhodes, and G. C. Van Orden, 2010, Trends Cognit. Sci. **14**, 223.

Kelso, J., J. Scholz, and G. Schöner, 1986, Phys. Lett. A **118**, 279.

Kelso, J. A., 1984, Am. J. Physiol., Regul. Integr. Comp. Physiol. **246**, R1000.

Kern, A., and R. Stoop, 2003, Phys. Rev. Lett. **91**, 128101.

Kimura, M., 1984, *The Neutral Theory of Molecular Evolution* (Cambridge University Press, Cambridge, England).

Kinouchi, O., L. Brochini, A. A. Costa, J. G. F. Campos, and M. Copelli, 2018, arXiv:1803.05537.

Kinouchi, O., and M. Copelli, 2006, Nat. Phys. **2**, 348.

Kitano, H., *et al.*, 2001, *Foundations of Systems Biology* (MIT Press, Cambridge, MA).

Kiyono, K., Z. Struzik, N. Aoyagi, S. Sakata, J. Hayano, and Y. Yamamoto, 2004, Phys. Rev. Lett. **93**, 178103.

Kiyono, K., Z. R. Struzik, N. Aoyagi, F. Togo, and Y. Yamamoto, 2005, Phys. Rev. Lett. **95**, 058101.

Kleiber, M., 1932, Hilgardia **6**, 315.

Koonin, E. V., 2011, *The Logic of Chance: The Nature and Origin of Biological Evolution* (FT Press, Upper Saddle River, NJ).

Koonin, E. V., Y. I. Wolf, and G. P. Karev, 2006, *Power Laws, Scale-Free Networks and Genome Biology* (Springer, New York).

Krause, J., and G. D. Ruxton, 2002, *Living in Groups* (Oxford University Press, New York).

Krawitz, P., and I. Shmulevich, 2007, Phys. Rev. Lett. **98**, 158701.

Krotov, D., J. O. Dubuis, T. Gregor, and W. Bialek, 2014, Proc. Natl. Acad. Sci. U.S.A. **111**, 3683.

Ktitarev, D., S. Lübeck, P. Grassberger, and V. Priezzhev, 2000, Phys. Rev. E **61**, 81.

Kuehn, C., 2012, Phys. Rev. E **85**, 026103.

Kuramoto, Y., 1975, Lect. Notes Phys. **39**, 420.

Kussell, E., and S. Leibler, 2005, Science **309**, 2075.

Langton, C., 1990, Physica D (Amsterdam) **42**, 12.

Laurson, L., X. Illa, and M. J. Alava, **2009**, J. Stat. Mech. 01, P01019 [http://stacks.iop.org/1742-5468/2009/i=01/a=P01019].

LeCun, Y., Y. Bengio, and G. Hinton, 2015, Nature (London) **521**, 436.

Lee, C. F., C. P. Brangwynne, J. Gharakhani, A. A. Hyman, and F. Jülicher, 2013, Phys. Rev. Lett. **111**, 088101.

Legenstein, R., and W. Maass, 2007, Neural Netw. **20**, 323.

Legenstein, T., 2005, in *Advances in Neural Information Processing Systems 17: Proceedings of the 2004 Conference*, Vol. 17 (MIT Press, Cambridge, MA), p. 145.

Lesk, A., 2017, *Introduction to Genomics* (Oxford University Press, New York).

Levina, A., J. M. Herrmann, and T. Geisel, 2007, Nat. Phys. **3**, 857.

Levina, A., J. M. Herrmann, and T. Geisel, 2009, Phys. Rev. Lett. **102**, 118110.

Li, F., T. Long, Y. Lu, Q. Ouyang, and C. Tang, 2004, Proc. Natl. Acad. Sci. U.S.A. **101**, 4781.

Li, L., H. Peng, J. Kurths, Y. Yang, and H. J. Schellnhuber, 2014, Proc. Natl. Acad. Sci. U.S.A. **111**, 8392.

Li, W., N. H. Packard, and C. G. Langton, 1990, Physica D (Amsterdam) **45**, 77.

Li, Y. C., and D. Retzloff, 2006, Math. Biosci. **203**, 137.

Liggett, T., 2004, *Interacting Particle Systems*, Classics in Mathematics (Springer, New York).

Lin, H. W., and M. Tegmark, 2017, Entropy **19**, 299.

Liu, M., and K. E. Bassler, 2006, Phys. Rev. E **74**, 041910.

Lizier, J. T., M. Prokopenko, and A. Y. Zomaya, 2008a, "The Information Dynamics of Phase Transitions in Random Boolean Networks," in *Proceedings of the Eleventh International Conference on the Simulation and Synthesis of Living Systems (ALife XI)* (MIT Press, Cambridge, MA), pp. 374–381.

