Colloquium: Criticality and dynamical scaling in living systems

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A celebrated and controversial hypothesis conjectures 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, huge 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 higher layers of complexity can rest. This hypothesis is very 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 thrilling implications, this is still in its embryonic state as a well-founded theory and, as such, it has elicited some healthy 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 set-ups and theoretical analyses are certainly needed to fully clarify the picture but, in any case, time seems to be ripe for bridging the gap between this theoretical conjecture and its empirical validation. Given the profound implications of shedding light on this issue, we believe that it is both pertinent and timely to review the state of the art –with an emphasis on existing empirical evidence– 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 thousand 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 of individuals group dozens of them, interacting in countless ways, forming entangled ecosystems, and giving rise to a mind-blowing hierarchy of *"complexity"*.

The standard viewpoint in biology, stemming from the reductionist tradition, is that each molecular component (protein, nucleic acid, metabolite...) is specific and requires individualized analysis. As stressed by the rapid advance of the "omics" sciences, this one-at-the-time approach has successfully identified and quantified most of the components and many of the basic interactions of life as we know it. Still, unfortunately, it offers no convincing explanation of how systemic properties emerge (Sauer *et al.*, 2007). Questions such as (Schrödinger, 1967)"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?" remain largely unanswered.

A complementary strategy consists in looking at complex biological problems from a global perspective, shifting the focus from specific details of the molecular machinery to integral aspects[1] (Alon, 2006; Bialek, 2012; Goldenfeld and Woese, 2011; Kaneko, 2006; Sauer *et al.*, 2007). 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 such elementary components on an individual basis. 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 and, more specifically, 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[2] (Alon, 2006; Amit, 1992; Anderson *et al.*, 1972; Bialek, 2012; Hopfield, 1982; Parisi, 1993; Schrödinger, 1967; Smith and Morowitz, 2016; Sneppen, 2014).

One of the most striking consequences of interactions among elementary constituents of matter (atoms, molecules, electrons...) is the emergence of diverse *"phases"* whose behavior bears little resemblance with that of their basic components or small groups of them (Anderson *et al.*, 1972; Chaikin and Lubensky, 2000; Goldenfeld, 1992; Stanley, 1987). Systems consisting of very many (microscopic) components may exhibit rather diverse types of (macroscopic) collective behavior (phases) with different levels of internal order. Moreover, slight changes in external conditions (e.g. temperature, pression...) 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); a non-exhaustive list of examples includes: (i) synchronization phase transitions in collective biological oscillators such as circadian clocks (Garcia-Ojalvo *et al.*, 2004); (ii) percolation transitions of fibers in connective tissues such as collagen (Alvarado *et al.*, 2013; Forgacs *et al.*, 1991; Newman *et al.*, 2004), (iii) melting phase transition in DNA strands (Li and Retzloff, 2006); (iv) transitions between different dynamical regimes (oscillations, bursting,...) in neuronal networks (Freeman, 2013; Freeman and Holmes, 2005; Friston, 1997; Haken, 2013; Rabinovich *et al.*, 2006; Werner, 2007), etc. Indeed, life –guided by evolution– has found its way to exploit very diverse types of order: crystalline structures at the basis of bio-mineralized materials (seashells, skeletons...), liquid states (blood, lymph, sap...), gels (vitreous humor, cell cytoplasm), etc. However, some aspects of biological systems –the ones of interest here, such as e.g. neural networks or flocks– show intermediate levels of organization, half way between order and disorder, less regular than perfect crystals but more structured than random gases. Remarkably, it has been conjectured that, under some circumstances, living systems –i.e. parts, aspects, or groups of them– could draw functional advantages from operating right at the borderline between ordered and disordered phases, i.e. at the very edge of a (continuous) phase transition or critical point[3] (Bak, 1996; Beggs, 2008; Chialvo, 2010; Chialvo

[1] The finding that humans have less genes than onions do –but amazingly more complex features– is suggestively supportive of the need of an interacting-system approach to genomics, and to life in general (Koonin, 2011; Sauer *et al.*, 2007).

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

[3] Phase transitions may occur in either a discontinuous/abrupt fashion (Binney *et al.*, 1993) –with associate bistability of the two different phases and an abrupt/discontinuous jump at the

et al., 2008; Kauffman, 1993; Marro and Chialvo, 2017; Plenz, 2013; Schuster *et al.*, 2014). For instance, rather generically, living systems need to achieve a tradeoff between robustness (resilience of the system state to external perturbations, a property of ordered phases) and flexibility (responsiveness to environmental cues and stimuli, 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. Aspects of criticality, such as the emergence of long-range spatio-temporal correlations and the exquisite sensitivity to stimuli (see below) 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 biological organization (Bak, 1996; Beggs, 2008; Chialvo, 2010; Kauffman, 1993; Mora and Bialek, 2011; Plenz, 2013; Schuster *et al.*, 2014). [4]

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 intelectual achievements of the second half of the $20th$ century, such as the scaling hypothesis and the renormalization group theory (Amit and Martín-Mayor, 2005; 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[5]. Concepts born in this context, such as scale-invariance (explaining the existence of a non-trivial organization across many different scales), pervade the way physicists picture the world today. A 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. Thus, criticality and its concomitant scale-invariance can be understood through simple stylized models, where many microscopic details are neglected, paving the road to the understanding of collective aspects of biological systems and the phase transitions they might experience, transcending specific details.

The advent of high-throughput experimental techniques and big data technologies have created new prospects in the exploration of biological systems. This is true in fields such as neuroscience where it is now possible to record activity from individual spiking neurons to entire brains with previously-unthinkable resolution (Markus and Freeman, 2015; Sejnowski *et al.*, 2014); in genomics, where amazingly detailed patterns of activity in gene regulatory networks can be monitored (Lesk, 2017); or in the study of animal collective motion owing to novel tracking technologies (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 the above 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, time seems to be ripe for bridging the gap between theoretical hypotheses and their empirical validation.

The purpose of the present paper 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 the reader with a self-consistent view of what is criticality and what it is not, as well as an overview of the literature on this active and fascinating research field with countless ramifications.

Let us mention that there exist some recent articles reviewing some of these topics; the list includes an influential paper on statistical aspects of criticality in living systems (Mora and Bialek, 2011), as well as works focused on neural dynamics (Beggs, 2008; Chialvo, 2010; Chialvo *et al.*, 2008; Cocchi *et al.*, 2017; Hesse and Gross, 2014; Massobrio *et al.*, 2015; Schuster *et al.*, 2014; Shew and Plenz, 2013), gene regulation (Roli *et al.*, 2015), and collective motion (Vicsek and Zafeiris, 2012) respectively. The present paper aims at overviewing, summarizing and complementing them, putting the emphasis on dynamical aspects rather than in purely statistical ones.

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", "quasi-critical", "dynamically critical", "generically critical", and "self-organized critical". Given the broad audience this review paper is aimed at, we esteem that a section devoted to present a synthetic overview of basic concepts and to fix ideas and notation is necessary[6]. Readers familiar with

transition point– or in continuous/progressive way with an associated critical point. Our main focus here is on continuous ones, but we will also encounter discontinuous transitions, which may also play a relevant role in biology.

[4] Let us mention that there have been recent attempts to define variants of criticality, specifically suited for biological systems (Bailly and Longo, 2008; De Vincenzo *et al.*, 2017).

[5] See, e.g. Binney *et al.* (1993); Canet *et al.* (2011); De Gennes (1979); Delamotte (2012); Goldenfeld (1992); Henkel *et al.* (2008); Kardar (2007); Le Bellac *et al.* (1991); Sethna (2006); Stanley (1987); Täuber (2014, 2017).

[6] For a more exhaustive introduction to critical phenomena we refer to the standard literature (Binney *et al.*, 1993; Christensen

these concepts can skip the next section.

1. Scale-invariance and power laws

Before discussing criticality let us introduce the more general concept of scale-invariance. In a seminal paper entitled "Problems in Physics with many scales of length" the Nobel laureate K. Wilson emphasized that "one of the more conspicuous properties of nature is the great diversity of size or length scales", and cites oceans as an example where currents persist for thousand of kilometers and coexist with waves of the order of meters, and with microscopic aggregates of water molecules (Wilson, 1979). These scales are usually decoupled and the "physics" at each one can be separately studied. However, there are phenomena where events at many scales make contributions of equal importance. A remarkable instance of this are the critical points of continuous phase transitions where structures/processes at the microscopic, macroscopic, and all intermediate mesoscopic scales are very similar. These situations with many equally-relevant scales are known as scale-invariant or scale-free (Mandelbrot, 1983), and are described statistically by power-law distributions, as exemplified by the Guttenberg-Richter equation for the probability distribution of observing an earthquake of magnitude M, $P(M) \propto M^{-\alpha}$ (see e.g. Corral (2004)). Power-law (or Pareto) distributions such as $P(x) = Ax^{-\alpha}$, where α is a positive real number and A a normalization constant, are the trademark of *scale-invariance*. Actually, they are the only possible probability distribution functions for which a change of scale from x to Λx, for some constant factor 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). Hence, as opposed to e.g. exponential distributions, power-laws lack a relevant characteristic scale (besides natural upper and lower cut-offs). In the next sections we will see that scale-invariance is a fingerprint of critical points but, also, that scale-invariant systems unrelated to criticality exist.

Power-law distributions (or, more in general, power laws in the tails of the distributions, i.e. asymptotically) 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 (Gisiger, 2001; Goldberger, 1992; Goldberger *et al.*, 2002; Hu *et al.*, 2012; West, 2010; West and Grigolini, 2010); for example, many physiological and clinical time-series data have a spectrum that decays as a power of the frequency. This effect is often called $1/f$ noise, although powers of the frequency f may appear (Mandelbrot, 2002). Also patterns of human and animal mobility often exhibit scale-free features (Anteneodo and Chialvo, 2009; Barabasi, 2005; Brockmann *et al.*, 2006; Proekt *et al.*, 2012). Moreover, a number of commonly-observed statistical patterns of natural-world data –such as Zipf's law[7] (Baek *et al.*, 2011; Marsili and Zhang, 1998; Mora and Bialek, 2011; Sornette, 2006; Visser, 2013), Bendford's law (Benford, 1938; Pietronero *et al.*, 2001), and Taylor's law (Taylor, 1961; Xu, 2015)– stem from underlying scale invariance, i.e. power-law distributions (Simkin and Roychowdhury, 2011).

Disputes on the validity and possible significance of power-laws have a long history in many research fields; for some authors they reveal fundamental mechanisms, while some others perceive them as largely uninformative (Kello *et al.*, 2010; Stumpf and Porter, 2012). Still, in some cases, there is very robust evidence of scale invariance and it certainly provides valuable insight[8] [9].

The detection and statistical characterization of power laws in real-world data is hindered by sampling problems as very rare but large events control the tail of the distribution. Indeed, the quality of power-law fits to empirical data has been scrutinized (Clauset *et al.*, 2009), showing that many claims of scale-invariance actually lack statistical significance. Improved and stringent statistical tests –combining maximum-likelihood fitting methods with Kolmogorov-Smirnov quality tests– have been designed and are now customarily employed to ascertain whether empirical data actually conform to power laws (Clauset *et al.*, 2009).

From the mathematical side, a handfull of mechanisms for the generation of (non-critical) power-law distributions have been put forward (Marković and Gros, 2014;

and Moloney, 2005; Goldenfeld, 1992; Henkel *et al.*, 2008; Kardar, 2007; Le Bellac *et al.*, 1991; Marro and Dickman, 1999; Sethna, 2006; Stanley, 1987).

[7] 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 ones. A typical example are words in a language: the $n-th$ most frequent word appears with a frequency that scales according to r^{-1} where r is its position in the ranking of most frequent words (Zipf, 2016).

[8] An important example are allometric scaling laws, which are power-law relationships between different measures of anatomy/physiology; e.g. Kleiber′s law (Kleiber, 1932) links organism mass M to metabolic rate R as $M \sim R^{3/4}$, and applies across species from bacteria to mammals (Banavar *et al.*, 2014, 2010b; Brown *et al.*, 2004; West *et al.*, 1997). Allometric scaling has been elegantly shown to stem from the constraint that living systems have an underlying optimal (e.g nutrient) transportation network (Banavar *et al.*, 1999; Simini *et al.*, 2010).

[9] Another example are (foraging) search strategies which, under some circumstances, have been argued to be optimized by performing scale-free distributed displacements (Humphries and Sims, 2014; Viswanathan *et al.*, 1999), i.e. Lévy flights (Metzler and Klafter, 2000).

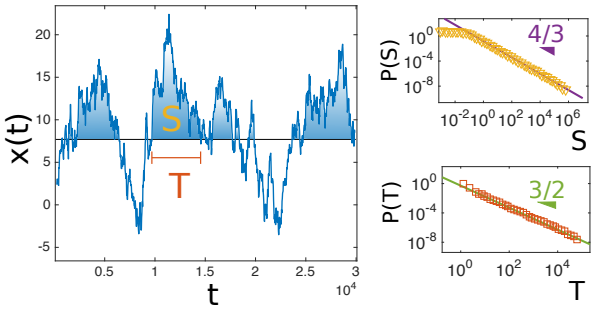

FIG. 1 Random walks, as the one-dimensional one illustrated in the left panel, lack a characteristic scale. As a consequence the distribution of return times to the origin, T, of one-dimensional (unbiased) random walkers obeys $P(T) \sim T^{-\alpha}$ with $\alpha = 3/2$ and the areas/sizes, S, covered by their excursions before returning to the origin are distributed as $P(S) \sim S^{-\tau}$ with $\tau = 4/3$ (right panels) (Redner, 2001; di Santo *et al.*, 2017b). Also, the averaged size as a function of time $\langle S(T)\rangle \sim T^{\gamma}$ scales as a power-law with $\gamma = 3/2$ (not shown). The above exponents can be related by means of a very general scaling relationship: $\gamma = (\alpha - 1)/(\tau - 1)$ (Baldassarri *et al.*, 2003). Many biological systems exhibit scaling stemming from effective random-walk processes (Berg, 1993; Gerstein and Mandelbrot, 1964).

Mitzenmacher, 2002; Newman, 2005; Simkin and Roychowdhury, 2011; Sornette, 2009). An incomplete list is: (i) the statistics of random walks as illustrated in Fig.1. (ii) the statistics of multiplicative processes (Reed and Hughes, 2002; Richmond and Solomon, 2001; Sornette, 1998; Sornette and Cont, 1997), (iii) preferential attachment processes (Barabási and Albert, 1999; Simon, 1955; Yule, 1925), (iv) optimization and constrained optimization (Carlson and Doyle, 2000; Seoane and Solé, 2015), (v) marginalization over un-observed relevant variables (Aitchison *et al.*, 2016; Macke *et al.*, 2011; Schwab *et al.*, 2014). Still, in many physical and biological systems with many degrees of freedom, a more general explanation for the generation of spatio-temporal scale-invariance exists: it can emerge as a collective phenomenon stemming from the system sitting close to the critical point of a continuous phase transition.

