On The Temporal Organization of Neuronal Avalanches

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ABSTRACT

In vitro and in vivo studies have shown that resting cortical dynamics is characterized by neuronal avalanches, cascades of activity exhibiting a power law in the size and duration distribution, which represents a typical feature of systems acting in a critical state. Here we focus on their temporal organization analyzing the waiting time distribution between successive avalanches in the rat cortex in vitro. This distribution shows a peculiar non monotonic behavior and clearly indicates the presence of correlations in avalanche dynamics. By means of numerical simulations we provide evidence that non-monotonicity in the waiting time distribution arises from the alternation between up states, or bursts, and down states, quiescent periods expression of a homeostatic mechanism controlling the excitability of the system. Indeed, by tuning homeostasis, a satisfactory agreement with the experimentally measured waiting time distribution is found. Under these conditions, the avalanche size and duration distributions reproduce the experimental scaling behavior, suggesting that the critical state realizes the correct balance between excitation and inhibition by means of the up-down states dynamics. Finally we show, both numerically and experimentally, that up and down states do exhibit universal scaling features.

Keywords: neuronal avalanches, rat cortex, waiting times, neuronal networks, criticality

1 INTRODUCTION

In vitro, as well as during sleep or under anesthesia, spontaneous activity can be roughly described as an alternation between quiescent periods, characterized by a low average spiking rate, and bursts, characterized by an intense spiking activity in large cortical areas (Cossart et al., 2003; Hahn et al., 2006; Cunningham et al., 2006). This dynamics observed at a network level, has its local physiological basis on the property of cortical neurons to oscillate between so-called up and down states (Steriade et al., 1993; Wilson, 2008): In the up-states the membrane potential is close to the action potential threshold
and neurons can fire at a high rate, whereas a strong hyperpolarization is responsible for the low spiking activity in the down-states.

For cortical neurons the up-state would be a metastable state, i.e. the membrane potential will soon decay down to the resting value, if network mechanisms would not give the necessary contribution to keep it close to the action potential threshold (Wilson, 2008; McCormick et al., 2003). Therefore up-states have to be considered as a network, rather than a cellular property. Accordingly, bursts are also called up-states, on account of the large population of neurons close to the firing threshold and fast responding to presynaptic inputs. Conversely quiescent periods are called down-states because of a general disfacilitation, i.e. a substantial lack of excitatory post-synaptic potentials in the network, which causes long-lasting return to resting potential in a large population of neurons (Timofeev et al., 2001). The emergence of these down-states can be due to different mechanisms: a decrease in the neurotransmitter released by each synopsis either due to the exhaustion of available glutamate (J. Staley et al., 1998; Stevens and Tsujimoto, 1995) or to the increase of a factor inhibiting their release (Thompson et al., 1992), the blockage of receptor channels by the presence, for instance, of external magnesium (Maeda et al., 1995), or else spike adaptation (Sanchez-Vives et al., 2000). It has been suggested that the transition towards down-states is caused by the extracellular accumulation of the nucleoside adenosine during up-states, which inhibits the release of excitatory neurotransmitters leading to an intense hyperpolarization of the postsynaptic neuron (Thompson et al., 1992). Conversely, spike adaptation is controlled by calcium entering the cell during an action potential, which activates potassium channels and hyperpolarizes the neuron the more spikes it fires (Sanchez-Vives et al., 2000). Whereas action potentials are rare during down-states, small amplitude depolarizing potentials, reminiscent of miniature potentials from spontaneous synaptic release, and some synaptic inputs occur at higher frequencies. The non-linear amplification of small amplitude signals contributes to the generation of larger depolarizing events bringing the system back into the up-state, as observed in cortical slabs (Timofeev et al., 2000) and slice cultures (Plenz and Aertsen, 1996).