Lizier, J. T., M. Prokopenko, and A. Y. Zomaya, 2008b, Phys. Rev. E **77**, 026110.

Loengarov, A., and V. Tereshko, 2008, Artif. Life **14**, 111.

Lopez-Garcia, C., A. M. Klein, B. D. Simons, and D. J. Winton, 2010, Science **330**, 822.

Losa, G. A., 1995, Pathologica **87**, 310 [https://europepmc.org/abstract/med/8570291].

Lukoševičius, M., H. Jaeger, and B. Schrauwen, 2012, Künstliche Intelligenz **26**, 365.

Maass, W., T. Natschlager, and H. Markram, 2002, Neural Comput. **14**, 2531.

MacArthur, B. D., R. J. Sánchez-García, and A. Maayan, 2010, Phys. Rev. Lett. **104**, 168701.

Magnasco, M. O., 2003, Phys. Rev. Lett. **90**, 058101.

Magnasco, M. O., O. Piro, and G. A. Cecchi, 2009, Phys. Rev. Lett. **102**, 258102.

Mandelbrot, B., 2002, *Gaussian Self-affinity and Fractals: Globality, the Earth, 1/f Noise, and R/S*, Vol. 8 (Springer Science & Business Media, Berlin).

Mandelbrot, B. B., 1983, *The Fractal Geometry of Nature*, Vol. 173 (MacMillan, London).

Manna, S., 1991, J. Phys. A **24**, L363.

Marković, D., and C. Gros, 2014, Phys. Rep. **536**, 41.

Markram, H., 2006, Nat. Rev. Neurosci. **7**, 153.

Markram, H., and M. Tsodyks, 1996, Nature (London) **382**, 807.

Markram, H., *et al.*, 2015, Cell **163**, 456.

Marre, O., D. Amodei, N. Deshmukh, K. Sadeghi, F. Soo, T. E. Holy, and M. J. Berry, 2012, J. Neurosci. **32**, 14859.

Marro, J., and R. Dickman, 1999, *Nonequilibrium Phase Transition in Lattice Models* (Cambridge University Press, Cambridge, England).

Marsili, M., I. Mastromatteo, and Y. Roudi, **2013**, J. Stat. Mech. 09, P09003.

Marsili, M., and Y.-C. Zhang, 1998, Phys. Rev. Lett. **80**, 2741.

Martin, P., A. Hudspeth, and F. Jülicher, 2001, Proc. Natl. Acad. Sci. U.S.A. **98**, 14380.

Martinello, M., J. Hidalgo, A. Maritan, S. di Santo, D. Plenz, and M. A. Muñoz, 2017, Phys. Rev. X **7**, 041071.

Massobrio, P., L. de Arcangelis, V. Pasquale, H. J. Jensen, and D. Plenz, 2015, Front. Syst. Neurosci. **9**, 4.

Mastromatteo, I., and M. Marsili, **2011**, J. Stat. Mech. 10, P10012.

Mattia, M., and M. V. Sanchez-Vives, 2012, Cognitive Neurodynamics **6**, 239.

Mazzoni, A., F. D. Broccard, E. Garcia-Perez, P. Bonifazi, M. E. Ruaro, and V. Torre, 2007, PLoS One **2**, e439.

Méhes, E., and T. Vicsek, 2014, Integr. Biol. **6**, 831.

Mehta, P., and D. J. Schwab, 2014, arXiv:1410.3831.

Meisel, C., and T. Gross, 2009, Phys. Rev. E **80**, 061917.

Meisel, C., E. Olbrich, O. Shriki, and P. Achermann, 2013, J. Neurosci. **33**, 17363.

Meisel, C., A. Storch, S. Hallmeyer-Elgner, E. Bullmore, and T. Gross, 2012, PLoS Comput. Biol. **8**, e1002312.

Meister, M., R. Wong, D. A. Baylor, and C. J. Shatz, 1991, Science **252**, 939.

Mejias, J. F., H. J. Kappen, and J. J. Torres, 2010, PLoS One **5**, e13651.

Melanie, M., J. P. Crutchfield, and P. T. Hraber, 1993, arXiv:adap-org/9306003.

Meunier, D., R. Lambiotte, and E. T. Bullmore, 2010, Front. Neurosci. **4**, 200.

Millman, D., S. Mihalas, A. Kirkwood, and E. Niebur, 2010, Nat. Phys. **6**, 801.

Ming, L., and P. Vitányi, 1990, Algorithms and Complexity, 187.

Mitzenmacher, M., 2004, Internet Math. **1**, 226.