2. Criticality in equilibrium systems and beyond

The concept of criticality was born in the context of systems at *thermodynamic equilibrium*. A paradigmatic example are ferromagnets, which can become permanently magnetized (i.e. with a net magnetization resulting from individual spins pointing predominantly in a preferred direction) at temperatures below the critical Curie temperature, T_c, but not for larger temperatures, for which thermal noise precludes such an ordering. A continuous/second-order phase transition occurs right at the critical point T_c below which the orientational symmetry of spins is broken, a preferred direction emerges spontaneously –i.e. the a symmetry is spontaneously broken– and a progressively more ordered/magnetized state emerges as the temperature is lowered. This change in the collective state is usually encoded in an "order parameter" (the overall magnetization in ferromagnets) which measures the degree of order as the phase transition proceeds, shifting from 0 in the disordered/symmetric state to a progressively larger value within the ordered/symmetry-broken phase.

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 systems at criticality and also that, as the system is incipiently becoming ordered, it is also highly fluctuating in choosing which direction to be selected. For example, classical experiments with liquid-gas transitions (e.g. with CO_2) show that, right at criticality, light of many different wavelengths scatter with internal structures of the mixture (density fluctuations of all possible length scales), causing the normally transparent liquid to appear cloudy in a phenomenon called critical opalescence; see, e.g. (Binney *et al.*, 1993; Wilson, 1979). The way in which macroscopic order emerges is scale-invariant and mostly independent of microscopic details; as already mentioned, a remarkable finding is that, properties at criticality are *universal*, as they depend only on general features such as symmetries and dimensionality.

Importantly, the concepts and methods developed in the context of equilibrium systems were soon extended to time-dependent (Hohenberg and Halperin, 1977) and non-equilibrium problems (Henkel *et al.*, 2008; Hinrichsen, 2000; Kamenev, 2011; Ma, 2000; Marro and Dickman, 1999; Ódor, 2004, 2008; Schmittmann and Zia, 1995; Täuber, 2014, 2017). All along this paper, we adopt a view of criticality and phase transitions focused on dynamical and non-equilibrium 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 that there exists an alternative "statistical-criticality" approach to the analysis of biological data. It focuses on the statistics of patterns/configurations rather than on dynamical/non-equilibrium aspects, and we discuss it only in passing[10].

[10] It can be argued that many fundamental questions in biology can be formulated in a probabilistic setting; e.g., deciphering the neural coding might require knowing the statistics of neural spiking patterns under given sets of stimuli (Rieke *et al.*, 1995). An approach to analyze biological data-rich problems relies on equilibrium statistical physics and information theory. It consists in analyzing the statistics of the observed configurations,

3. Non-equilibrium phase transitions: an example

In order to turn the foregoing wordy explanations into a more formal approach, we describe in detail –as a guiding example– one of the simplest possible dynamical models exhibiting a non-equilibrium phase transition.

The *contact process* (CP) (Harris, 2002; Henkel *et al.*, 2008; Hinrichsen, 2000; Marro and Dickman, 1999) is a prototypical toy model to study the dynamics of propagation of some type of "activity" (as e.g. infections in epidemic spreading). At any given time, each of the nodes i 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/nodes) is in a state s_i that can be either occupied/active ($s_i = 1$) or empty/quiescent ($s_i = 0$). The (Markovian) dynamics consists in the following processes: occupied sites are emptied at rate $\mu = 1$ and new active nodes are created at (empty) randomly-selected nearest neighbors of active ones at rate λ. Considering, for the sake of simplicity, a fully connected network with N nodes and performing a large-N expansion of the corresponding Master equation (Gardiner, 2009; Van Kampen, 1992), one readily obtains:

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

where the dot stands for time derivative of the activity density $\rho = \sum_{i=1}^{N} s_i/N$.

This simple one-variable, "mean-field", or deterministic approximation already illustrates some of the essential features of criticality. Inspection of Eq.(1) reveals the presence of a bifurcation (see e.g. Strogatz 2014) at a value $\lambda_c = 1$, separating a subcritical/absorbing phase ($\lambda < 1$) in which transient activity decays to the only possible steady-state, $\rho_{st} = 0$, from a supercritical/active one ($\lambda > 1$) with a sustained activity $\rho_{st} = 1 - 1/\lambda$ (see Fig.2). Thus, near the bifurcation/critical point, $\rho_{st} \sim \delta$ for small δ, where $\delta = |\lambda - 1|$ is the distance to criticality. In the quiescent (or absorbing) phase[11], an initial density decays exponentially, $\rho(t) = \rho(0)\exp(-\delta t)$, implying that there is a characteristic time scale proportional to δ^{-1}, that diverges at criticality, i.e. it takes a (divergently) 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, $\rho(t) = \rho(0)/(1+\rho(0)t)$, which decays asymptotically as a power-law, $\rho(t) \sim t^{-1}$.

Introducing an external field that creates activity at empty sites at rate h, the overall response or "susceptibility", defined as $\Xi = \frac{\partial \rho_{st}}{\partial h}|_{h\to 0}$, 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 transitions consists in performing "spreading experiments" in which the evolution of a single localized seed of activity in an otherwise absorbing/quiescent state is monitored (see Fig.2C). 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 above. Stochastic cascades of spatio-temporal activity, or "avalanches" of variable sizes and durations can be generated from the initial seed before the system reaches the quiescent state (extinction). In this framework the critical point separates a regime of sure extinction (absorbing phase) from one of non-sure extinction (active phase), and is characterized by highly variable shapes, sizes, and durations (as illustrated in Fig.2C). Indeed, right at the critical point, the sizes and durations of avalanches are scale-free, i.e. distributed as power-laws with anomalously large (formally "infinite") variance[12]. 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 $\sigma^2 = (\lambda+1)/N$. This square-root noise term stems from the central limit theorem (Van Kampen, 1992). A simple (first-return-time to the origin) analysis of the resulting stochastic equation 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, avalanches sizes s obey $P(s) \sim s^{-\tau}$, with $\tau = 3/2$ [13]. These mean-field exponents coincide with those of the (Galton-Watson) unbiased branching process (Harris, 2002; Liggett, 2004; Watson and Galton, 1875), introduced to describe the statistics of family-

assuming that it encodes key relevant features. Given that huge data sets from biological systems are now available, reconstructions of the possible underlying network of interactions between constitutive units from observed statistical patterns have become feasible. Probabilistic models can be constructed such that they match the statistics of observed empirical data, and among these models one selects the one that makes the smaller number of assumptions. Remarkably, such probabilistic models for biological data have been found to have parameters close to the edge of a phase transition, i.e. to be critical. See the Appendix for an extended discussion of this approach.

[11] A similar argument holds in the active phase.

[12] The large variability of possible patterns is a generic key feature of criticality; for instance, in systems at thermodynamic equilibrium, spatial variability results in the divergence at criticality of the specific heat, which is a good predictor of the microscopic variability of the underlying configurations (Mora and Bialek, 2011).

[13] See di Santo *et al.* (2017b) for a pedagogical derivation of these results. In finite-dimensional lattices, the associated critical point as well as the critical exponents (i.e. the exponents of the power-law dependences) deviate from the mean-field predictions above (Hinrichsen, 2000). For a compendium of exponent values and scaling relationships, see (Muñoz *et al.*, 1999).

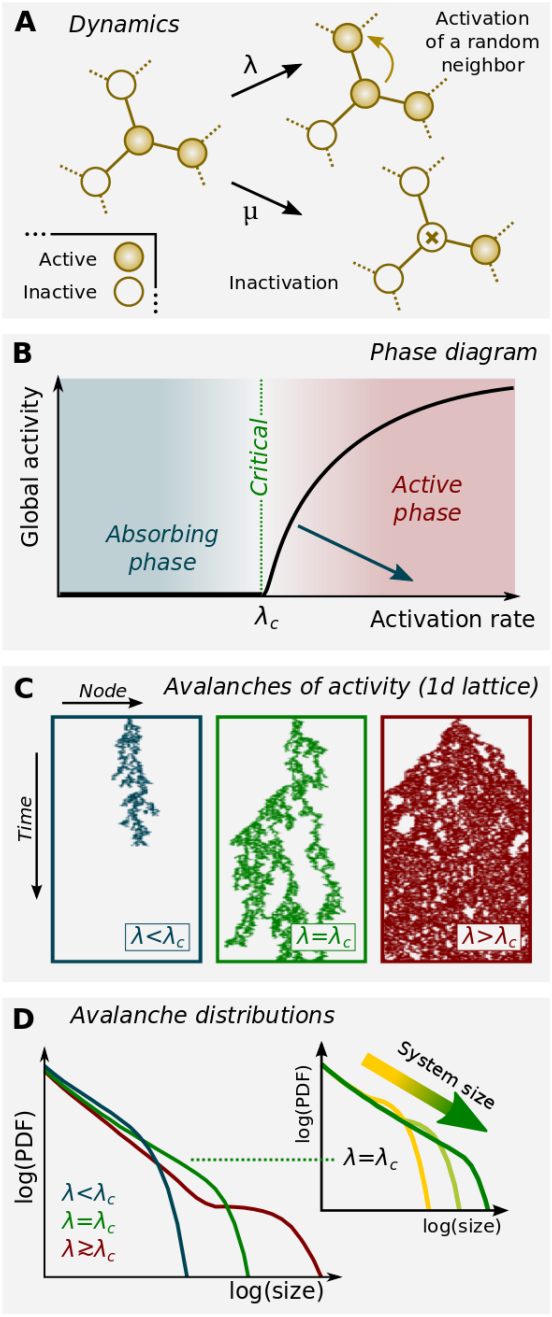

FIG. 2 Sketch of the main aspects of the contact process. (A) Dynamical rules. (B) Phase diagram. (C) Temporal raster plots of activity (avalanches) in the different regimes, illustrating the fractal-like complex patterns emerging at criticality. (D) Avalanche size distributions in the different phases (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).

names, and often employed to illustrate the statistics of critical avalanches. Away from criticality, as well as in finite systems, cut-offs appear in the avalanche distributions (see Fig.2). In particular, as a reflection of the underlying scale-invariance at criticality, the finite-size cut-offs obey scaling laws such as

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

where the power-law $s^{-\tau}$ is cut-off by an unspecified function, $\mathcal{G}$, at an N-dependent scale (Binder, 1981; Binney *et al.*, 1993; Stanley, 1987). This enforces that plotting $P(s,N)s^{\tau}$ as a function of s/N at the critical point 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/divergences can only appear in the infinite-size limit, not possibly reached in biological problems. 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 diverge at (true) criticality; this is used as a proxy for "approximate" criticality in finite systems[14].

As a result of universality, all models exhibiting a phase transition to an absorbing/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 *et al.*, 2008)[15].

Even if the simple contact processes 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, defined as follows. Two identical replicas of

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

[15] To analytically 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, leading to

$$\dot{\rho}(x,t) = \delta\rho(x,t) - \lambda\rho^2(x,t) + D\partial_x^2\rho(x,t) + \sqrt{\rho(x,t)}\eta(x,t), \tag{3}$$

where D is a diffusion constant and ∂_x stands for spatial derivatives (Henkel *et al.*, 2008; Hinrichsen, 2000; Ódor, 2008). Mean-field results hold only above four spatial dimensions; below such a dimension, fluctuations cannot be neglected. A detailed computation of critical exponents can only be achieved by employing renormalization group techniques (Amit and Martín-Mayor, 2005; Binney *et al.*, 1993; Delamotte, 2012; Fisher, 1974; Wilson and Kogut, 1974); a complete perturbative calculation for Eq.(3) can be found e.g. in Henkel *et al.* (2008); see also Grinstein and Muñoz (1996) for a simple discussion.

the same system are considered; a localized perturbation in the state of one unit/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 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 organization/order[16]. Even if the actual dynamics might be much more complicated, the resulting damage spreading process is susceptible to be described by a much simple model –such as the contact process– if local effective error "propagation" and error "healing" rates can be estimated. This approach is often employed in e.g. gene regulatory networks as we shall see.

4. Families of criticality

Importantly, not all phase transitions of relevance in biology occur between quiescent and active phases, nor can be described by an associated activity-propagation process, such as the contact process. Other important families of phase transitions to be found across this paper are: (i) synchronization transitions, at which coherent behavior of oscillators emerges, as described by the prototypical *Kuramoto model* (Acebrón *et al.*, 2005; Kuramoto, 1975); (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) static percolation transitions (Christensen and Moloney, 2005). Each of these classes has its own type of emerging ordering and its own set of critical exponents and 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.

5. Phase transitions on complex networks

The peculiarities of phase transitions on heterogeneous complex networks have been the focus of many analyses after the seminal works of Barabási and Albert (1999) and Watts and Strogatz (1998). In many systems, including biological ones, it has been observed that the architecture of the underlying network of connections may be highly heterogeneous (actually scale free), with a few highly connected nodes and many loosely connected ones (Barabási and Albert, 1999); this fact has profound implications on the dynamics of processes running on such scale-free networks and on the phase transitions they exhibit; for instance, the quiescent phase can disappear and synchronization transitions proceed in a way different from that of networks (Albert and Barabási, 2002; Arenas *et al.*, 2008; Barrat *et al.*, 2008; Boccaletti *et al.*, 2006; Caldarelli, 2007; Dorogovtsev *et al.*, 2008; Newman, 2003, 2010; Pastor-Satorras *et al.*, 2015).

Another important concept in this context is network modularity (Newman, 2006). Biology is "modular" in many aspects (Alon, 2006; Barabasi and Oltvai, 2004; Ravasz *et al.*, 2002), meaning that some components in biological networks (nodes) are connected among themselves more often or more strongly that they do with the rest (Newman, 2003). This property has been argued to confer robustness and stability on networks (Alon, 2003) and, more in general, it can severely affect the features of dynamical processes; for instance, synchronization transitions occur first within moduli and then across them (Arenas *et al.*, 2008; Barrat *et al.*, 2008). In particular, if network modules are heterogeneous, extended critical-like regions can emerge (Muñoz *et al.*, 2010) with important implications in e.g. in neuroscience (Moretti and Muñoz, 2013) (see Sect4).