Up and down-states alternate on time scales of several hundreds of milliseconds or larger. At smaller time scales spontaneous activity is instead organized in neuronal avalanches, cascades of activity characterized by a scale free distribution of size and duration (Beggs and Plenz, 2003; Mazzoni et al., 2007; Pasqualé et al., 2008; Petermann et al., 2009; Shriki et al., 2013), a typical feature of a system acting in a critical state (Stanley, 1971). Here we investigate the basic properties of the their temporal organization, with relation to the up-down state dynamics in cortex slice cultures. Each avalanche \( j \) is characterized by its starting and ending times, \( t^u_j \) and \( t^d_j \) and we analyze the distribution of waiting times \( \Delta t_j = t^u_{j+1} - t^d_j \) between successive avalanches (Lombardi et al., 2012). The waiting time distribution is widely investigated for stochastic natural phenomena and is able to discriminate between a simple Poisson and a correlated process. In the first case the distribution is indeed an exponential, whereas it exhibits a more complex behavior with power law regime if correlations are present. For a wide variety of phenomena, earthquakes, solar flares (de Arcangelis et al., 2006a), rock fracture, etc., this distribution is always monotonic. Universal scaling features have been observed for earthquake waiting times distribution evaluated restricting to earthquakes larger than a given magnitude threshold. Different magnitude threshold values give rise to distinct distributions, which collapse onto the same universal curve after rescaling by the average rate (Corral, 2004). This property reveals that seismicity has a complex organization in time with universal properties: the removal of some events by increasing the lower threshold does not affect the fundamental features of earthquake occurrence. In a recent paper (Ribeiro et al., 2010) the waiting time distribution has been analyzed for spike avalanches in freely behaving (FB) and anaesthetized rats (AR). The distributions show consistently a monotonically decreasing behavior. Universal scaling features are observed for freely behaving rats when waiting times are rescaled by the average occurrence rate, whereas curves for anaesthetized rats do not collapse onto a unique function.
2 MATERIAL & METHODS

2.1 EXPERIMENTAL SETUP

Coronal slices from rat dorsolateral cortex (postnatal day 0-2; 350 µm thick) are attached to a poly-D-lysine coated 60-microelectrode array (MEA; Multichannelsystems, Germany) and grown at 35.5°C in normal atmosphere in standard culture medium without antibiotics for 4-6 weeks before recording. Avalanche activity is measured from cortex-striatum-substantia nigra triple cultures or single cortex cultures as reported previously (1). In short, spontaneous avalanche activity is recorded outside the incubator in standard artificial cerebrospinal fluid (ACSF; laminar flow of 1 ml/min) under stationary conditions for up to 10 hrs. The spontaneous local field potential (LFP) is sampled continuously at 1 kHz at each electrode and low-pass filtered at 50 Hz. Negative deflections in the LFP (nLFP) were extracted. Neuronal avalanches are defined as spatio-temporal clusters of nLFPs on the MEA (26). A neuronal avalanche consists of a consecutive series of time bins of width δt that contain at least one nLFP on any of the electrodes. Each avalanche is preceded and ended by at least one time bin with no activity. Without loss of generality, the present analysis is done with width δt individually estimated for each culture from the average inter nLFP interval on the array at which the power law in avalanche sizes s, \( P(s) \sim s^{-\alpha} \), yields \( \alpha = 3/2 \). δt ranged between 3-6 ms for all cultures. Avalanche size is defined as the sum of absolute nLFP amplitudes (µV) on active electrodes or simply the number of active electrodes. Size distributions are obtained using logarithmic binning for sizes expressed in µV. A waiting time \( \Delta t \) is defined as the time interval between the ending time of an avalanche \( t_{j}^{f} \) and the starting time \( t_{j+1}^{f} \) of the following one, namely \( \Delta t_{j} = t_{j+1}^{f} - t_{j}^{f} \). Waiting time distributions are obtained using logarithmic binning for waiting times expressed in ms.

Up and down-state. The following procedure is used to discriminate between up and down-states. An up-state consists of a consecutive series of avalanches separated by a waiting time lower than \( T \), where \( T \) is the longest \( \Delta t \) falling within the power law regime of the waiting time distribution. Conversely every waiting time greater than \( T \) is a down-state and a consecutive series of avalanches separated by waiting times greater than \( T \) is then a down-state. The mean rate in the up-state is defined as \( r_{up} = 1/\langle \Delta t \rangle_{up} \), whereas the mean rate in the down-state is defined as \( r_{dw} = 1/\langle \Delta t \rangle_{dw} \).