Mora, T., and W. Bialek, 2011, J. Stat. Phys. **144**, 268.

Mora, T., S. Deny, and O. Marre, 2015, Phys. Rev. Lett. **114**, 078105.

Mora, T., A. Walczak, W. Bialek, and C. Callan, Jr., 2010, Proc. Natl. Acad. Sci. U.S.A. **107**, 5405.

Mora, T., A. M. Walczak, L. Del Castello, F. Ginelli, S. Melillo, L. Parisi, M. Viale, A. Cavagna, and I. Giardina, 2016, Nat. Phys. **12**, 1153.

Moreau, L., and E. Sontag, 2003, Phys. Rev. E **68**, 020901.

Moreira, A. G., and R. Dickman, 1996, Phys. Rev. E **54**, R3090.

Moretti, P., and M. A. Muñoz, 2013, Nat. Commun. **4**, 2521

Muñoz, M., R. Juhász, C. Castellano, and G. Ódor, 2010, Phys. Rev. Lett. **105**, 128701.

Murphy, B. K., and K. D. Miller, 2009, Neuron **61**, 635.

Nadell, C. D., V. Bucci, K. Drescher, S. A. Levin, B. L. Bassler, and J. B. Xavier, 2013, Proc. R. Soc. B **280**, 20122770.

Newman, M. E. J., 2003, SIAM Rev. **45**, 167.

Newman, M. E. J., 2005, Contemp. Phys. **46**, 323.

Newman, M. E. J., 2010, *Networks: An Introduction* (Oxford University Press, New York).

Newman, S. A., G. Forgacs, B. Hinner, C. W. Maier, and E. Sackmann, 2004, Phys. Biol. **1**, 100.

Nonnenmacher, M., C. Behrens, P. Berens, M. Bethge, and J. H. Macke, 2017, PLoS Comput. Biol. **13**, e1005718.

Novikov, E., A. Novikov, D. Shannahoff-Khalsa, B. Schwartz, and J. Wright, 1997, Phys. Rev. E **56**, R2387.

Nowak, M. A., 2006, *Evolutionary Dynamics* (Harvard University Press, Cambridge, MA).

Nykter, M., N. D. Price, M. Aldana, S. A. Ramsey, S. A. Kauffman, L. E. Hood, O. Yli-Harja, and I. Shmulevich, 2008, Proc. Natl. Acad. Sci. U.S.A. **105**, 1897.

Nykter, M., N. D. Price, A. Larjo, T. Aho, S. A. Kauffman, O. Yli-Harja, and I. Shmulevich, 2008, Phys. Rev. Lett. **100**, 058702.

Ódor, G., 2008, *Universality in Nonequilibrium Lattice Systems: Theoretical Foundations* (World Scientific, Singapore).

Olami, Z., H. J. S. Feder, and K. Christensen, 1992, Phys. Rev. Lett. **68**, 1244.

Oprisa, D., and P. Toth, 2017a, arXiv:1702.08039.

Oprisa, D., and P. Toth, 2017b, arXiv:1705.11023.

Ospeck, M., V. M. Eguíluz, and M. O. Magnasco, 2001, Biophys. J. **80**, 2597.

Packard, N. H., 1988, *Adaptation Toward the Edge of Chaos* (University of Illinois at Urbana–Champaign, Center for Complex Systems Research, Champaign-Urbana).

Pal, M., S. Ghosh, and I. Bose, 2014, Phys. Biol. **12**, 016001.

Palmigiano, A., T. Geisel, F. Wolf, and D. Battaglia, 2017, Nat. Neurosci. **20**, 1014.

Palva, J. M., A. Zhigalov, J. Hirvonen, O. Korhonen, K. Linkenkaer-Hansen, and S. Palva, 2013, Proc. Natl. Acad. Sci. U.S.A. **110**, 3585.

Parfitt, D.-E., and M. M. Shen, 2014, Phil. Trans. R. Soc. B **369**, 20130542.

Parga, N., and L. F. Abbott, 2007, Front. Neurosci. **1**, 57.

Parisi, G., 1993, Phys. World **6**, 42.

Pasquale, V., P. Massobrio, L. Bologna, M. Chiappalone, and S. Martinoia, 2008, Neuroscience (N.Y.) **153**, 1354.

Pastor-Satorras, R., C. Castellano, P. Van Mieghem, and A. Vespignani, 2015, Rev. Mod. Phys. **87**, 925.

Pearlmutter, B. A., and C. J. Houghton, 2009, Neural Comput. **21**, 1622.

Perotti, J. I., O. V. Billoni, F. A. Tamarit, D. R. Chialvo, and S. A. Cannas, 2009, Phys. Rev. Lett. **103**, 108701.