6. Self-organized criticality

Many different natural phenomena –from earthquakes to type-II superconductors, and Barkhausen noise, to name but a few– exhibit features of criticality as if they were sitting in the vicinity of a continuous phase transition in a spontaneous self-organized way, i.e. without any apparent need for parameter fine tuning. Aimed at understanding how possibly this comes about, Bak and collaborators introduced the concept of "self-organized criticality" (SOC) through a series of archetypical models (Bak, 1996; Bak *et al.*, 1990; Bak and Tang, 1989; Corral *et al.*, 1995; Dhar, 1999; Drossel and Schwabl, 1992; Frette *et al.*, 1996; Olami *et al.*, 1992), including its most famous representative, the Bak-Tang-Wiesenfeld *sandpile* model (Bak *et al.*, 1987).

Although the sandpile model is an oversimplification of real sandpiles, it illustrates very important and useful concepts, so that we discuss it here in some detail. In the sandpile model a type of "stress" or "energy" (sandgrains) accumulates at a very slow timescale at the sites of a (two-dimensional) lattice. When the accumulated stress overcomes a local instability threshold, it is instantaneously redistributed among nearest neighbor sites –and, possibly, released/dissipated at the open boundaries of the system. This possibly creates a cascade or "avalanche" of further instabilities, which finishes when all sites are stable. After that, the slow charging process restarts. In the limit in which these accumulation and release processes occur at well separated timescales, the durations and sizes of such avalanches turn out to be dis-

[16] 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, 1995a,b; Hinrichsen and Domany, 1997).

tributed as power laws, i.e. the system becomes critical without any apparent need for fine tuning[17] (Bak, 1996; Bak *et al.*, 1987; Christensen and Moloney, 2005; Dickman *et al.*, 2000; Jensen, 1998; Pruessner, 2012; Turcotte, 1999; Watkins *et al.*, 2015).

In a nutshell, the mechanism for self-organization to criticality in sandpile models works as follows[18](Dickman *et al.*, 2000). Imagine a system with a phase transition into an absorbing or quiescent state (see Fig.3), without driving nor dissipation; i.e. with a well-defined control parameter. Assume now that the control parameter (e.g. the total amount of energy/stress/sandgrains) is itself a dynamical variable, whose dynamics depends crucially on the system's state (as illustrated in Fig.3). If the system is in an absorbing/quiescent state then the control parameter increases ("slow driving" mechanism), while if the system is in the active phase, then it decreases at the boundaries ("dissipation" mechanism); the alternation of these two opposing forces operating at infinitely separated timescales makes the system self-organize to the very critical point, as can be analytically shown[19] within the mean-field approach to systems with absorbing states.

The described mechanism for self-organization to the edge of a phase transition, characterized by a dynamical feedback that acts differentially depending on the actual system state, is just an example of a broader class that has been extensively analyzed in the context of *control theory* (Magnasco *et al.*, 2009; Moreau and Sontag, 2003; Sornette, 1994). In particular, this type of mechanism can also account for the self-organization to the edge of a discontinuous phase transition with bistability (rather than a continuous one with a critical point). This has been dubbed "self-organized bistability" (SOB) and could be relevant e.g. in neuroscience (di Santo *et al.*, 2016).

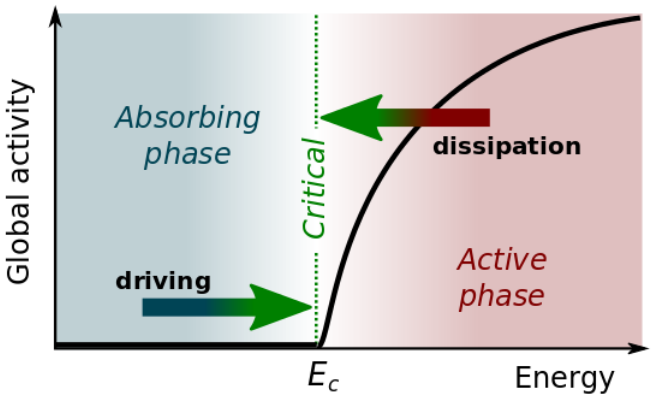

FIG. 3 The self-organization-to-criticality (SOC) mechanism works by establishing a feedback loop between the dynamics of the activity and that of the control-parameter (total accumulated energy/stress/sandgrains) at separated timescales. In particular, the control parameter itself becomes a dynamical variable that operates in opposite ways depending on the system's state: dissipative dynamics (negative force) dominates while the control parameter lies within the active phase and by slow driving dynamics (positive force) dominates in the absorbing/quiescent phase. This feedback self-organizes the system to the critical point of its second-order phase transition (of the transition obtained for a fixed control parameter) if the separation between slow and fast timescales is infinitely large and the dynamics is conservative; otherwise the system is just self-organized to the neighborhood of the critical point with excursions around it (Bonachela and Muñoz, 2009; Dickman *et al.*, 2000).

In spatially-extended systems (i.e. beyond mean-field) the self-organization to criticality achieved by the above SOC mechanism is exact if the bulk dynamics is conservative (dissipation occurring only at the boundaries), but it is only approximate for non-conservative systems or if the separation of timescales is not perfect (Grinstein, 1995). In these latter cases, the self-organization mechanism drags the system back and forth around the critical point without sitting exactly at it; still, power-laws and effective scale-invariance can be observed across quite a few scales (Bonachela and Muñoz, 2009). This type of dynamics organizing the system to a relatively broad neighborhood around a critical point has been named "self-organized quasi-criticality" (SOqC) (Bonachela and Muñoz, 2009). This seems more likely to apply to biological systems (such as e.g. neural networks) than standard SOC, given that biological systems are not usually conservative nor do they exhibit perfect separation of timescales.

A concept similar to SOC has appeared in recent years under the name of *adaptive criticality* (Bornholdt and Rohlf, 2000; Dorogovtsev and Mendes, 2002; Droste *et al.*, 2012; Gros, 2008; Gross and Blasius, 2008; Kuehn, 2012; MacArthur *et al.*, 2010; Meisel and Gross, 2009; Perotti *et al.*, 2009; Rohlf, 2008; Rybarsch and Born-

[17] Stochastic variants of the original sandpile model, such as the one in Manna (1991) and the Oslo ricepile (Christensen *et al.*, 1996) show much cleaner scaling behavior that the original sandpile with deterministic rules, which present some scaling anomalies (Bagnoli *et al.*, 2003; De Menech and Stella, 2000; Ktitarev *et al.*, 2000; Tebaldi *et al.*, 1999).

[18] For more details see Bonachela and Muñoz (2009); Vespignani *et al.* (1998, 2000); Vespignani and Zapperi (1998); and Zapperi *et al.* (1995).

[19] Indeed, using Eq.(1), $\dot{\rho}(t) = (\lambda - 1)\rho - \lambda\rho^2$, and expressing the control parameter $\lambda - 1$ as $a + E$ (where "a" is a constant and E is an "energy" or "stress" variable; for sandpiles, E represents the total density of sandgrains while ρ is the density of "active" sites above the instability threshold), so that the critical point, $\lambda = 1$ corresponds $E_c = -a$. Assuming that E has a slow driving dynamics as described above: $\dot{E}(t) = +h - \epsilon\rho$, where h stands for the driving rate and ϵ is the dissipation rate coupled to the activity, then in the limit $h, \epsilon \to 0$ with $h/\epsilon \to 0$ (i.e. slow-driving and small dissipation at infinitely separated timescales) the only steady-state solution is $\rho = 0$ with $E = -a = E_c$, i.e. the system self-organizes exactly to its critical point.

holdt, 2014; Saito and Kikuchi, 2013; Solé *et al.*, 2002b). This 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 co-adaptive process, similar to the one sketched in Fig.3 but operating on the network architecture. Under some conditions, this can drive the dynamics to criticality (Bianconi and Marsili, 2004; Dorogovtsev *et al.*, 2008; Liu and Bassler, 2006) and the network architecture may become highly structured, capturing the non-trivial coupling between structure and dynamics in biological systems.

7. Generic scale invariance I

We have presented the paradigm of a critical point – with its concomitant spatio-temporal scale-invariance– separating two alternative phases. However, in some systems with peculiar symmetries or conservation laws, critical-like features may appear in extended regions in the phase space and not just at the edge of phase transitions. This is called *generic scale invariance* (Grinstein, 1991). This type of scenarios –that we discuss in what follows– can in some cases account for empirically reported scale-invariance without the need to invoke criticality. We refer to Grinstein (1991, 1995) for insightful discussions of mechanisms for generic scale invariance. A well-known example is the breaking of a continuous symmetry in low-dimensional systems, as it happens e.g. in some models of magnetism (such as the so-called XY model) in which each spin can point in any arbitrary direction in a plane (Binney *et al.*, 1993). These systems, instead of an usual ordered phase at low temperature, exhibit a whole quasi-ordered phase characterized by local order together with generic power-law decaying correlations (Grinstein, 1995). This type of ordering is relevant for bacterial-colony patterns (Ramos *et al.*, 2008) and will be briefly discussed here in the context of collective motion (section IV.D).

8. Generic scale-invariance II: Heterogeneity & Griffiths phases

An essential aspect of living systems is heterogeneity. For instance, there are dozens of neuron types interconnected in extremely inhomogeneous ways. Thus, models of biological collective properties need to address what is the role of diversity among their basic components. 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 inhomogeneities (see Fig.4). This form of disorder can alter the nature of phase transitions (see e.g.Villa Martín *et al.* (2014) and Vojta (2006)),

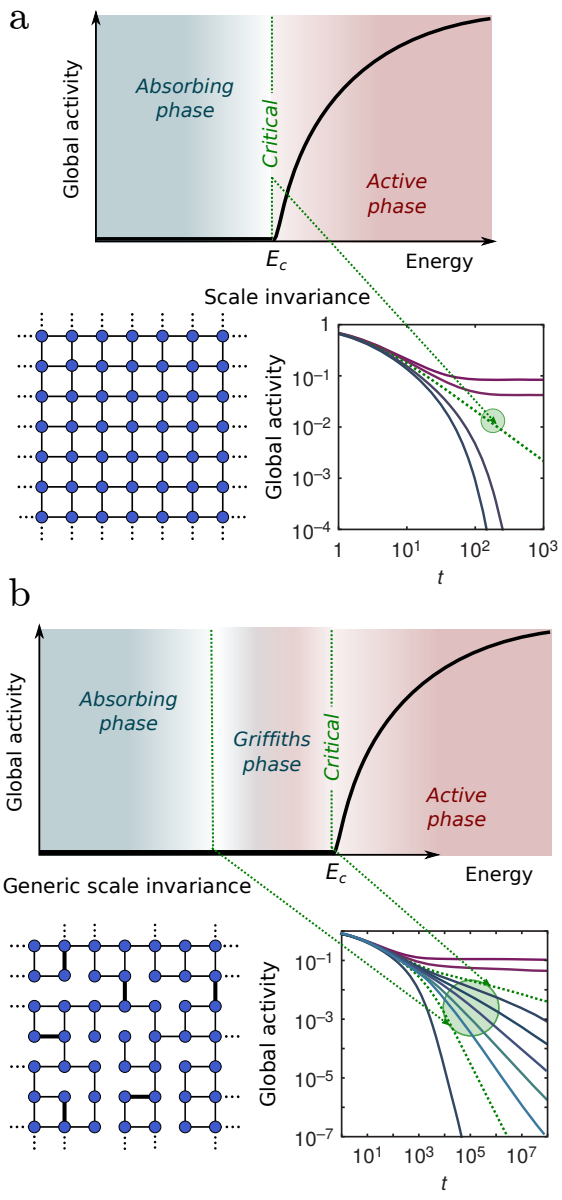

FIG. 4 Schematic representation of the phase diagram of a homogeneous (top) and a heterogeneous (bottom) system exhibiting an absorbing state phase transition. The second one is represented by a disordered two-dimensional lattice but other possible heterogeneous networks could have been considered. An intermediate (Griffiths) phase –with generic scale invariance– emerges in the neighborhood of the phase transition of (some) heterogeneous systems. In particular, a fully occupied system $\rho = 1$ decays as a power law only at the critical point of the pure system, but it does so in a whole region in parameter space of the heterogeneous one.

and can also induce novel phases absent in homogeneous systems. For instance, in the contact process, quenched disorder can be implemented by assuming a disordered lattice (such as that sketched in Fig.4b), a more complex (disordered) network, or considering a node-dependent propagation rate λ (Cafiero *et al.*, 1998; Moreira and

Dickman, 1996). In all these cases, a novel phase called a *Griffiths phase* (Griffiths, 1969) emerges. This novel phase stems from the existence of arbitrarily large, even if rare, local regions characterized by parameter values which differ significantly from their corresponding system averages. For example, for the disordered contact process, some tightly connected regions have an inherent tendency to be locally active, while other more loosely-connected ones have more propensity to become inactive. Thus, even if the system is globally in its absorbing phase, activity can linger for extremely long times confined to locally active regions giving rise to asymptotic power-law decay of the global activity (as illustrated in Fig.4b) and very large responses (Cafiero *et al.*, 1998; Vojta, 2006). This critical-like features appear generically, all across the so-called Griffiths phase. Thus, it is as if the critical behaviour extended to a stretched finite region in parameter space (see Fig.4). This type of phase can be very relevant for inhomogeneous biological systems exhibiting phase transitions; for example, empirically observed scale-invariance in heterogeneous brain networks (see below) may be easier to rationalize in terms of Griffiths phases than in terms of standard criticality (Moretti and Muñoz, 2013; Villegas *et al.*, 2016a, 2014), justifying the observation of broad critical-like regions in large-scale models of neural dynamics (Friedman and Landsberg, 2013; M. Kaiser, 2010; Rubinov *et al.*, 2011; Wang *et al.*, 2011a; Wang and Zhou, 2012).