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2.2 NUMERICAL MODEL

Network and dynamics. We consider \( N \) neurons at random positions, characterized by their potential \( v_i \). Neurons are connected by a scale-free network. More precisely to each neuron \( i \) we assign an out-going connectivity degree, \( k_{out} \), in agreement with the experimentally measured properties of the functional connectivity network (Eguíluz et al., 2005). Choosing different networks does not affect the scaling behaviour of avalanche distributions (de Arcangelis et al., 2006b; Pellegrini et al., 2007; de Arcangelis and Herrmann, 2012). Once the network of output connections is established, we identify the resulting degree of in-connections, \( k_{in,j} \), for each neuron \( j \). To each synaptic connection we assign an initial random strength \( g_{ij} \), where \( g_{ij} \neq g_{ji} \), and to each neuron an excitatory or inhibitory character, with a fraction \( p_{in} \) of inhibitory synapses. Whenever at time \( t \) the value of the potential at a site \( i \) is above a certain threshold \( v_i \geq v_{max} \), the neuron sends action potentials which arrive to each of the \( k_{out} \) pre-synaptic buttons and lead to a change in the potentials of the post-synaptic neurons proportional to the strength of the synapse \( g_{ij} \).

\[
v_j(t+1) = v_j(t) \pm \frac{v_i \cdot k_{out}}{k_{in,j}} \cdot g_{ij} \sum_k g_{ik},
\]  

(1)
where the plus or minus sign is for excitatory or inhibitory synapses respectively and the sum over \( k \) is on all neurons connected to \( i \). After firing, a neuron is set to a zero resting potential and in a refractory state lasting \( t_{ref} = 1 \) time step, during which it is unable to receive or transmit any charge. At the end of an avalanche, we implement an Hebbian-like plasticity rule. The strength of the used connections is increased proportionally to the membrane potential variation of the postsynaptic neuron induced by the presynaptic neuron
\[
g_{ij}(t+1) = g_{ij}(t) + |(v_j(t+1) - v_j(t))/v_{max},
\]
whereas the strength of all inactive synapses is reduced by the average strength increase per bond
\[
\Delta g = \sum_{ij,t} \delta g_{ij}(t)/N_B,
\]
where \( N_B \) is the number of bonds. An external stimulus then triggers further activity in the system. Since this plasticity acts on time scales longer than avalanche durations, we apply the plasticity protocol for a given number of stimulations, representing the age or experience of the system, and then study avalanche activity without changing synaptic strengths. In this sense our plasticity rules implement a long term plastic adaptation.

**Up-down state dynamics.** We implement the transition between up and down states by means of a mechanism relying on the basic idea that an up state terminates when the system is not able to sustain it anymore, namely when either the exhaustion of available synaptic vesicles (J. Staley et al., 1998) or the increase of factors inhibiting the release (Thompson et al., 1992) causes a sharp transition towards a down state. For simplicity, we assume that the transition happens after a sufficiently large discharge event, which causes a lack of available neurotransmitters and a sufficiently strong network inhibition.