Peruani, F., J. Starruß, V. Jakovljevic, L. Søgaard-Andersen, A. Deutsch, and M. Bär, 2012, Phys. Rev. Lett. **108**, 098102.

Petermann, T., T. A. Thiagarajan, M. Lebedev, M. Nicolelis, D. R. Chialvo, and D. Plenz, 2009, Proc. Natl. Acad. Sci. U.S.A. **106**, 15921.

Phillips, J., 2009, Proc. Natl. Acad. Sci. U.S.A. **106**, 3107.

Pietronero, L., E. Tosatti, V. Tosatti, and A. Vespignani, 2001, Physica A (Amsterdam) **293**, 297.

Pikovsky, A., M. Rosenblum, and J. Kurths, 2003, *Synchronization: A Universal Concept in Nonlinear Sciences*, Vol. 12 (Cambridge University Press, Cambridge, England).

Pinto, O. A., and M. A. Munoz, 2011, PLoS One **6**, e21946.

Plenz, D., 2013, Physics **6**, 47.

Plenz, D., and E. Niebur, 2014, *Criticality in Neural Systems* (John Wiley & Sons, New York).

Plenz, D., and T. C. Thiagarajan, 2007, Trends Neurosci. **30**, 101.

Poblanno-Balp, R., and C. Gershenson, 2011, Artif. Life **17**, 331.

Poil, S.-S., R. Hardstone, H. D. Mansvelder, and K. Linkenkaer-Hansen, 2012, J. Neurosci. **32**, 9817.

Poland, D., and H. A. Scheraga, 1970, *Theory of Helix-coil Transitions in Biopolymers* (Academic Press, New York).

Pollack, G. H., and W.-C. Chin, 2008, *Phase Transitions in Cell Biology* (Springer, New York).

Priesemann, V., M. H. Munk, and M. Wibral, 2009, BMC Neurosci. **10**, 40.

Priesemann, V., M. Valderrama, M. Wibral, and M. Le Van Quyen, 2013, PLoS Comput. Biol. **9**, e1002985.

Priesemann, V., M. Wibral, M. Valderrama, R. Pröpper, M. Le Van Quyen, T. Geisel, J. Triesch, D. Nikolić, and M. H. Munk, 2014, Front. Syst. Neurosci. **8**, 00108.

Proekt, A., J. Banavar, A. Maritan, and D. Pfaff, 2012, Proc. Natl. Acad. Sci. U.S.A. **109**, 10564.

Prokopenko, M., 2013, in *ALIFE* (MIT Press, Cambridge, MA), pp. 140–144.

Pruessner, G., 2012, *Self-organised Criticality: Theory, Models and Characterisation* (Cambridge University Press, Cambridge, England).

Puckett, J. G., and N. T. Ouellette, 2014, J. R. Soc. Interface **11**, 20140710.

Rabinovich, M., P. Varona, A. Selverston, and H. Abarbanel, 2006, Rev. Mod. Phys. **78**, 1213.

Raichle, M. E., 2011, Brain Connectivity **1**, 3.

Raichle, M. E., A. M. MacLeod, A. Z. Snyder, W. J. Powers, D. A. Gusnard, and G. L. Shulman, 2001, Proc. Natl. Acad. Sci. U.S.A. **98**, 676.

Ramaswamy, S., 2010, Annu. Rev. Condens. Matter Phys. **1**, 323.

Rämö, P., S. Kauffman, J. Kesseli, and O. Yli-Harja, 2007, Physica D (Amsterdam) **227**, 100.

Rämö, P., J. Kesseli, and O. Yli-Harja, 2006, J. Theor. Biol. **242**, 164.

Ramos, F., C. López, E. Hernández-García, and M. A. Munoz, 2008, Phys. Rev. E **77**, 021102.

Ravasz, E., A. L. Somera, D. A. Mongru, Z. N. Oltvai, and A.-L. Barabási, 2002, Science **297**, 1551.

Redner, S., 2001, *A Guide to First-passage Processes* (Cambridge University Press, Cambridge, England).

Reed, W. J., and B. D. Hughes, 2002, Phys. Rev. E **66**, 067103.

Ribeiro, A. S., S. A. Kauffman, J. Lloyd-Price, B. Samuelsson, and J. E. Socolar, 2008, Phys. Rev. E **77**, 011901.

Ribeiro, T. L., M. Copelli, F. Caixeta, H. Belchior, D. R. Chialvo, M. A. L. Nicolelis, and S. Ribeiro, 2010, PLoS One **5**, e14129.

Richmond, P., and S. Solomon, 2001, Int. J. Mod. Phys. C **12**, 333.