9. Generic scale-invariance III: Neutral theories

We discuss "neutral theories" as they can produce a type of generic scale-invariance which has been recently discovered to be important in biological systems (see below). Neutral theories play a fundamental role in population genetics (Kimura, 1984), population ecology (Azaele *et al.*, 2016; Hubbell, 2001), epidemics (Pinto and Muñoz, 2011), etc. They all have in common the fact that they neglect differences among possible coexisting "species" (let them be alleles of a gene, types of trees, bacterial strains,...) and assume they are all dynamically equivalent, i.e. *neutral* (Blythe and McKane, 2007). Usually neutral dynamics is represented in terms of the so-called *voter model* (Dornic *et al.*, 2001; Liggett, 2004), but here –for the sake of coherence with examples above– we discuss a variant of the contact process that includes different species or "colors" (i.e. a multispecies contact process). We consider an arbitrary parameter $\lambda > 1$, such that the model sits anywhere within its active phase, and introduce also a small rate for spontaneous creation of activity, h. Every time a particle is spontaneously created, it is defined as a novel species and a new "color" or label is assigned to it; this color is inherited by all its possible offspring and their progeny. Individuals have the same rates regardless of their color, and thus they are "neutral"; the overall dynamics is blind to colors and thus it is exactly as in the standard contact process. However, some colors may proliferate more than others owing solely to demographic fluctuations. Even if the system is in its steady state, species can spontaneously disappear owing to fluctuations in particle numbers, and others can emerge out of spontaneous creation, giving rise to invasions or "avalanches". It has been shown that the sizes and durations of such avalanches are generically scale-free, regardless the precise value of λ, i.e. without the need for the system to be at the critical point ($\lambda_c = 1$) (Martinello *et al.*, 2016). The reason behind this apparently surprising fact is that the dynamics of each single species is marginal with respects to the others (owing to neutrality), and thus it does not have a net tendency to either grow or shrink, resulting in an effectively marginal dynamics and thus into scale-free avalanche distributions without any need for parameter fine tuning (Lopez-Garcia *et al.*, 2010; Martinello *et al.*, 2016).

III. FUNCTIONAL ADVANTAGES OF CRITICALITY

Given that –as we shall profusely illustrate in the next section– scale-invariance and putative criticality are empirically observed within a wealth of biological systems, it seems pertinent to ask: *what are the potential virtues of criticality, susceptible to be exploited by living systems to enhance their functionality and performance?*

To shed light onto this question, we first describe a remarkably 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 number of other possible functional advantages.

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 that, as proposed in Gold (1948), oscillate spontaneously even in the absence of stimuli (Choe *et al.*, 1998; Martin *et al.*, 2001) and are able to resonate with acoustic inputs. Such oscillations are damped if the concentration of Calcium ions is low, but as such a concentration increases there is a Hopf bifurcation above which oscillations are self-sustained (see e.g. Strogatz (2014)).

Empirical evidence reveals that, by regulating the ion concentration[20], hair cells operate in a regime very close

[20] Self-regulation to the instability point is achieved by using a local

to the Hopf bifurcation (Ospeck *et al.*, 2001), and this has been argued to entail important consequences for signal processing as we discuss now (Choe *et al.*, 1998; Eguíluz *et al.*, 2000; Hudspeth *et al.*, 2010; Martin *et al.*, 2001).

A hair cell can be effectively described as Hopf oscillator (Hudspeth, 2014):

$$\dot{\phi}(t) = (a + i\tilde{\omega})\phi(t) - |\phi|^2\phi(t) \tag{4}$$

where the phase ϕ is a complex number, $\tilde{\omega}$ a resonance frequency, and a the control parameter (ion concentration) setting the dynamical regime. Eq.(4) 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[21]. Introducing stimuli of the characteristic frequency $\omega = \tilde{\omega}$ and amplitude F (i.e. adding $+Fe^{i\tilde{\omega}t}$ to Eq.(4)), and writing $\phi(t) = R(t)e^{i\omega t}$, one finds

$$\dot{R}(t) = R(t)[a - R^2(t)] + F. \tag{5}$$

In the stationary state, for $a > 0$ and small F, the linear-response regime holds, i.e. the response R is proportional to F. However, at the bifurcation point, $a = 0$, the response R is strongly non-linear, as $R = F^{1/3}$ and, consequently, the ratio response-to-force $R/F = F^{-2/3}$ exhibits an essential singularity as $F \to 0$, implying a diverging response to tiny signals of the characteristic frequency. Given that the response decays abruptly as the frequency deviates from the resonance, i.e. as $\omega \neq \tilde{\omega}$, 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 uni-dimensional) array of diverse and coupled hair cells. When coupling many different Hopf oscillators, collective phenomena –such as a phase transition– emerge, leading to sharpened frequency response (Duke and Jülicher, 2003; Magnasco, 2003), increased input sensitivity (Gomez *et al.*, 2015; Kern and Stoop, 2003), as well as to power-law distributed avalanches of hair-cell co-activations (Stoop and Gomez, 2016).

Summing up, a criticality-based mechanism (combined with other important effects not discusse here) has been shown to constitute the basis for all the extraordinary features of vertebrate hearing, even the most intricate ones (Stoop and Gomez, 2016). Similar phenomena have been explored in the olfactory system (Bushdid *et al.*, 2014) and the visual cortex (Shew *et al.*, 2015), and in the cortex as a whole (Shew and Plenz, 2013) (see also Chialvo (2006) and Friston *et al.* (2012)).

feedback control mechanism (Camalet *et al.*, 2000; Moreau and Sontag, 2003).

[21] See Kern and Stoop (2003) from where this discussion is adapted.

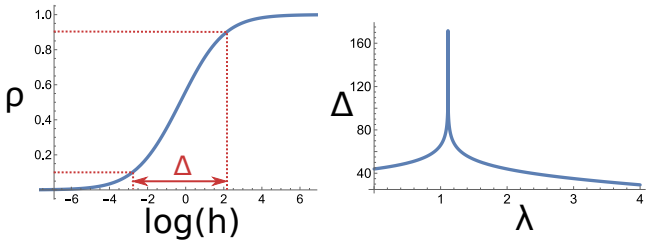

FIG. 5 Sketch of the behavior of the dynamic range near a critical point. (Left) Steady state as a function of the driving h (in log scale) for a given value of the control parameter λ; Δ –the dynamic range– signals the interval where distinguishable responses (steady states, characterized by their activity density ρ) can be measured. (Right) Δ exhibits a pronounced peak (a divergence) at criticality.

B. Exploiting criticality

1. Maximal sensitivity and dynamic range

An important trademark of critical points is the divergence of the response or susceptibility which is likely to be exploited in biological sensing systems, as discussed above. A related quantity, dubbed *dynamic range*, was introduced in Kinouchi and Copelli (2006). These authors considered a model for activity propagation (similar to the contact process) with a critical point ($\lambda_c = 1$) running on a random network. If the system was additionally exposed to an external stimulus/driving, h, able to spontaneously create activity at empty nodes then the dynamic range $-\Delta = 10\log[h(\rho = 0.9)/h(\rho = 0.1)]$– gauges the range of diverse stimuli intensities (in log scale) where variations in h can be robustly coded by variations in the stationary density ρ (i.e. the response), discarding stimuli that give a too-weak response ($\rho < 0.1$) or too close to saturation ($\rho > 0.9$) (see Fig.5)[22]. Δ turns out to have a marked peak at the critical point $\lambda_c = 1$ (see Fig.5), indicating that the system can respond distinctively to a very large variety of inputs. Instead, away from criticality it is only in a much smaller window of h values that the system is able to produce discriminative outputs.

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 in e.g. neural systems where coherent behavior across extended areas is observed (Tagliazucchi

[22] The choice of the interval is arbitrary; it does not affect significantly the behavior.

et al., 2012) and flocks of birds or insect swarms for coordination purposes (Cavagna *et al.*, 2010), as we shall discuss. Similarly, the divergence of correlation times and critical slowing down may provide systems with a useful mechanism for the generation of long-lasting and/or slow-decaying memories at multiple timescales (see e.g. Deco and Jirsa (2012)).

3. Computation exploiting criticality

By "computation" it is usually meant an algorithm or system that –aiming at performing some tasks– assigns outputs to inputs following some internal logic; and the computational power of a given device/system is quantified by estimating the complexity and diversity of associations of inputs to outputs that it can support. It was conjectured long ago 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; Carpenter and Grossberg, 2016; Grossberg, 1982; Hopfield, 1982). In particular, it was shown that networked systems operating at criticality can have exceptionally high computational capabilities, as first suggested in (Ashby, 1960; Turing, 1950) and much further developed in the context of machine learning (Crutchfield and Young, 1988; Langton, 1990; Li *et al.*, 1990; Packard, 1988). 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[23] at the "edge of chaos" are especially suitable to perform complex computations[24]. The "edge of chaos" or critical point (as we rather call it here) is the borderline between two distinct phases or regimes: the chaotic/disordered one in which perturbations and noise propagate unboundedly (thereby corrupting information storage) and the frozen/ordered phase whereas changes are rapidly erased (hindering the possibility for the system to react and limiting enormously its capability of transmitting meaningful information). Thus, the critical point confers on computing devices an optimal tradeoff between information storage and information transmission, two of the key ingredients proposed by Turing as indispensable for universal computing machines (Turing, 1950).

Aspects of criticality can be particularly useful in the context of "*reservoir computing*" (Lukoševičius *et al.*, 2012; Szary *et al.*, 2011; Verstraeten *et al.*, 2007). This type of computation was developed independently in the fields of machine learning ("echo state networks" of Jaeger (2001)) and computational neuroscience ("liquid state machine" in Maass *et al.* (2002)). These artificial-intelligence machines are a type of networks of nodes and links, "the reservoir", where each node represents an abstract neuron and links between them mimic the connectivity of actual biological circuits. An input signal is fed into the network and the dynamics of the system projects it into a higher-dimensional space. A simple mechanism is trained to read out the state of the reservoir and map it to the desired output, without affecting the reservoir itself, which is a very convenient computational strategy. A series of seminal papers showed that such machines can perform real-time computations in a coherent yet flexible way –in the sense of responding in real-time to time varying input signals by generating time-dependent outputs– if they operate near a critical point (Bertschinger and Natschlager, 2004; Boedecker *et al.*, 2012; Legenstein and Maass, 2007; Legenstein, 2005; Maass *et al.*, 2002). Also, recent work reveals 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 *et al.*, 2015).

Let us finally mention that the relationship between recent and spectacular developments in machine learning, i.e. the so-called deep learning machines (see e.g. LeCun *et al.* (2015)) and criticality has been recently investigated (Lin and Tegmark, 2016; Mehta and Schwab, 2014; Oprisa and Toth, 2017a,b; Song *et al.*, 2017).

4. Statistical complexity and large repertoires

In systems at equilibrium, the divergence of the specific heat at criticality reflects the huge variability of possible internal states (Binney *et al.*, 1993). Similarly, in dynamical problems the variability of dynamical transitory patterns is maximal at criticality (as illustrated above for the contact process), allowing for a very wide spectrum of possible responses, sometimes called "dynamical repertoire". This is consistent with the finding that e.g. models for brain activity reach 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 amount of response patterns (Rämö *et al.*, 2007, 2006), (iii) the variability of phase synchrony structures (Yang *et al.*, 2012), (iv) the variability of attractors to support memories in neural systems (de Arcangelis and Herrmann, 2010) or cellular genetic regulatory networks (Krawitz and Shmulevich, 2007), and (v) the diversity in structure-dynamics relationships (Nykter *et al.*, 2008b) have been shown to be maximized at criticality. All this suggests that in order to spontaneously generate complex patterns, required e.g. to store highly diverse tokens of

[23] Cellular automata in this case (Wolfram, 2002).

[24] This proposal triggered a heated debate; see, e.g. Crutchfield (2012); Crutchfield and Young (1988); and Mitchell *et al.* (1993).

information, operating near criticality can be an excellent solution.

5. Optimal information transmission

Information transmission is usually quantified in terms of mutual information among internal parts of the systems or between the system and external sources (Cover and Thomas, 1991; Mezard and Montanari, 2009). Mutual information measures the amount of information that the knowledge of one variable provides about another and, hence, can be used as an estimator of the information transfer between them (Prokopenko *et al.*, 2009; Ribeiro *et al.*, 2008). Several studies have unveiled that the overall transmission of information between units is maximal if the underlying dynamical process is critical (Beggs, 2008; Li *et al.*, 1990; Luque and Ferrera, 2000; Prokopenko, 2013; Rämö *et al.*, 2007; Ribeiro *et al.*, 2008). Similarly, information transfer and transfer entropy (Lizier *et al.*, 2008b; Shriki and Yellin, 2016; Solé and Miramontes, 1995; Solé and Valverde, 2001), Fisher information (Wang *et al.*, 2011b) and, more in general, statistical complexity (as discussed above) (Krawitz and Shmulevich, 2007; Lizier *et al.*, 2008a; Rämö *et al.*, 2007) have been thoroughly analyzed and shown to be maximal at criticality is critical[25].

C. Adaptation and evolution towards criticality

In the preceding paragraphs we have discussed a number of properties that are optimal at criticality. It remains to be clarified how do adaptive (GellMann, 1994; Gros, 2008) and/or evolutionary (Nowak, 2006) mechanisms –characteristic of life[26]– lead biological systems toward critical states.

Aimed at shedding light on this, Goudarzi *et al.* (2012) considered an ensemble of individuals or "agents", each of them represented as a dynamical network, with a binary variables defined at each node, with some input nodes (reading information from the environment) and some readout nodes, providing an output or response. The states of nodes are updated following random binary (Boolean) functions which allot a specific output to a set of inputs. Larger "fitness" values are assigned to networks that are able to perform better a series of computational tasks, each one consisting in having to assign a specified output to a series of different inputs. Diverse tasks are alternated in time. By allowing for random "mutations" in their internal structure, i.e. in the binary functions connecting the agents can explore different network states and dynamical regimes. Employing a genetic algorithm (Goldberg and Holland, 1988) it was shown that the agents converge to a state close to criticality. In other words, critical dynamics emerge as the optimal solution under the combined selective pressures of having to learn different tasks (i.e. having to produce different outcomes/attractors) and being able to readily shift among them, following changes in the inputs.

In a similar setting, it has been found that the overall dynamics of networks that have already learnt to perform a given set of tasks is very close to criticality and that the adaptive learning process leads nodes to become heterogeneous: those receiving inputs become locally supercritical (in the sense of propagation of perturbations) allowing for large reactivity, while those in the network core –where, in order to to successfully perform the task, information has to flow more reliably/deterministically– become subcritical locally (Villegas *et al.*, 2016b). This opens promising research avenues, as it distinguishes different dynamical states in different parts of the network. Also, in the presence of strong external noise -which randomly modifies the states of nodes– optimal networks tend to be slightly subcritical, rather than critical, thus compensating for extrinsic sources of variability (Villegas *et al.*, 2016b).

Hidalgo *et al.* (2014) showed –relying on an information-theoretic approach– that communities of similar adaptive agents trying to communicate with each other, converge to a peak of the (generalized) susceptibility (which, in particular, may be a critical state). More specifically, the task consists in being able to infer the state of other agents in an efficient way, thus creating a "common language". This approach was argued to provide a parsimonious mechanism for the emergence of critical-like behavior in groups of individuals needing to coordinate themselves as an ensemble (see also, Hidalgo *et al.* (2016)).

IV. EMPIRICAL EVIDENCE OF CRITICALITY IN LIVING SYSTEMS

In what follows we present some of the most-remarkable existing empirical evidence of criticality in biological 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 very appealing, evidence in many cases is not complete and conclusions should be always taken with caution. Indeed, for many of the forthcoming examples, we also discuss existing criticisms and potential technical or interpretative problems.