Accordingly, at the end of each avalanche we measure its size in terms of the sum of depolarizations \( \delta v_i \) of all neurons, \( s_{\Delta V} = \sum_i \delta v_i \). When the last avalanche is larger than a threshold \( s_{\Delta V}^{\min} \cdot s_{\Delta V} \leq s_{\Delta V}^{\min} \), the system, transitions into a down state and neurons become hyperpolarized proportionally to their previous activity; namely, we reset
\[
v_i = v_i - h \cdot \delta v_i.
\]
This rule models the local inhibition experienced by a neuron, due to spike adaptation (Sanchez-Vives et al., 2000), adenosine accumulation (Thompson et al., 1992), synaptic vesicles depletion (J. Staley et al., 1998) or blockade of receptor channels by the presence of external magnesium (Maeda et al., 1995). Conversely, if the avalanche just ended has a size \( s_{\Delta V} \leq s_{\Delta V}^{\min} \), the system either will remain in or will transition into an up state, which typically happens at the end of a down state. All neurons firing in the previous avalanche are set to the depolarized value
\[
v_i(t+1) = v_{max}(1 - s_{\Delta V}(t)/s_{\Delta V}^{\min}).
\]
This equation states that the neuron potential depends on the response of the whole network via \( s_{\Delta V} \), in agreement with measurements of the neuronal membrane potential, which remains close to the firing threshold in the up state (Wilson, 2008). The threshold \( s_{\Delta V}^{\min} \) controls the extension of the up state and, therefore, the level of excitability of the system.

The high activity in the up state must be sustained by collective effects in the network otherwise the depolarized potentials would soon decay to zero. Therefore, the stimulation in the up state has a random value in the interval \( d_u(t) = [0, s_{\Delta V}^{\min}/s_{\Delta V}(t-1)] \), whose amplitude depends on past activity through the size of the previous avalanche \( s_{\Delta V}(t-1) \).

Conversely, during the down state, the stimulation of the system has a small constant amplitude applied at a random site. This drive reproduces the effect of the small depolarizations due to miniature potentials (minis) from spontaneous synaptic release observed in the down state (Timofeev et al., 2001). The drive slowly brings the system back in an up state not correlated to past activity.
Figure 1. Distribution of waiting times for six cortex slice cultures. (a) Distribution of waiting times for the overall avalanche activity: All curves show an initial power law regime with an exponent $\mu$ ranging between 2.0 and 2.5. For larger $\Delta t$, distributions are characterized by a local minimum followed by a more or less pronounced maximum at $\Delta t \simeq 1 - 2 s$. (b) Distribution of waiting times between successive avalanches occurring in the up-state. The curves, rescaled by the mean rate $r_{up}$, show a universal power law scaling. The dashed line represents a power law with exponent -2.2. (c) Distribution of waiting times between successive avalanches occurring in the down-state. In this case, rescaling by the mean rate $r_{dw}$ does not lead to a universal behavior.

Equations 4 and 5 each depend on a single parameter, $h$ and $s_{\Delta V}^{min}$, which introduce a memory effect at the level of single neuron activity and the entire system respectively. We will show that in order to reproduce experimentally observed behavior, we only need to control the ratio $R = h / s_{\Delta V}^{min}$.

3 RESULTS

3.1 WAITING TIME DISTRIBUTION

In Fig.1a we show the distribution of waiting times between successive avalanches in six different cortex slice cultures (see Material & Methods). The curves exhibit a complex non-monotonic behavior with the following common features: an initial power law regime and a local minimum followed by a more or less pronounced maximum. Depending on the experimental sample, the power law regime extends over two or three decades and exhibits an exponent $2.0 \leq \mu \leq 2.5$. Non-monotonic distributions of waiting times are not usually observed in natural phenomena and suggest that avalanche occurrence has a complex temporal organization. In particular, the power law regime observed up to $200 - 300 ms$, indicates that avalanches are temporally correlated if they are sufficiently close in time, which requires a sustained synaptic and firing activity in the network. Therefore we expect avalanches to be significantly correlated during up-states and not on longer time scales, because of the sparse synaptic activity in down-states.

In order to investigate the origin of the observed non-monotonic behavior, we simulate avalanche activity by means of a neuronal network model able to reproduce the scaling properties of neuronal avalanches, in which we implement the up and down state properties (see Materials & Methods). We assume that the transition between these two states happens after a sufficiently large discharge event, which can cause a lack of available neurotransmitter and a sufficiently strong network inhibition. Accordingly, we implement
this mechanism fixing a threshold value, $s^{\text{min}}_{\Delta V}$, for the avalanche size. When in a down-state, the system experiences a general disfacilitation mimicked by the weak random stimulation, while locally neurons are hyperpolarized proportionally to their previous activity. The hyperpolarization at a single neuron level is controlled by the parameter $h$ (see Material & Methods). After the first small avalanche, the system transitions to the next up-state. Here, the stimulation, as well as the single neuron potentials, depends on the whole network activity (see Material & Methods).