Ridden, S. J., H. H. Chang, K. C. Zygalakis, and B. D. MacArthur, 2015, Phys. Rev. Lett. **115**, 208103.

Rieke, F., D. Bodnar, and W. Bialek, 1995, Proc. R. Soc. B **262**, 259.

Ringel, Z., and R. de Bem, 2018, arXiv:1802.02154.

Rohlf, T., 2008, Europhys. Lett. **84**, 10004.

Rohlf, T., and S. Bornholdt, 2002, Physica A (Amsterdam) **310**, 245.

Rohlf, T., N. Gulbahce, and C. Teuscher, 2007, Phys. Rev. Lett. **99**, 248701.

Rosenbaum, R., and B. Doiron, 2014, Phys. Rev. X **4**, 021039.

Rosenfeld, S., 2013, Gene Regul. Syst. Biol. **7**, GRSB.S10885.

Rössert, C., P. Dean, and J. Porrill, 2015, PLoS Comput. Biol. **11**, e1004515.

Rubinov, M., O. Sporns, J.-P. Thivierge, and M. Breakspear, 2011, PLoS Comput. Biol. **7**, e1002038.

Rybarsch, M., and S. Bornholdt, 2014, "Self-organized criticality in neural network models," in *Criticality in Neural Systems* (Wiley-VCH Verlag, Berlin), pp. 227–254.

Sadilek, M., and S. Thurner, 2015, Sci. Rep. **5**, 10015.

Saito, N., and M. Kikuchi, 2013, New J. Phys. **15**, 053037.

Sanchez-Vives, M. V., and D. A. McCormick, 2000, Nat. Neurosci. **3**, 1027.

Sauer, U., M. Heinemann, and N. Zamboni, 2007, Science **316**, 550.

Schneidman, E., M. J. Berry, R. Segev, and W. Bialek, 2006, Nature (London) **440**, 1007.

Scholz, J., J. Kelso, and G. Schöner, 1987, Phys. Lett. A **123**, 390.

Schrödinger, E., 1967, *What is Life?* (Cambridge University Press, Cambridge, England).

Schwab, D. J., I. Nemenman, and P. Mehta, 2014, Phys. Rev. Lett. **113**, 068102.

Segev, R., and E. Ben-Jacob, 2001, Physica A (Amsterdam) **302**, 64.

Segev, R., Y. Shapira, M. Benveniste, and E. Ben-Jacob, 2001, Phys. Rev. E **64**, 011920.

Sejnowski, T. J., P. S. Churchland, and J. A. Movshon, 2014, Nat. Neurosci. **17**, 1440.

Seoane, L. F., and R. Solé, 2015, arXiv:1510.08697.

Serra, R., M. Villani, A. Graudenzi, and S. Kauffman, 2007, J. Theor. Biol. **246**, 449.

Serra, R., M. Villani, and A. Semeria, 2004, J. Theor. Biol. **227**, 149.

Sethna, J., 2006, *Statistical Mechanics: Entropy, Order Parameters, and Complexity*, Vol. 14 (Oxford University Press, New York).

Sethna, J. P., K. A. Dahmen, and C. R. Myers, 2001, Nature (London) **410**, 242.

Shanahan, M., 2010, Chaos **20**, 013108.

Shew, W. L., W. P. Clawson, J. Pobst, Y. Karimipanah, N. C. Wright, and R. Wessel, 2015, Nat. Phys. **11**, 659.

Shew, W. L., and D. Plenz, 2013, Neurosci. **19**, 88.

Shew, W. L., H. Yang, T. Petermann, R. Roy, and D. Plenz, 2009, J. Neurosci. **29**, 15595.

Shin, C.-W., and S. Kim, 2006, Phys. Rev. E **74**, 045101.

Shmulevich, I., and E. R. Dougherty, 2010, *Probabilistic Boolean Networks: The Modeling and Control of Gene Regulatory Networks* (SIAM, Philadelphia).

Shmulevich, I., S. A. Kauffman, and M. Aldana, 2005, Proc. Natl. Acad. Sci. U.S.A. **102**, 13439.

Shriki, O., J. Alstott, F. Carver, T. Holroyd, R. N. Henson, M. L. Smith, R. Coppola, E. Bullmore, and D. Plenz, 2013, J. Neurosci. **33**, 7079.

Shriki, O., and D. Yellin, 2016, PLoS Comput. Biol. **12**, e1004698.

Simini, F., T. Anfodillo, M. Carrer, J. R. Banavar, and A. Maritan, 2010, Proc. Natl. Acad. Sci. U.S.A. **107**, 7658.