[25] Some authors suggest that the maxima are not exactly at criticality (Barnett *et al.*, 2013; Toyoizumi and Abbott, 2011).

[26] This is, beyond purely self-organization mechanisms, such as SOC, also exhibited by inanimate systems.

A. Spontaneous neural activity

1. Endogenous cortical activity

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). Remarkably, the cerebral-cortex of mammalians is never silent, not even under resting conditions nor in the absence of stimuli. Instead, it is in a state of ceaseless spontaneous electrochemical activity (Arieli *et al.*, 1996; Fox and Raichle, 2007; Raichle, 2011; Yuste *et al.*, 2005). Neurons integrate presynaptic excitatory and inhibitory inputs from other neurons, and fire an action potential when a given threshold is overcome, stimulating further ongoing activity. This generates irregular outbursts –i.e. the synchronization events during which many neurons fire coherently within a short time– interspersed by quiescent periods, as empirically observed both *in vitro* (Eytan and Marom, 2006; Sanchez-Vives and McCormick, 2000; Segev and Ben-Jacob, 2001; Segev *et al.*, 2001; Tabak and Latham, 2003) and *in vivo* (Meister *et al.*, 1991; Steriade *et al.*, 1993), and as sketched in Fig.6. Understanding the genesis and functionality of spontaneous cortical activity – which accounts for about 20% of the total oxygen consumption of a person is at rest– is key to shedding light onto how the cortex processes information and computes, and ultimately on how the brain works (Arieli *et al.*, 1996; Deco *et al.*, 2011, 2013a; He, 2014). Criticality might play a relevant role in this context as we discuss in what follows.

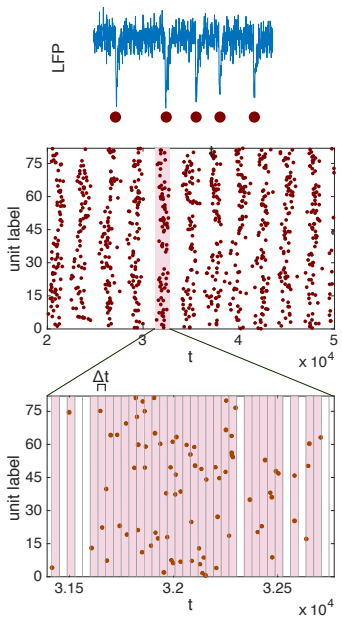

FIG. 6 Sketch illustrating how neuronal avalanches are measured. (top) Local field potential (LFP) are measured at different locations; negative peaks of a LFP timeseries correlate with local population spikes of the underlying neurons. (Middle) Raster plot illustrating the times at which peaks of the LPF occurs for different measurement sites. Observe that these events are clustered in time; i.e. they occur in a close to synchronous fashion. (Bottom) Enhancing the temporal resolution, it is possible to resolve the spatio-temporal organization of local events; they occur in the form of "neuronal avalanches" (shaded columns) interspersed by periods of quiescence (white columns).

2. Neuronal avalanches

Beggs and Plenz (2003), in a remarkable breakthrough, succeeded at resolving the internal spatio temporal organization of individual bursts of activity. They analyzed mature cultures as well as acute slices of rat cortex, and recorded spontaneous local field potentials (LFP) –which provide coarse-grained measurements of electrochemical activity– in different locations as a function of time. 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.6, events at different sites have a tendency to cluster in time in a close-to-synchronous way, producing "network spikes"; but each of these peaks of synchrony, when temporally resolved, consists in a cascade of succesive 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 cut-offs that increase with system size. These exponents are in agreement with the (mean-field) theory of critical contact/branching processes as described in Section I. Importantly, this conclusion breaks down when data are temporally reshuffled, which results in exponential avalanche distributions, i.e. large events disappear and long-ranged temporal correlations are washed away. Furthermore, the averaged branching ratio, i.e. the expected value of the quotient between the number of active sites at a given time and at its preceding time, was found to be very close to unity, consistent with criticality of the underlying activity-propagation process[27] (Beggs and Plenz, 2003; Plenz and Thiagarajan, 2007). Consistent results have been obtained *in vitro* (Mazzoni *et al.*, 2007; Pasquale *et al.*, 2008) and *in vivo* for different species (Gireesh and Plenz, 2008; Hahn *et al.*, 2010; Petermann *et al.*, 2009; Ribeiro *et al.*, 2010; Yu *et al.*, 2011) and across resolution scale, from single neuron spikes

[27] Also, inter-avalanche correlations have been analyzed, revealing, e.g. that avalanche sizes are significantly correlated with the duration of the preceding quiescence time (Lombardi *et al.*, 2012, 2014, 2016; Pittorino *et al.*, 2017).

to rather coarse-grained measurements[28]. 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[29].

Not only critical exponents but also other generic features of spatio-temporal scale-invariance have been empirically reported. In particular, avalanche distributions for different sample sizes obey finite-size scaling Eq.(2), as they can be collapsed into a unique re-scaled curve (Beggs and Plenz, 2003; Mazzoni *et al.*, 2007; Petermann *et al.*, 2009). Similarly, the mean temporal profile of neuronal avalanches of widely varying durations is quantitatively described by a single universal scaling function (Friedman *et al.*, 2012; Sethna *et al.*, 2001), and scaling relationships between the measured exponents are fulfilled (Friedman *et al.*, 2012).

All this seems to make a strong case in favor of criticality. However, some caveats exist. Some of them are:

(i) Thresholding: A source of ambiguities in extracting (discrete) events from (continuous) time-series analyses comes from thresholding; i.e. from the fact that activity at any given spatio-temporal location needs to overcome some threshold to be declared an "event". Petermann *et al.* (2009) compared results for different thresholds in LFPs timeseries; obviously, avalanches can split into smaller ones as the threshold is raised and some events may disappear. Remarkably, avalanche (size and duration) distributions were reported to remain unaffected by this process, suggesting the existence of an underlying scale-invariant organization of events (Petermann *et al.*, 2009). Thus, thresholding can be viewed as a sort of coarse-graining procedure that –if properly performed– should preserve universal properties such as exponents of truly scale invariant processes. A word of caution is required as recent works have underlined the "perils" associated with thresholding, which in some controlled cases has been shown to generate effective avalanche exponents (at least for small sizes/times) as well as correlations in the timings of consecutive avalanches (Font-Clos *et al.*, 2015; Janićević *et al.*, 2016; Laurson *et al.*, 2009). Advancing along these research lines remains an important task.

(ii) Time binning: Avalanches can only be defined 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.6). This introduces some ambiguity, and the measured avalanche exponents have been shown to be sensitive to the choice of the time-bin. However, taking this to coincide with the mean inter-event interval, the mean-field branching process exponents seem to be systematically recovered (Beggs and Plenz, 2003; Haimovici *et al.*, 2013; Petermann *et al.*, 2009; Tagliazucchi *et al.*, 2012). Still, in our opinion, further work is needed to clarify the effect of time binning in the analysis of avalanches.

(iii) Sub-sampling: A closely related issue is that of sub-sampling as a result of technological resolution limitations. The effects of sub-sampling have been carefully discussed in Priesemann *et al.* (2009, 2013, 2014), where it was argued that empirical data are better characterized by a slightly sub-critical dynamics rather than by a critical one; see also Tomen *et al.* (2015).

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

(v) Alternative explanations: Some authors support different interpretations of the observed power-laws (Touboul and Destexhe, 2010, 2017) or claim that they are not power-laws whatsoever[30].

However, additional experimental signatures of criticality, beyond scale-free avalanches, have been also reported in cortical networks, as we describe in what follows.

3. Neural synchronization

Much attention has been historically devoted to brain rhythms observed in EEG, MEG, and LFP measurements (Buzsaki, 2009). These rhythms emerge owing to the transient synchronization (Pikovsky *et al.*, 2003) between different neural regions/circuits, and they play a key role in neural function (Steriade *et al.*, 1996). Indeed, clusters of neurons with coherent neural activity have a much stronger coordinated effect on other neuronal assemblies than asynchronous neurons do (Brunel and Hakim, 2008;

[28] This includes single unit recordings (Bellay *et al.*, 2015), local field potentials (LFP) (Beggs and Plenz, 2003; Petermann *et al.*, 2009), electroencephalography (EEG) (Allegrini *et al.*, 2010; Freeman *et al.*, 2003; Meisel *et al.*, 2013) and electrocorticography (ECoG) (Solovey *et al.*, 2012), magnetoencephalography (MEG) (Novikov *et al.*, 1997; Palva *et al.*, 2013; Poil *et al.*, 2012; Shriki *et al.*, 2013), and functional magnetic resonance imaging (fMRI) (Haimovici *et al.*, 2013; Tagliazucchi *et al.*, 2012), among others.

[29] Some studies suggest that even single neurons can be intrinsically critical to optimize e.g. their inherent excitability (Gal and Marom, 2013; Gollo *et al.*, 2013).

[30] For more details, see Bédard *et al.* (2006); Dehghani *et al.* (2010); Destexhe (2009); Destexhe *et al.* (2007); Touboul and Destexhe (2010, 2017), as well as Yu *et al.* (2014) for a criticism to some of these works.

Kelso *et al.*, 1986; Scholz *et al.*, 1987). 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, schizophrenia, or autism (Yang *et al.*, 2012). Empirically, the measured level of synchronization across brain regions and across time has been found to be highly variable and with strong long-range correlations. This can be interpreted as a template for variability in the possible responses to stimuli and, hence, as a basis of a large dynamical repertoire (Arieli *et al.*, 1996) and to achieve a balance between integration and segregation (Tononi *et al.*, 1994). The role that criticality might play in keeping intermediate and variable levels of synchrony has been empirically analyzed.

Spontaneous bursts of coordinated activity (much as in Fig.6) have been detected in cortical slice cultures (Yang *et al.*, 2012). The overall level of phase synchrony between different electrodes was recorded under different pharmacological conditions, ranging from excitation-dominated to inhibition-dominated regimes. It was observed that there is a transition point where excitation and inhibition balance. At such a point –i.e. "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 are concomitantly observed (Gireesh and Plenz, 2008; di Santo *et al.*, 2017a; Yang *et al.*, 2012).

4. Diverging correlations and responses

Here we summarize diverse features characteristic of criticality that have been empirically identified in the awake/healthy brain.

Analyses of different timeseries (e.g. measurements of cortical activity oscillations in EEG and MEG analyses) reveal the emergence of power-laws in the form of $1/f$ power spectra of amplitude fluctuations, reflecting an intricate composition of frequencies across many different timescales (Allegrini *et al.*, 2009; He, 2011; Miller *et al.*, 2009; Novikov *et al.*, 1997; Pritchard, 1992; Zare and Grigolini, 2013). $1/f$ power spectra can be taken as evidence that ongoing neural dynamics is strongly autocorrelated (West and Grigolini, 2010), meaning that timeseries carry a long-range memory of their own dynamics across time, as directly verified in EEG data using a variety of analyses (Hardstone *et al.*, 2012; Linkenkaer-Hansen *et al.*, 2001), and this might be suggestive of criticality. However, evidence based on $1/f$ spectra by itself does not make a strong case to support criticality, as a large variety of alternative mechanisms –not relying on criticality– have been proposed to explain $1/f$ power spectra, both in general terms (Amaral *et al.*, 2004; De Los Rios and Zhang, 1999; Hausdorff and Peng, 1996; Mandelbrot, 2002; Manneville, 1980) and specifically for neural systems (Bédard *et al.*, 2006; Dehghani *et al.*, 2010; Pettersen *et al.*, 2014). Still, $1/f$ noise in concomitance with other empirical signatures of criticality, such as spatial long-range correlations, can reinforce existing evidence.

Two-point spatial correlation functions (as determined e.g. from resting-state fMRI data) have been also analyzed and shown to exhibit self-similarity in both space and time (Expert *et al.*, 2011; He, 2011). This is done by the application of successive spatial coarse-graining steps (space) and by the presence of a $1/f$ power-spectrum (time), respectively. Remarkably, correlations are much larger in the awake than in the anesthetized state suggesting that criticality (at least large correlations) might be a feature of the awake brain (Bellay *et al.*, 2015).

The dynamic range has been experimentally measured in cortical neural networks *in vitro* (Shew *et al.*, 2009) and *in vivo* (Gautam *et al.*, 2015). By pharmacologically altering the ratio of excitation to inhibition –thus tuning the dynamical state– the authors were able to measure the stimulus/response curve (see Fig.5) as a function of the distance to the critical point –as defined by the precise balance between excitation and inhibition– and to verify that Δ exhibits a pronounced peak at the critical point, which is also where scale-free avalanches are observed.

Cortical ongoing activity has been vividly shown to be in a state of high sensitivity/susceptibility (Arieli *et al.*, 1996). Also, when a stimulus is presented repeatedly, the variability of the evoked cortical response is often as large as the response itself (Arieli *et al.*, 1996). Even more remarkably, it has been reported that experimentally modifying the state of a single neuron can dramatically alter the global brain state (Cheng-yu *et al.*, 2009; Houweling and Brecht, 2007).

5. Global activity at the edge of stability

Solovey *et al.* (2012) analyzed high-temporal-resolution electrocorticography (ECoG) data from recordings in humans, observing time-dependent levels of activity across different locations. The system state can be represented a a vector, whose time evolution can be approximated by employing an auto-regressive analysis, a commonly-used tool in time-series analyses which maps the actual continuous-time dynamics to a series of linear (matricial) transformations between successive discrete-in-time vector states (Akaike, 1969). By performing an eigenvector decomposition of each of the matrices, it is possible to monitor the evolution of the leading eigenvalues as a function of time. In awake individuals, eigenvalues turn out to oscillate closely around the threshold of instability, indicating that the dynamics is self-regulated at the edge of a

phase transition. Remarkably, in anesthetized subjects, eigenvalues become much more stabilized, suggesting that deviations from the instability point could be used as a measure of loss of consciousness (Alonso *et al.*, 2014).

6. Models at criticality and optimal data fits

A series of works have analyzed the performance of computational models –tuned to operate in their different possible dynamical regimes– to produce the best possible fit to empirical data from neural systems.

(i) Aburn *et al.* (2012) found that tuning a model of cortical activity to its critical point reproduces strong auto-correlations of local timeseries, as observed in EEG measurements (Allegrini *et al.*, 2010; Meisel *et al.*, 2013; Poil *et al.*, 2012; Van de Ville *et al.*, 2010).