Under these assumptions, numerical simulations generate a sequence of up and down states, whose duration is distributed as shown in Fig.2 together with experimental data (see Material & Method). We notice here that, both numerically and experimentally, the two states are characterized by time scales differing by about one order of magnitude. Moreover their respective distributions $P(T)$ exhibit a distinct functional behavior. The durations of down-states are, on average, exponentially distributed, between 50 ms and about 4 s (Millman et al., 2010). Deviations observed at longer $T$ arise from the long tail observed in the waiting time distribution of some samples. Indeed, as we notice from the waiting time distributions (Fig.1, a), at large time scales experimental samples show significant differences, and long waiting times basically correspond to down-state durations. Conversely, the distribution $P(T)$ for the up-state is compatible with a steep power law, which is equivalent to an exponential behavior.

By separately controlling the two parameters $h$ and $s^{\text{min}}_{\Delta V}$, we obtain numerical distributions $P(\Delta t)$ of waiting times which exhibit a non-monotonic behavior and a power law regime with the same exponent $\mu \sim 2$ as experimental data. In Fig.3 we compare numerical results with two of the experimental curves shown in Fig.1a. The agreement between the numerical and the experimental distributions is confirmed by a Kolmogorov-Smirnov test at a $p = 0.05$ significance level. Both distributions pass the statistical test with $p = 0.99$ (upper panel) and $p = 0.68$ (lower panel). Insets of Fig.3 show the contribution to the overall waiting time distribution coming from each of the two states (see Material & Methods). In the up-states waiting times clearly follow a power law distribution and the good agreement between numerical and experimental curves indeed confirms that it originates from close in time correlated avalanches (Fig.3, lower insets). Conversely, down-states produce long waiting times mostly contributing to the tail of the overall $P(\Delta t)$, exhibiting a distribution with a characteristic value $\tau_d$, as found numerically (Fig.3, upper insets). This behavior has a simple interpretation: The recurrence of up states, has a more or less pronounced characteristic time. When the distribution of waiting times in the down-state is clearly peaked around a particular value $\tau_d$ and is sufficiently narrow, then a non-monotonic behavior can be observed in the waiting time distribution of the entire avalanche activity.
Figure 3. Waiting time distributions measured experimentally are compared with the average numerical distributions for 100 networks with N = 64000 neurons. Top: numerical curve ($s_{\Delta V}^{\text{min}} = 140$ and $h = 0.017$) fitting the experimental curve with blue squares in Fig.1a; bottom: numerical curve ($s_{\Delta V}^{\text{min}} = 110$ and $h = 0.02$) fitting the experimental curve with red diamonds in Fig.1a. In the insets: the waiting time distribution evaluated separately in the up (upper insets) and down state (lower insets) for the numerical (symbols) and the experimental data (green curves). For the numerical curves, statistical error bars are comparable with the symbol size.

Therefore, the minimum and the relevance of the relative maximum are sample dependent and simulations are able to reproduce the different behaviors by tuning the parameters $h$ and $s_{\Delta V}^{\text{min}}$. For each sample, the agreement with experimental data only depends on the ratio $R = h/s_{\Delta V}^{\text{min}}$ between these two parameters and in both cases we found $R \approx 10^{-4}$ (Lombardi et al., 2012). For instance, increasing the threshold value $s_{\Delta V}^{\text{min}}$ while keeping $h$ fixed, clearly produces a major shift in the data (SI, Fig.1). In order to recover a good agreement with the experimental curves, we need to increase $h$ in such a way $R \approx 10^{-4}$ (SI, Fig.1). We then conclude that $h$ and $s_{\Delta V}^{\text{min}}$ drive two competing factors, whose balance results in the waiting time distributions measured experimentally. The threshold $s_{\Delta V}^{\text{min}}$ basically controls the amount of excitatory inputs neurons receive between successive avalanches in the up-state. Indeed the stimulation has a random value in an interval whose size depends on $s_{\Delta V}^{\text{min}}$ in such a way the larger is $s_{\Delta V}^{\text{min}}$ the larger that interval and the stronger the stimulation (see Material & Methods). By means of $s_{\Delta V}^{\text{min}}$, we then control
the excitation in the system. On the other hand, the parameter $h$, controlling the hyperpolarization locally experienced by neurons after up states, represents a sort of dynamical inhibition. Therefore $R$ has to be interpreted as the ratio between dynamical excitation and inhibition in the network (Lombardi et al., 2012).