Simkin, M. V., and V. P. Roychowdhury, 2011, Phys. Rep. **502**, 1.

Simon, H. A., 1955, Biometrika **42**, 425.

Sneppen, K., 2014, *Models of Life* (Cambridge University Press, Cambridge, England).

Sneppen, K., P. Bak, H. Flyvbjerg, and M. H. Jensen, 1995, Proc. Natl. Acad. Sci. U.S.A. **92**, 5209.

Sokolov, A., I. S. Aranson, J. O. Kessler, and R. E. Goldstein, 2007, Phys. Rev. Lett. **98**, 158102.

Solé, R., 2011, *Phase transitions* (Princeton University Press, Princeton, NJ).

Solé, R., and T. Deisboeck, 2004, J. Theor. Biol. **228**, 47.

Solé, R. V., 2003, Eur. Phys. J. B **35**, 117.

Solé, R. V., D. Alonso, and A. McKane, 2002, Phil. Trans. R. Soc. B **357**, 667.

Solé, R. V., R. Ferrer-Cancho, J. M. Montoya, and S. Valverde, 2002, Complexity **8**, 20.

Solé, R. V., S. C. Manrubia, M. Benton, S. Kauffman, and P. Bak, 1999, Trends in Ecology & Evolution **14**, 156.

Solé, R. V., S. C. Manrubia, B. Luque, J. Delgado, and J. Bascompte, 1996, Complexity **1**, 13.

Solé, R. V., and O. Miramontes, 1995, Physica D (Amsterdam) **80**, 171.

Solovey, G., K. J. Miller, J. G. Ojemann, M. O. Magnasco, and G. A. Cecchi, 2012, Front. Integrative Neurosci. **6**, 00044.

Song, J., M. Marsili, and J. Jo, 2017, arXiv:1710.11324.

Soriano, J., C. Colombo, and A. Ott, 2006, Phys. Rev. Lett. **97**, 258102.

Soriano, J., S. Rüdiger, P. Pullarkat, and A. Ott, 2009, Biophys. J. **96**, 1649.

Sornette, D., 1994, J. Phys. I (France) **4**, 209.

Sornette, D., 1998, Phys. Rev. E **57**, 4811.

Sornette, D., 2006, *Critical Phenomena in Natural Sciences* (Springer, New York).

Sornette, D., 2009, in *Encyclopedia of Complexity and Systems Science* (Springer, New York), pp. 7009–7024.

Sornette, D., and R. Cont, 1997, J. Phys. I (France) **7**, 431.

Sporns, O., 2010, *Networks of the Brain* (MIT Press, Cambridge, MA).

Sporns, O., D. R. Chialvo, M. Kaiser, and C. C. Hilgetag, 2004, Trends Cognit. Sci. **8**, 418.

Sporns, O., G. Tononi, and R. Kötter, 2005, PLoS Comput. Biol. **1**, e42.

Stanley, H. E., 1987, *Introduction to phase transitions and critical phenomena* (Oxford University Press, New York).

Stassinopoulos, D., and P. Bak, 1995, Phys. Rev. E **51**, 5033.

Stepp, N., D. Plenz, and N. Srinivasa, 2015, PLoS Comput. Biol. **11**, e1004043.

Steriade, M., F. Amzica, and D. Contreras, 1996, J. Neurosci. **16**, 392.

Steriade, M., A. Nunez, and F. Amzica, 1993, J. Neurosci. **13**, 3252.

Stewart, C. V., and D. Plenz, 2008, J. Neurosci. Methods **169**, 405.

Stokić, D., R. Hanel, and S. Thurner, 2008, Phys. Rev. E **77**, 061917.

Stoop, R., and F. Gomez, 2016, Phys. Rev. Lett. **117**, 038102.

Strogatz, S. H., 2014, *Nonlinear Dynamics and Chaos: With Applications to Physics, Biology, Chemistry, and Engineering* (Westview Press, Boulder, CO).

Stumpf, M. P., and M. A. Porter, 2012, Science **335**, 665.

Summers, J., and S. Litwin, 2006, J. Virol. **80**, 20.

Sumpter, D. J., 2010, *Collective Animal Behavior* (Princeton University Press, Princeton, NJ).

Sussillo, D., T. Toyoizumi, and W. Maass, 2007, J. Neurophysiol. **97**, 4079.

Suweis, S., F. Simini, J. R. Banavar, and A. Maritan, 2013, Nature (London) **500**, 449.

Tabak, J., and P. E. Latham, 2003, NeuroReport **14**, 1445.

Tagliazucchi, E., P. Balenzuela, D. Fraiman, and D. R. Chialvo, 2012, Front. Physiol. **3**, 15.