(ii) It has also been found that models of cortico-thalamic activity need to operate at points of instability to describe multistability and the emergence of empirically recorded (α) oscillations (Freyer *et al.*, 2009, 2011).

(iii) Functional magnetic resonance imaging (fMRI) studies performed in the resting-state –i.e., while the subject is awake not performing any specific task– reveal the emergence of spatio-temporal patterns of strongly coherent fluctuations in the level of activity. This allows to determine so-called "resting state networks", encoding pairwise correlations between different brain regions, which collectively become active or inactive, and that are consistently found in healthy individuals[31]. Running diverse simple dynamical models on top of the empirically determined network of physical (neuro-anatomical) connections of the human brain –i.e. on the "*human connectome network*"– it was found that spatio-temporal correlations similar to the empirically-measured ones, are reproduced if and only if the models operate at criticality (Cabral *et al.*, 2011; Fraiman *et al.*, 2009; Haimovici *et al.*, 2013; Plenz, 2013). This suggests that resting-state spatio-temporal patterns of activity emerge from the interplay between the critical dynamics and the large-scale underlying architecture of the brain. Thus, resting state networks reflect structured/critical fluctuations among a set of possible attractors –among which the brain state can jump– suggestive of a state of alertness facilitating rapid task-dependent shifts (Deco and Jirsa, 2012; Deco *et al.*, 2013b; Ghosh *et al.*, 2008; Ponce-Alvarez *et al.*, 2015).

(iv) More recent studies have employed the Kuramoto model for the synchronization of coupled oscillators (Acebrón *et al.*, 2005; Arenas *et al.*, 2008; Breakspear *et al.*, 2010; Kuramoto, 1975; Strogatz, 2000) on top of the human connectome network. These models unveil that, owing to the highly heterogeneous architecture of brain networks –with a hierarchical modular organization[32]– there can be a broad region in parameter space where large levels of variability and intermittency in synchrony are observed. This implies that the dynamics would not require to be exactly critical to reproduce empirical findings, but just to be located in a broad region in parameter space resembling a Griffiths phase, as described in Sect.I (Sadilek and Thurner, 2015; Shanahan, 2010; Villegas *et al.*, 2016a, 2014; Wildie and Shanahan, 2012).

7. A percolation-like phase transition

Tagliazucchi *et al.* (2012) related cortical dynamics to a percolation phenomenon (Christensen and Moloney, 2005; Peters and Neelin, 2006). More specifically, by employing a thresholding method to continuous fMRI time series in the resting state, the authors derived spatio-temporal point process (a series of discrete "events"). Using the density of active sites at a given time as an effective measure of an "control parameter", while the size of the largest connected cluster at each time as a (percolation-like) "order parameter", it was found that there is a value of the control parameter at which both the total number of clusters and their size-variability exhibit a peak, as happens at the threshold of percolation-like transitions. Data are observed to stay most of the times close to such a critical values, but with broad excursions to both, sub- and super-critical phases, suggesting that regulatory mechanisms keep the system hovering around a percolation transition[33]. Furthermore, the cluster-size distribution is a power-law spanning almost four orders of magnitude when the system is in the critical region. These model-independent results reveal that the resting brain spends most of the time near the point of marginal percolation of activity, neither "too" inactive nor exceedingly active.

8. Disruptions of criticality and abnormal behavior

Experimental analyses of neural activity under modified physiological, pharmacological, or pathological con-

[31] See the extensive literature on this e.g. (Beckmann *et al.*, 2005; Biswal *et al.*, 1995; Deco *et al.*, 2011, 2013a; Diez *et al.*, 2015; Greicius *et al.*, 2003; Raichle *et al.*, 2001).

[32] The network of neuro-anatomical connections, e.g. the *human connectome*, turns out to be a network organized in moduli – characterized by a much larger intra than inter connectivity-structured in a hierarchical nested fashion across many scales (Betzel *et al.*, 2013; Breakspear, 2017; Bullmore and Sporns, 2009; Kaiser, 2011; Meunier *et al.*, 2010; Sporns, 2010; Sporns *et al.*, 2004, 2005).

[33] This is similar to what happens in self-organized quasi-criticality; see Sect.I.

ditions provide an important piece of evidence that criticality might be specific of awake and healthy brain activity. For instance, repressing inhibitory mechanisms –i.e. breaking the perfect balance between excitation and inhibition that characterizes functional neural networks (Barral and Reyes, 2016; Rosenbaum and Doiron, 2014; van Vreeswijk and Sompolinsky, 1996)– induces a tendency to super-critical propagation of activity, including many large system-spanning avalanches, clearly disrupting scale-invariant behavior (Beggs and Plenz, 2003; Mazzoni *et al.*, 2007).

Signatures of criticality have been reported to fade away during epileptic seizures (Hobbs *et al.*, 2010; Meisel *et al.*, 2012) as well as during anomalously large periods of wakefulness (Meisel *et al.*, 2013) or while performing simple tasks (Hahn *et al.*, 2017). Similarly, long-range temporal correlations –characteristic of the awake state– break down during deep sleep (Tagliazucchi *et al.*, 2013), anesthesia (Bellay *et al.*, 2015; Ribeiro *et al.*, 2010), and under unconsciousness (Tagliazucchi *et al.*, 2016), suggesting that critical dynamics is specific to the state of wakefulness. In this context, sleep has been proposed as a mechanism to reset the dynamics to criticality (Pearlmutter and Houghton, 2009).

Experimental evidence supports 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 towards criticality only when they become mature (Stewart and Plenz, 2008; Tetzlaff *et al.*, 2010).

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 (Hobbs *et al.*, 2010; Massobrio *et al.*, 2015).

9. Models of neuro-criticality

Since the idea that the computational power of the brain could emerge out of collective properties (Hertz *et al.*, 1991; Hopfield, 1982), a large and disparate number of modeling approaches –with varying levels of sophistication– have been proposed to scrutinize neural dynamics (Amit, 1992; Amit and Brunel, 1997; Dayan and Abbott, 2006; Izhikevich, 2004, 2007; Kandel *et al.*, 2000; Mattia and Sanchez-Vives, 2012). These reveal a large variety of phases and possible dynamical regimes such as up and down states (Cortes *et al.*, 2013; Hidalgo *et al.*, 2012; Holcman and Tsodyks, 2006; Mattia and Sanchez-Vives, 2012; Mejias *et al.*, 2010; Parga and Abbott, 2007), 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. Rather, we focus on approaches aimed at justifying the possible emergence of criticality in actual neural networks.

P. Bak[34] is to be acknowledged for first proposing that concepts of criticality and self-organization (i.e. SOC) could play a role in neural dynamics[35]. Herz and Hopfield (1995) readily pointed out that stylized integrate-and-fire models of neuronal networks were mathematically equivalent to SOC archetypes. Thereafter, some works explored simple neural-network dynamics similar to SOC (sandpile) models, in which stress is accumulated and then released to neighboring units in a conserved way, i.e. without leakage. de Arcangelis *et al.* (2006) introduced a conservative neural-network model, inspired by SOC, but also including a number of physiological features such as refractory periods and long-term Hebbian synaptic plasticity[36]. This setting, which actually leads to criticality, gave rise to a number of important studies on the interplay between critical dynamics, memory and learning (de Arcangelis, 2011, 2012; de Arcangelis and Herrmann, 2010, 2012; de Arcangelis *et al.*, 2014).

Levina and collaborators proposed in a series of seminal works to use short-time synaptic depression (Markram and Tsodyks, 1996; Sussillo *et al.*, 2007; Tsodyks and Markram, 1997) as a mechanism to control neural networks and to auto-organize them to the edge of a phase transition (Levina *et al.*, 2007, 2009) (see also (Gómez *et al.*, 2008)). In particular, synaptic strengths become depressed after firing of pre-synaptic neurons (due to temporary neurotransmitter depletion) –thus reducing the level of overall 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) generate a feedback loop that, allegedly, guides the networks to criticality, much as in SOC.

Similar models for the self-organization to criticality relying on diverse regulatory or homeostatic mechanisms (Cortes *et al.*, 2012) such as spike-timing dependent plasticity (Effenberger *et al.*, 2015; Meisel and Gross, 2009; Rubinov *et al.*, 2011; Shin and Kim, 2006), retro-synaptic signals (Hernandez-Urbina and Herrmann, 2017), and Hebbian plasticity (de Arcangelis, 2011; de Arcangelis and Herrmann, 2010, 2012; de Arcangelis *et al.*, 2014, 2006; Bienenstock and Lehmann, 1998; Uhlig *et al.*, 2013), have been analyzed.

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[34] Together with D. Chialvo and other close collaborators.

[35] See e.g. (Bak, 1996; Bak and Chialvo, 2001; Chialvo, 2004; Chialvo and Bak, 1999; Stassinopoulos and Bak, 1995). Also, early work by Haken, Kelso and coworkers brought about the possibility of bifurcations in neural dynamics and stressed the potential role that critical fluctuations and critical slowing-down might play (Haken, 1977, 2013; Kelso *et al.*, 1986; Scholz *et al.*, 1987).

[36] Hebbian plasticity is believed to underlie many instances of learning (Hebb, 1949).

However, doubts have been cast on the limits of validity of this type of SOC-like approaches. Actually, they might be not truly biologically plausible as they rely on conservative or almost-conservative dynamics (while neurons and synapses are leaky) and, even more importantly, they require of an unrealistically large (infinite) separation of timescales to actually self-tune the dynamics to a critical state (de Andrade Costa *et al.*, 2015; Bonachela *et al.*, 2010; Bonachela and Muñoz, 2009). If the separation of timescales in these models is fixed to moderate/intermediate values, such a self-organization is not achieved, leading to different possible scenarios (such as, e.g. the system hovering up and below the critical point (Bonachela *et al.*, 2010) or not being critical at all).

Another very important and influential model was claimed to explain self-organized criticality without assuming conservative dynamics nor an infinite separation of timescales (Millman *et al.*, 2010). As a matter of fact, this model (consisting of a network of leaky integrate-and-fire neurons with synaptic plasticity) was shown to exhibit a discontinuous phase transition –lacking a critical point– between an up and a down state, with high and low levels of activity, respectively. This is relevant as similar up and down states are empirically known to emerge under deep sleep or anesthesia (Holcman and Tsodyks, 2006; Steriade *et al.*, 1993). Remarkably, the model was also found to display scale-free avalanches all across its active phase. This is puzzling from the view point of models of activity propagation that –under standard conditions– generate scale-free avalanches only at criticality. This apparent paradox has been recently solved (Martinello *et al.*, 2016); it has been shown that indeed the model exhibits the reported scale-free avalanches occurring all across its active/up phase, but these are neutral avalanches (see Sec.II..9) unfolding in a background of ongoing spontaneous activity. Thus, such avalanches can only be detected if species labels are identified; i.e. only by employing information about causal relationships on which neuron triggers the firing of which other (Martinello *et al.*, 2016), and this type of information is usually not accessible in experiments (see, however, Williams-Garcia *et al.* (2017)). Furthermore, if avalanches are measured as in experiments (i.e. employing a temporal binning) they turn out not to be scale-free (Martinello *et al.*, 2016). Thus, the model fails to describe the empirical finding on temporally-defined scale-free avalanches. The same criticism applies also to other more neuro-physiologically realistic models (see Stepp *et al.* (2015)). This observation reveals a gap in the literature between time-binned defined avalanches (in experiments) and causally defined avalanches (in models).

All the models discussed above have in common that they identify neural criticality with the edge of an activity-propagation phase transition. Recently, some other models have 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; di Santo *et al.*, 2017a; Yang *et al.*, 2012) (see above for empirical evidence of this). However, these models provide no mechanistic explanation of why the dynamics should operate precisely at the edge of the synchronization phase transition.

Last but not least, the amazingly 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 stress that theoretical approaches not relying on criticality whatsoever have been proposed to account for the empirically observed scale-free avalanches. For instance, a novel mechanism providing an alternative explanation for the emergence of broadly heterogeneous avalanches away from any phase transition has been recently put forward. This mechanism, called "stochastic amplification of fluctuations", is able to produce long tailed avalanche distributions without the need of precise fine tuning (Benayoun *et al.*, 2010). It relies on the (approximate but not perfect/critical) balance between excitatory and inhibitory couplings. Mathematically, it requires the presence of a stable fixed point of the dynamics, whose associated stability matrix is "non-normal"[37] together with inherent stochasticity.

Also, very importantly, it has been argued that avalanche scale-free statistics can emerge naturally in networks of neurons operating in self-sustained irregular regimes away from criticality (Touboul and Destexhe, 2017). Remarkably, they showed that a set of spiking neurons, described as Poissonian point processes, sharing a common time-dependent irregular firing rate, do exhibit generically scale-free avalanches. Fully clarifying these findings and their relevance in connection with empirical observations is a very important current task.

Thus, summing up –even if sound and very interesting dynamical models, supporting the idea of criticality in the brain have been proposed– we believe that none of them provides a definitive theoretical support to the idea that the real cortex "should" operate at the edge of a

[37] Nonnormal matrices are such that their eigenvectors are not mutually orthogonal. If they are used as a basis set, information deriving from a standard local stability analysis can be deceiving: even if amplitudes decay to zero in time, strong transitory growth can appear (Murphy and Miller, 2009; Trefethen and Embree, 2005).

phase transition. Thus, understanding the nature of the overall dynamical state of the cortex remains a matter of debate and constitutes a key open challenge.

B. Genetic and cell networks

Living cells exhibit stable and robust characteristic features even under highly variable conditions, while they also exhibit flexibility allowing them to adapt to radical environmental changes. This is feasible owing to the fact that a unique set of genes (i.e. a "genotype") can give rise to diverse cellular states ("phenotypes"), consisting of diverse gene-expression patterns in which some genes are differentially expressed, while others are silenced[38]. Cells can thus be seen as "machines" executing complex gene-expression programs that involve the coordinated expression of thousands of genes[39](Alon, 2006; Buchanan, 2010; Crick, 1970; Kitano *et al.*, 2001; Koonin, 2011; Koonin *et al.*, 2006).

Since the pioneering proposal 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/repression) interactions are represented as directed links between them. The development of powerful experimental high-throughput technologies in molecular biology (such as DNA microarray experiments) paved the way to the experimental investigation of gene-expression patterns in large regulatory networks (Filkov, 2005) and, in particular, provided empirical evidence that, indeed, 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 *et al.*, 2004; Huang *et al.*, 2005; Li *et al.*, 2004). Consequently, the study of information processing in cells shifted progressively from single genes to increasingly complex circuits/networks of genes and regulatory interactions, shedding light on collective states (Garcia-Ojalvo, 2011; Hartwell *et al.*, 1999; Shmulevich and Dougherty, 2010).