Tagliazucchi, E., D. R. Chialvo, M. Siniatchkin, E. Amico, J.-F. Brichant, V. Bonhomme, Q. Noirhomme, H. Laufs, and S. Laureys, 2016, J. R. Soc. Interface **13**, 20151027.

Tagliazucchi, E., F. von Wegner, A. Morzelewski, V. Brodbeck, K. Jahnke, and H. Laufs, 2013, Proc. Natl. Acad. Sci. U.S.A. **110**, 15419.

Tang, Q.-Y., Y.-Y. Zhang, J. Wang, W. Wang, and D. R. Chialvo, 2017, Phys. Rev. Lett. **118**, 088102.

Täuber, U. C., 2014, *Critical Dynamics: A Field Theory Approach to Equilibrium and Non-equilibrium Scaling Behavior* (Cambridge University Press, Cambridge, England).

Täuber, U. C., 2017, Annu. Rev. Condens. Matter Phys. **8**, 185.

Taylor, L., 1961, Nature (London) **189**, 732.

Tetzlaff, C., S. Okujeni, U. Egert, F. Wörgötter, and M. Butz, 2010, PLoS Comput. Biol. **6**, e1001013.

Tinker, J., and J. L. P. Velazquez, 2014, Front. Syst. Neurosci. **8**, 73.

Tkačik, G., O. Marre, D. Amodei, E. Schneidman, W. Bialek, and M. J. Berry II, 2014, PLoS Comput. Biol. **10**, e1003408.

Tkačik, G., O. Marre, T. Mora, D. Amodei, M. J. Berry II, and W. Bialek, **2013**, J. Stat. Mech. 03, P03011.

Tkačik, G., T. Mora, O. Marre, D. Amodei, S. E. Palmer, M. J. Berry, and W. Bialek, 2015, Proc. Natl. Acad. Sci. U.S.A. **112**, 11508.

Tkačik, G., E. Schneidman, I. Berry, J. Michael, and W. Bialek, 2009, arXiv:0912.5409.

Tomen, N., D. Rotermund, and U. Ernst, 2014, Front. Syst. Neurosci **8**, 151.

Toner, J., and Y. Tu, 1995, Phys. Rev. Lett. **75**, 4326.

Toner, J., Y. Tu, and S. Ramaswamy, 2005, Ann. Phys. (Amsterdam) **318**, 170.

Tononi, G., O. Sporns, and G. M. Edelman, 1994, Proc. Natl. Acad. Sci. U.S.A. **91**, 5033.

Torres-Sosa, C., S. Huang, and M. Aldana, 2012, PLoS Comput. Biol. **8**, e1002669.

Touboul, J., and A. Destexhe, 2010, PLoS One **5**, e8982.

Touboul, J., and A. Destexhe, 2017, Phys. Rev. E **95**, 012413.

Toyoizumi, T., and L. F. Abbott, 2011, Phys. Rev. E **84**, 051908.

Tsodyks, M., and H. Markram, 1997, Proc. Natl. Acad. Sci. U.S.A. **94**, 719.

Tsuchiya, M., A. Giuliani, M. Hashimoto, J. Erenpreisa, and K. Yoshikawa, 2015, PLoS One **10**, e0128565.

Tsuchiya, M., A. Giuliani, M. Hashimoto, J. Erenpreisa, and K. Yoshikawa, 2016, PLoS One **11**, e0167912.

Turcotte, D., 1999, Rep. Prog. Phys. **62**, 1377.

Turing, A. M., 1950, Mind **LIX**, 433.

Turing, A. M., 1952, Phil. Trans. R. Soc. B **237**, 37.

Tyrcha, J., Y. Roudi, M. Marsili, and J. Hertz, **2013**, J. Stat. Mech. 13, P03005 [http://iopscience.iop.org/article/10.1088/1742-5468/2013/09/P09003/meta].

Tyson, J. J., K. C. Chen, and B. Novak, 2003, Curr. Opin. Cell Biol. **15**, 221.

Uhlig, M., A. Levina, T. Geisel, and M. Herrmann, 2013, Front. Comput. Neurosci. **7**, 00087.

Van Kampen, N. G., 1992, *Stochastic Processes in Physics and Chemistry*, Vol. 1 (Elsevier, New York).

Vanni, F., M. Luković, and P. Grigolini, 2011, Phys. Rev. Lett. **107**, 078103.

van Vreeswijk, C., and H. Sompolinsky, 1996, Science **274**, 1724.

Varela, F., J.-P. Lachaux, E. Rodriguez, and J. Martinerie, 2001, Nat. Rev. Neurosci. **2**, 229.