1. Models of genetic regulatory networks

Many genes are empirically observed to exhibit bistability, i.e. their gene-expression levels are either "high" (on) or very "low" (off) depending on conditions. These

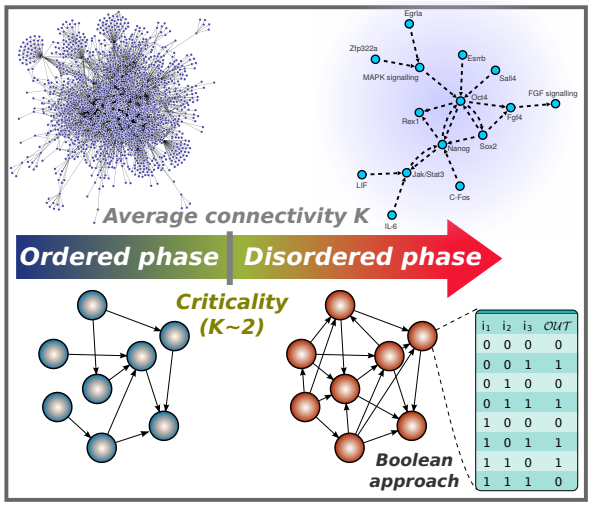

FIG. 7 The upper panels represent two gene regulatory networks: (Left) a large scale one (for E. Coli (Gama-Castro *et al.*, 2015)) and (Right) a small scale one (mouse embryonic stem-cell subnetwork (Parfitt and Shen, 2014)); in both cases, nodes stand for genes and links between them for (transcriptional) regulatory interactions. 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 (relating inputs to outputs) for a given node.

binary states are believed to be the building blocks of genetic logical circuits (Tyson *et al.*, 2003). Hence, genetic regulatory networks can be 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.7)[40] (Kauffman, 1993; Shmulevich and Dougherty, 2010). 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 observed cell cycles e.g. growth, division, apoptosis, etc. (Aldana, 2003; Bornholdt, 2005, 2008; De Jong, 2002; Drossel, 2008; Gros, 2008; Kauffman, 1996, 1993; Macía *et al.*, 2009; Serra *et al.*, 2007).

In the simplest setup, the network architecture is described as a random directed network[41] and regulatory

[38]

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

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

[41] More realistic network architectures including for example node heterogeneity and modularity have also been considered (Aldana, 2003; Poblanno-Balp and Gershenson, 2011).

interactions are described as random Boolean functions (Albert, 2004; Alon, 2006; De Jong, 2002; Gros, 2008; Kauffman, 1969, 1993) (see Fig.7). Random Boolean networks (RBNs) can operate in different regimes, depending on e.g. the averaged connectivity. The ordered or frozen phase (low connectivity) is characterized by a small set of stable attractors which are largely robust to perturbations. 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 e.g. stochasticity and/or continuous levels of activity, share a very similar phenomenology (Rohlf and Bornholdt, 2002).

Kauffman conjectured that models operating at their critical point might provide the best possible representation of real biological networks (Kauffman, 1996, 1993), and that this might entail a large variety of essential functional advantages (Aldana *et al.*, 2007; Kauffman *et al.*, 2003; Krawitz and Shmulevich, 2007; Nykter *et al.*, 2008b; Ribeiro *et al.*, 2008; Torres-Sosa *et al.*, 2012). In the ordered regime, convergence in state space implies that distinctions between different inputs are readily erased, precluding reliable discrimination among them. On the other hand, 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 tradeoff 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 an optimal balance between robustness and evolvability under changing conditions (Aldana *et al.*, 2007; Gershenson, 2012; Kaneko, 2012; Torres-Sosa *et al.*, 2012; Wagner, 2005).

2. Experimental results

DNA microarrays made it possible to measure the difference of the expression levels of very many genes in two cells (Brown and Botstein, 1999). This, combined with gene knock-out experiments, consisting in silencing the expression of an individual gene, allow to perform "damage spreading" experiments as defined above (Derrida and Pomeau, 1986; Rohlf *et al.*, 2007) and to monitor the difference in gene-expression of a perturbed with respect to an unperturbed cell. Using empirical gene-expression data from the yeast (*Saccharomyces cerevisae*) (Hughes *et al.*, 2000), the statistics of the size of "avalanches" caused by single-gene perturbations has been analyzed (Rämö *et al.*, 2006; Serra *et al.*, 2007, 2004). Comparing the empirical data with results of a RBN model it came out that the best correspondence between empirical results and the model predictions, was obtained for the model operating close to its critical point (Rämö *et al.*, 2006; Serra *et al.*, 2007, 2004). 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. An important caveat is that it is not clear what the influence of thresholding is. Higher thresholds would reduce the tail of the size distribution and smaller ones would allow for much larger avalanches, probably altering the size distribution. More precise empirical measurements are certainly needed to fully elucidate the statistics of avalanches after gene knock-out.

Empirical analyses of hundreds of microarray experiments allow to infer the whole network of regulatory interactions among genes, i.e. who regulates whom (Filkov, 2005; Yeung *et al.*, 2011). It has been consistently found that the in-degree distribution is Poissonian while the out-degree distribution is scale-free (see Aldana (2003) and Drossel and Greil (2009) and refs. therein)[42]. Performing damage-spreading computational analyses of diverse dynamical random Boolean models running on top of networks with the empirically-determined architecture of diverse organisms (such as *Sacharomices cerevisiae* and *Escherichia 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; Chowdhury *et al.*, 2010; Darabos *et al.*, 2009).

Alternatively to inferring the architecture of the underlying network of interactions –which is a difficult problem (Filkov, 2005)– information-theoretic methods have been employed to asses the dynamical state directly from empirical measurements from multiarrays. For example, one such method relies on information-theoretic estimators of the "complexity" or "information content" of gene-expression time series in microarrays (those with repetitive or simple patterns have a low complexity, while others with a rich pattern structure exhibit larger complexities) (Benedetto *et al.*, 2002; Ming and Vitányi, 2014; Ziv and Lempel, 1978). The overall dynamical network state is identified by computing how the complexity of a set of timeseries for different genes changes in time (Kauffman *et al.*, 2003; Shmulevich *et al.*, 2005). In particular, empirical measurements of complexity for eukariotic cells were compared with computational estimations from random Boolean networks operating in different regimes. Results are compatible with the actual dynamics being either ordered or critical but not chaotic (Kauffman *et al.*,

[42] An important avenue for future developments is to better characterize the architecture of actual regulatory networks –which are highly heterogeneous, modular (Shen-Orr *et al.*, 2002) and hierarchical (Corominas-Murtra *et al.*, 2013; Lagomarsino *et al.*, 2007; Treviño III *et al.*, 2012; Yu and Gerstein, 2006). These structural facts might strongly influence the dynamics on them (Moretti and Muñoz, 2013).

2003; Shmulevich *et al.*, 2005). However, similar studies for the macrophage (in which two cells are transiently perturbed in different ways) produced results compatible only with critical (marginal) propagation dynamics in a model independent way (Nykter *et al.*, 2008a).

Finally, the relevance of criticality in stem-cell decision making has been theoretically discussed (Garcia-Ojalvo and Arias, 2012; Halley *et al.*, 2009) and it has been found experimentally that criticality in the overall gene-regulatory network emerges as a general mechanism to coordinate cell-fate change, and in particular, for the development of state transitions in cancer cells (Tsuchiya *et al.*, 2015, 2016).

3. Zipf's law in gene-expression

Inspection of gene expression databases of diverse organisms (e.g. yeast) revealed that the abundances of expressed genes are distributed as a power-law with exponent close to -1, i.e. they obey the Zipf's law (Furusawa and Kaneko, 2003). Obviously, this problem cannot be analyzed with the Boolean approximation. Furusawa and Kaneko (2012a) analyzed an abstract dynamical model describing a cellular reaction network –i.e. the network formed by the set of molecules (nodes) which interact with others to give products within the cell– with chemical/nutrient uptake, and showed that the Zipf's law (which can be taken as a signature of criticality, as discussed in the Appendix) is a universal feature of self-regulated cells optimizing their growth rate in nutrient-rich environments. This suggests that criticality corresponds in this setting to the maximal capacity to assimilate and use nutrients for recursive formation of other products, and that actual cells adapt to exploit it (Erez *et al.*, 2017; Furusawa and Kaneko, 2012a; Kaneko, 2006). See also Hanel *et al.* (2010) and Stokić *et al.* (2008).

C. Cells and morphogenesis

We have, so far, discussed the possibility of criticality within individual cells. But, also ensembles of cells in pluricellular organisms can exhibit collective behavior and scale invariance (Nadell *et al.*, 2013).

1. Stem cell pluripotency

Clonal populations of unicellular organisms such as viruses or bacteria often exhibit phenotypic diversity, and this is believed to constitute a sort of "bet-hedging" strategy by which diversified communities can rapidly adapt to changing environmental conditions (Kussell and Leibler, 2005; Veening *et al.*, 2008; Wolf *et al.*, 2005). Similarly, large diversity has been observed in the levels of gene expression in multipotent stem-cell populations of pluricellular organisms (Goodell *et al.*, 2015). A recent study has analyzed a particular type of (hematopoietic) multipotent stem cells. These can differentiate onto either erythroid or myeloid blood cells 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 maxima. Such a distribution can be modeled in terms of a Fokker-Planck equation, capturing not just its steady state but also time-dependent aspects; as a function of its parameters, the model can exhibit either a stable low-*Sca1* or a stable high-*Sca1*. Separating these regimes in the model there is a line of discontinuous transitions (with bistability), which finishes at a critical point. Remarkably, the best fit to empirical data of gene-expression is obtained fixing model parameters close to criticality, where maximal variability of 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).

2. The progeny of stem cells

The number of stem cells at the basis of human epithelia remains constant in time. Thus, after division, half of their daughter cells becomes differentiated and migrates up in the epithelium, and the other half remains as undifferentiated stem cells (see Lopez-Garcia *et al.* (2010) from where this discussion is adapted). An important question posed to understand how this process works is: what is the size of the future progeny of a given stem cell? It has been experimentally observed that the distribution of sizes of such progenies is scale free. Remarkably, the process can be modeled and understood as a neutral dynamics among diverse but equivalent classes of stem cells, which –as discussed in Sect.II..9– compete for limited space (Lopez-Garcia *et al.*, 2010; Yamaguchi *et al.*, 2017), giving rise to generic scale invariance and thus a large variability of possible outcomes.

3. 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 model organism studied in this context is the Hydra polyp, which has a remarkable regeneration power, as an entire new individual can be spontaneously re-assembled even from dissociated cells of an

adult (Bosch, 2007). Along such a regeneration process, first a cell bilayer is formed with a spherical (hollow) shape. The question remains, 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 has been empirically reported that precisely before the spherical symmetry is broken, the size distribution of *ks1*-rich domains across the sphere becomes scale-free, as in critical percolation (Soriano *et al.*, 2006). Indeed, when a spanning cluster emerges the symmetry is spontaneously broken and the head-tail axis is defined at the center of such a cluster. A physical model –based solely on the spontaneous production and local cellular exchange of *ks1*-promoting factors is able to reproduce in a self-organized way the experimentally observed spontaneous symmetry breaking (Gamba *et al.*, 2012); see also Livshits *et al.* (2017) and Mercker *et al.* (2015). This suggests that a critical state with collective fluctuations of gene-expression levels is exploited to break the rotational symmetry, defining a head-tail axis (Soriano *et al.*, 2006, 2009).

4. Morphogenesis II: Gap genes in Drosophila

A set of so-called *"gap"* genes is responsible for the emergence of spatial gene-expression patterns, that are at the origin of the formation of different segments along the head-tail axis in the development of the fruit-fly (Drosophyla) embryo. Empirical inspection of the expression levels of gap genes revealed a number of remarkable features that include: slow dynamics, correlations of expression-level fluctuations over large distances, and non-Gaussianity in the distribution of such fluctuations. Krotov *et al.* (2014) proposed a simple dynamical model in which the process is controlled by two mutually repressing gap genes, whose expression levels are called x_1 and x_2 respectively. Assuming that a fixed point (x_1^*, x_2^*) 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. At this point, an eigen-direction –linear combination of x_1 and x_2– becomes marginally unstable. Krotov *et al.* (2014) argued that if the dynamics of the coupled system is tuned to operate at this instability point, then it constitutes and excellent qualitative description of all the above-mentioned 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/developing systems. Very similar ideas have been developed in the context "cell differentiation" (Pal *et al.*, 2014). On the other hand, recent work has challenged the above conclusion, arguing that the system actually operates at the edge of a discontinuous phase transition where two alternative stable expression-level states coexist (Weissmann *et al.*, 2015).

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 *et al.*, 1999; Couzin and Krause, 2003; Krause and Ruxton, 2002; Sumpter, 2010) and also, at smaller scales, in bacterial colonies (Chen *et al.*, 2012; Peruani *et al.*, 2012) and groups of cells (Méhes and Vicsek, 2014). Flocking, schooling, swarming, milling, and herding constitute –among others– 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 e.g. rapid escape manoeuvres when attacked by predators, which confers obvious fitness advantages to the group as a whole. The inspiring concept of collective intelligence vividly encapsulates this notion (Couzin, 2007, 2009).

Not surprisingly, these collective phenomena have attracted the attention of statistical physicists who have tackled the problem employing: (i) individual-based models of self-propelled particles such as the one in Vicsek *et al.* (1995) that models collective motion by assuming that an individual in a group essentially follows the trajectory of its neighbors, with some deviations modeled as noise [43], and (ii) continuum theories more amenable to theoretical analysis (Toner and Tu, 1995, 1998; Toner *et al.*, 2005). These models have in common the existence of phase transitions between phases of coherent and incoherent motion. E.g. 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; e.g. Buhl *et al.* (2006) investigated the behavior of locusts and reported on a density-driven phase transition from disordered movement of individuals to highly aligned collective motion (Dyson *et al.*, 2015). More elaborated models (e.g. for fish) exhibit richer phase diagrams including a swarming phase with aggregation but no cohesion, a schooling phase in which individual velocities become aligned; and, also, a milling phase with individuals rotating around an empty core

[43] See Chaté *et al.* (2008); Chaté *et al.* (2008); Ginelli (2016); and Grégoire and Chaté (2004) for detailed statistical-mechanics analyses of Vicsek models and variants of it.

(Calovi *et al.*, 2014; Gautrais *et al.*, 2012), all of them observed in real groups.

At a speculative level, marginally coordinated (critical) motion can be hypothesized to constitute an optimal tradeoff solution to deal with conflicting imperatives such as e.g. (i) the need to behave cohesively as a unique entity and (ii) being highly responsive to information from transitorily well-informed individuals, e.g. to escape from predators (Couzin *et al.*, 2011, 2005). Similar dichotomies will come up in what follows.

1. Flocks of birds

On the empirical side, pioneering work by Cavagna, Giardina and collaborators (Ballerini *et al.*, 2008; Cavagna *et al.*, 2010) on starling flocks allowed to record individual trajectories (with purposely devised tracking technology) and to analyze their statistics. It was empirically found that interactions between individuals depend on "topological" rather than "metric" distance, i.e. each bird seems to modify its velocity according to information from a fixed number of its neighbors. By analyzing the fluctuations in flight directions with respect to the average velocity of the group, these analyses provided strong 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 fluctuations and speed– 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 Sec.II..7 leads to generic scale-invariance without the need to sit exactly at criticality. However, the presence of scale-free correlations of the (scalar) speed cannot be explained in this way, suggesting that the flock may be tuned to a critical point with maximal susceptibility.

Bialek *et al.* (2012) constructed a maximum entropy method to determine a statistical model consistent with the empirically measured correlations (see Appendix). They concluded that the interaction strength and the number of interacting neighbors do not change with flock size in the optimal 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 model's operating close to its critical point (Bialek *et al.*, 2014; Mora and Bialek, 2011)[44]. Let us remark that –as briefly described in Appendix– criticisms to this type of (purely statistical) inferred-model approach have been raised (Marsili *et al.*, 2013; Mastromatteo and Marsili, 2011). On the other hand, without resorting to inferred models, Attanasi *et al.* (2014a) performed experiments on starling flocks to measure how the information of the turning of one individual propagated across the flock, showing that this occurs in a very fast and efficient way, behaving almost as a superfluid, which can be taken as a direct evidence of the existence of scale-free correlations in flocks.

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). Tracking individual trajectories, velocity fluctuations were measured and, from these, a correlation length and a susceptibility –determining the total correlation between insects– were estimated. As discussed above, true criticality only occurs in infinite systems, from which biological groups are far away.

To circumvent this difficulty, Attanasi et al. performed finite-size analyses of swarms, and showed that both the correlation length and the susceptibility grow with the swarm size, while the spacing between midges decreases. Moreover, these 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[45]. In particular, midges obey 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). Furthermore, not only spatial, but also spatio-temporal correlation functions in different swarms can be rescaled by using a single characteristic time, confirming the existence of dynamical scale invariance at least up to some scale (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 (Chaté and Muñoz, 2014; Kelley and Ouellette, 2013; Puckett and Ouellette, 2014).

3. Social-insect strategies

Groups of mobile animals may exploit collective sensing/exploring strategies of complex environments

[44] For recent developments see Attanasi *et al.* (2014a); De Vincenzo *et al.* (2017); Mora *et al.* (2016); and Vanni *et al.* (2011).

[45] The Vicsek model exhibits signatures of a first-order transition at large sizes. For smaller systems there exists a wide regime where correlations peak at the transition and finite-size-scaling holds (Baglietto *et al.*, 2012; Chaté *et al.*, 2008; Grégoire and Chaté, 2004; Vicsek *et al.*, 1995).

(Berdahl *et al.*, 2013). Studies of ant foraging and cooperative transport strategies (Beekman *et al.*, 2001; Bhattacharya and Vicsek, 2014; Gallotti and Chialvo, 2017; Li *et al.*, 2014; Loengarov and Tereshko, 2008; Solé, 2011). For colonies to achieve an efficient foraging strategy, a tradeoff needs to be reached between exploratory behavior of some individuals and predominant compliance with the rules (Feinerman and Korman, 2017). It has been recently 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 exceedingly gregarious strategies, thus resulting in effective criticality. This entails efficient group-level processing of information emerging out of a optimal amplification of individual information (Gelblum *et al.*, 2015). Similar ideas are being presently explored for the design of artificial systems, i.e. in swarm robotics (Beni, 2004; Erskine and Herrmann, 2014).

4. Mammal herds

A quantitative study of a large group of social herbivores (Merino sheep) in a well-controlled homogeneous environment suggested the existence of two conflicting needs to be balanced: (i) the protection from predators offered by being part of large cohesive group and (ii) the exploration of foraging space by wandering individuals (Ginelli *et al.*, 2015). 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.

5. Fish schools

Schooling fish constitute a potentially important playground to experimentally explore collective behavior and phase transitions (Rosenthal *et al.*, 2015; Tunstrøm *et al.*, 2013; Ward *et al.*, 2008). Recently, the responsiveness to perturbations (e.g. to the behavior of one specific individual) as well as the overall susceptibility (total correlation of velocity fluctuations) in a data-driven model for fish schools have been analyzed (Calovi *et al.*, 2015). It was found that these quantities take the largest possible values at the edge of the transition between schooling and milling phases (see above); however, empirical evidence that actual fish in the wild operate at this transition point is still missing (Makris *et al.*, 2009).

6. Bacterial motion

In colonies of *Bacillus subtilis* bacteria move collectively, forming dynamic clusters. It has been empirically found that correlations of velocity and orientation fluctuations are scale invariant in such dynamic bacterial clusters, much as in flocks, as described above[46] (Chen *et al.*, 2012). It has been argued that scale-invariant correlations may give some evolutionary advantages as "information of an external stimulus, such as a predator or food, can propagate quickly through the whole system" (Chen *et al.*, 2012).

E. A sample of other allegedly critical biological systems

To conclude, we enumerate a sample of some other biological systems in which some empirical evidence of criticality has been reported, but for the lack of space we just mention them rather briefly.

1. Critical fluctuations in cell membranes

Cell membranes are not just rigid impenetrable walls separating the interior of cells from the outside environment. They can mediate and/or regulate the kind, direction, and amount of substances that can pass across them. Cell membranes are permeable at some locations and, for this, their local composition needs to be heterogeneous (Cicuta, 2013; Hyman and Simons, 2012; Lee *et al.*, 2013). There is compelling empirical evidence that the mixtures of lipids that constitute the skeleton of cell membranes operate at temperatures very close to the demixing phase transition, at which their different components segregate (Cicuta, 2013; Ehrig *et al.*, 2011; Honerkamp-Smith *et al.*, 2008; Veatch *et al.*, 2008, 2007). In this way, composition fluctuations are extremely large, enabling very diverse structural domains with rather different compositions and properties to emerge spontaneously; these domains are variable and transient, providing the membrane with a large spectrum of possible local structures, at which different processes may occur, entailing a rich repertoire of functional possibilities.

2. 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 *et al.*, 1988,

[46] See (Peruani *et al.*, 2012; Sokolov *et al.*, 2007) for possibly conflicting conclusions.

1989; Eigen and Schuster, 1979). It was conjectured –and also partially verified experimentally (Crotty *et al.*, 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[47] (Drake and Holland, 1999; Eigen, 2002; Solé *et al.*, 1999, 1996).

3. Physiological rhythms

The presence of temporal scale-invariance in physiological rhythms of healthy subjects, as well as its break-down in abnormal conditions, have been long explored (Bassingthwaighte *et al.*, 1994; Glass, 2001; Goldberger *et al.*, 2002; Losa, 1995; West and Grigolini, 2010). In particular, to mention one example, the connection between the complex fluctuations of human heart-rate variability and criticality has been proposed and analyzed (Ivanov, 2007; Ivanov *et al.*, 1999; Kiyono *et al.*, 2004, 2005) and, in the related context of blood-pressure regulation, vaso-vagal syncopes have been associated with large "avalanches" in a self-organized cardiovascular regulatory system poised at criticality (Fortrat and Gharib, 2016). Similarly, the generator of circadian rhythms in mammals, i.e. the suprachiasmatic nucleus, which is involved in heart regulation, also exhibits scale-free fluctuations (Hu *et al.*, 2012). Such regulation to scale-free behavior seems to impart health advantages, including system integrity and adaptability (Goldberger *et al.*, 2002).

4. Miscellanea

Criticality has also been claimed to play a relevant role in various other important biological contexts, such as the immune system (Burgos and Moreno-Tovar, 1996; Mora *et al.*, 2010), cancer and carcenogenesis (Davies *et al.*, 2011; Rosenfeld, 2013; Solé and Deisboeck, 2004; Solé, 2003), proteins (Phillips, 2009; Tang *et al.*, 2017), mitochondria (Aon *et al.*, 2004; Zamponi *et al.*, 2016), 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 (Adami, 1995; Bak and Sneppen, 1993; Biroli *et al.*, 2017; Sneppen *et al.*, 1995; Solé *et al.*, 2002a, 1999; Suweis *et al.*, 2013), illustrating that the ideas discussed here can be extended to larger scales in the hierarchy of biological complexity.

[47] 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.

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. Throughout this essay we discussed *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 e.g. in Mora and Bialek (2011). In this latter the focus is on analyzing the statistics of existing patterns, neglecting the dynamical generative mechanisms behind them. Such statistical models, describing biological data in an optimal way, happen to be close to criticality in a sense explained in some detail in the Appendix. Even if both approaches might have deep interconnections, here we chose to focus on the dynamical one.

At a theoretical (or conjectural) level, a large variety of possible functional benefits of criticality have been proposed in the literature: unparalleled sensitivity to stimuli, huge dynamical repertoires, maximal transmission and storage of information, optimal computational capabilities, etc. 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 achieve functional tasks. Similar tradeoffs, as discussed along the paper, underline the potential of operating at the edge between different types of order.

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 dynamical mechanism generating complex spatio-temporal 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 spatio-temporal structures it spontaneously generates– can be identified as a scaffold upon which (multiscale) biological systems may build up further layers of complexity.

Statistical physics teaches us that under some circumstances–including e.g. 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 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 spatio-temporal scale invariance.

From the experimental viewpoint, along the presentation 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 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 example, where experimental evidence and mathematical theory/modeling match perfectly; i.e. we still do not have a "smoking gun". Still, the existing collection of remarkable pieces of evidence is certainly very 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-like 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 –not very different from the one put forward in the context of statistical criticality (see Appendix)– consists in the observation that if (interesting) empirical data are highly structured, with no distinctive characteristic scale, then it could seem almost a tautology to say that the best fit comes about near the critical point of the proposed model, as near-criticality is typically the only region in parameter space where feature-rich patterns, with many characteristic scales are generated. In contrast, from an 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 a (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 outmost 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 a knowledge? We believe that, the design of strategies to control neural/genetic networks based on notions of criticality, the construction of algorithms of artificial intelligence exploiting scale-invariance, and the application of ideas of collective motion/intelligence to the design of e.g. swarms of robots, could constitute important avenues to provide a constructive answer to the above question.

To close, novel advances, both at 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.

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APPENDIX: STATISTICAL CRITICALITY

Probabilistic models can be constructed such that they match the statistics of observed empirical data, and among these models one selects the one that makes the smaller number of assumptions (Rieke *et al.*, 1995). Without loss of generality, an observed pattern 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 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 such that it reproduces the averaged values of $\langle s_i \rangle$ as well as the covariances $\langle s_i s_j \rangle$ for all i and j, as estimated from data. Imposing a maximum entropy principle (i.e. selecting the model with the smallest number of assumptions as in statistical physics (Banavar *et al.*, 2010a; Cover and Thomas, 1991)) it is easy to derive the explicit form of the optimal distribution

$$P_{\text{Ising}}(\mathbf{s}) = \frac{1}{Z} \exp\left[\sum_{i<j} J_{ij} s_i s_j + \sum_i h_i s_i\right] \qquad (6)$$

where Z ensures normalization and which coincides with the Boltzmann equilibrium distribution of the Ising model in statistical mechanics. Parameters h_i and J_{ij} need to be fitted, so that the imposed constraints are maximally satisfied (Ackley *et al.*, 1985). Obtaining the optimal parameter set –i.e. inferring effective interactions from correlations– is a computationally costly task, usually referred as "inverse Ising problem" (Aurell and Ekeberg, 2012; Cocco *et al.*, 2009; Cocco and Monasson, 2011; Schneidman *et al.*, 2006). This type of approach has been successfully applied to many different situations, from retinal populations (Schneidman *et al.*, 2006; Tkačik *et al.*, 2014, 2013, 2015) and cortical networks (Cocco *et al.*, 2009), to the collective motion of bird flocks (Bialek *et al.*, 2014, 2012) and the immune system (Mora *et al.*, 2010). In particular, Bialek and coworkers introduced a fictitious (inverse) temperature, β, by replacing each estimated parameter, g, in Eq.(6), by βg. Varying β there is a relative change of the configuration probabilities, generating a family of distributions $P(\mathbf{s}|\beta g)$ interpolating between the low and high temperature phases. At the critical value β_c there is a peak in the generalized susceptibility, which corresponds to a (finite-size) critical point. Bialek and coauthors found that diverse inference problems in biology produce models in which $\beta_c \approx 1$, –or converge to 1 as the system size is enlarged– i.e. that inferred models appear to be close to the very critical point, (Mora and Bialek, 2011).

Recently, some doubts on the validity of this approach have been cast. It has been argued that the approach is not reliable in analyzing the possible criticality of high-dimensional data and non-critical data look critical when inspected with this strategy (Macke *et al.*, 2011; Nonnenmacher *et al.*, 2016; Saremi and Sejnowski, 2014). Marsili and collaborators elaborated upon a result in *information geometry* that establishes that most distinguishable inferred models are necessarily concentrated in the regions where the generalized susceptibility (also called "Fisher information" in this context) peaks, i.e. in vicinity of critical points. In this way, inferred models fitting real-world data do, most likely, look near critical within such a scheme (Marsili *et al.*, 2013; Mastromatteo and Marsili, 2011). In other words, concluding that an inferred model is near to a critical point can be a potentially misleading assessment, as the distance from the critical point should be measured in terms of the number of distinguishable models in between (Mastromatteo and Marsili, 2011). Put differently, if structured (non-trivial) empirical data are fitted to an Ising model, the only possibility for the fitted model would be to lie "near" the critical point, without further specification of what "near" means (Haimovici and Marsili, 2015).

To close, let us briefly mention that a very elegant calculation allowed Mora and Bialek to map the Zipf's law to statistical criticality. Thus, empirical evidence of Zipf's law can be traded by empirical evidence of underlying statistical criticality in a precise sense (see Mora and Bialek (2011)). Using this setting, Schwab *et al.* (2014) contended that marginalization over hidden relevant variables leads generically to the Zipf's law, and thus to statistical criticality. In other words, Zipf's law and its concomitant statistical criticality can emerge as spurious effects stemming from an effective average over non-observed hidden variables, even in non-critical systems (Aitchison *et al.*, 2016). Here, we shall not delve further into the controversy about the meaning and significance of this type of purely statistical approaches to criticality.

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