Vattay, G., D. Salahub, I. Csabai, A. Nassimi, and S. A. Kaufmann, 2015, J. Phys. Conf. Ser. **626**, 012023.

Veatch, S. L., P. Cicuta, P. Sengupta, A. Honerkamp-Smith, D. Holowka, and B. Baird, 2008, ACS Chem. Biol. **3**, 287.

Veatch, S. L., O. Soubias, S. L. Keller, and K. Gawrisch, 2007, Proc. Natl. Acad. Sci. U.S.A. **104**, 17650.

Veening, J.-W., W. K. Smits, and O. P. Kuipers, 2008, Annu. Rev. Microbiol. **62**, 193.

Vespignani, A., R. Dickman, M. A. Muñoz, and S. Zapperi, 1998, Phys. Rev. Lett. **81**, 5676.

Vespignani, A., R. Dickman, M. A. Muñoz, and S. Zapperi, 2000, Phys. Rev. E **62**, 4564.

Vicsek, T., A. Czirók, E. Ben-Jacob, I. Cohen, and O. Shochet, 1995, Phys. Rev. Lett. **75**, 1226.

Vicsek, T., and A. Zafeiris, 2012, Phys. Rep. **517**, 71.

Villa Martín, P., J. A. Bonachela, and M. A. Muñoz, 2014, Phys. Rev. E **89**, 012145.

Villani, M., *et al.*, 2015, Artif. Life **21**, 412.

Villegas, P., P. Moretti, and M. A. Muñoz, 2014, Sci. Rep. **4**, 5990.

Villegas, P., J. Ruiz-Franco, J. Hidalgo, and M. A. Muñoz, 2016, Sci. Rep. **6**, 34743.

Visser, M., 2013, New J. Phys. **15**, 043021.

Vojta, T., 2006, J. Phys. A **39**, R143.

Wagner, A., 2005, *Robustness and Evolvability in Living Systems* (Princeton University Press, Princeton, NJ).

Wang, X. R., J. T. Lizier, and M. Prokopenko, 2011, Artif. Life **17**, 315.

Watkins, N. W., *et al.*, 2016, Space Sci. Rev. **198**, 3.

Watson, H. W., and F. Galton, 1875, J. of the Anthropological Institute of Great Britain and Ireland **4**, 138.

Watts, D. J., and S. H. Strogatz, 1998, Nature (London) **393**, 440.

Werner, G., 2007, BioSystems **90**, 496.

West, B. J., 2010, Front. Physiol. **1**, 12.

West, G., 2017, *Scale* (Orion Publishing Group, Limited, London).

West, G. B., J. H. Brown, and B. J. Enquist, 1997, Science **276**, 122.

Williams-Garcia, R., J. M. Beggs, and G. Ortiz, 2017, Europhys. Lett. **119**, 18003.

Williams-García, R. V., M. Moore, J. M. Beggs, and G. Ortiz, 2014, Phys. Rev. E **90**, 062714.

Willinger, W., D. Alderson, J. C. Doyle, and L. Li, 2004, in *Proceedings of the Winter Simulation Conference*, Vol. 1 (IEEE, New York).

Wilson, K., 1979, Sci. Am. **241**, 158.

Wilson, K., and J. Kogut, 1974, Phys. Rep. **12**, 75.

Wolf, D. M., V. V. Vazirani, and A. P. Arkin, 2005, J. Theor. Biol. **234**, 227.

Wolfram, S., 2002, *A New Kind of Science* (Wolfram Media, Champaign, IL).

Yamaguchi, H., K. Kawaguchi, and T. Sagawa, 2017, Phys. Rev. E **96**, 012401.

Yang, H., W. L. Shew, R. Roy, and D. Plenz, 2012, J. Neurosci. **32**, 1061.

Yu, S., A. Klaus, H. Yang, and D. Plenz, 2014, PLoS One **9**, e99761.

Yu, S., H. Yang, H. Nakahara, G. S. Santos, D. Nikolić, and D. Plenz, 2011, J. Neurosci. **31**, 17514.

Yule, G. U., 1925, Phil. Trans. R. Soc. B **213**, 21.

Yuste, R., J. N. MacLean, J. Smith, and A. Lansner, 2005, Nat. Rev. Neurosci. **6**, 477.

Zamponi, N., E. Zamponi, S. A. Cannas, O. V. Billoni, P. R. Helguera, and D. R. Chialvo, 2018, Sci. Rep. **8**, 363.

Zapperi, S., K. B. Lauritsen, and H. E. Stanley, 1995, Phys. Rev. Lett. **75**, 4071.

Zipf, G. K., 1949, *Human Behavior and the Principle of Least Effort* (Addison-Wesley, Cambridge).