Indeed altering $R$, not only leads up to a major shift of numerical waiting times from experimental ones (SI, Fig.1), but also alters the scaling behavior in the size distributions, a fact which is related to pathological experimental conditions (Beggs and Plenz, 2003; Shew et al., 2009). Reducing inhibition using the $GABA_A$-receptor antagonist picrotoxin (PTX) (see Materials & Methods), we observe an excess of large avalanches and a decrease in the value of the exponent $\alpha$ (Fig 4,(a)). As shown in Fig.4,(b) numerically we find the same behavior when we increase the threshold value $s_{\Delta V}$, indeed confirming that $s_{\Delta V}^{\text{min}}$ controls the excitation in the system.

Tuning either of the parameters leads to the optimal value of $R$, namely to an optimal balance between excitation and inhibition. The abrupt transition between the up and down-state, controlled by a threshold mechanism, originates the minimum observed experimentally. However, this mechanism alone is not sufficient to reproduce the non monotonic behavior. Indeed, simulations of up-states and down-states only in terms of different drives, without the dependence of the single neuron state on up and down-states (see Material & Methods), provide a monotonic behavior (Lombardi et al., 2012).

### 3.2 UNIVERSALITY IN THE TEMPORAL OCCURRENCE OF AVALANCHES

Recent results (Ribeiro et al., 2010) on freely behaving rats provide a monotonic waiting time distribution uniquely controlled by the average occurrence rate, whereas anaesthetized rats do not exhibit universal scaling features. Here we show that the different behavior with respect to alive rats can be attributed to the significant separation in characteristic temporal scales between up and down-states. Indeed, in freely behaving rats one does not observe alternation between these two states and the dynamics is characterized by a single temporal scale.

First, we apply the procedure described in (Corral, 2004; Ribeiro et al., 2010) to the experimental and numerical distributions in Fig.3. In Fig.5 we show the distribution $P(\Delta t)$ evaluated restricting the analysis to avalanches with size $s$ above a given threshold $s_c$. For each value $s_c$, we obtain a new curve with a slightly different behavior. As reported for anaesthetized rats, rescaling these distributions by a
Figure 5. Experimental waiting time distributions for different values of the threshold $s_c$ on avalanche size. (a) Experimental curve in Fig. 3, lower panel; (b) experimental curve in Fig. 3, upper panel.

single parameter, namely the mean avalanche rate $r = 1/\langle \Delta t \rangle$, does not lead to a collapse of the curves onto a single one (SI, Fig. 3). Furthermore we notice that in many cases one or more peaks appear on the time scales characterized by the power law regime in the original distribution (Fig. 5, c); SI, Fig. 2), which clearly indicates that multiple time scales characterize avalanche dynamics. We next apply the same procedure separately to the two states, namely we rescale the distribution in the up state by $r_{up} = \langle \Delta t \rangle_{up}$ and the one in the down-states by $r_{dw} = \langle \Delta t \rangle_{dw}$. In this case we observe a collapse onto two distinct universal curves: A power law for the up-state (Fig. 6, a), c)) and a distribution peaked around a characteristic value for the down-state (Fig. 6, b), d)).

Finally we repeat the same analysis for all the other samples in Fig. 1a. As shown in Fig. 8, down-states exhibit universal features in each sample, thus implying that their waiting time distribution is uniquely controlled by the mean rate $r_{dw}$. On the other hand, the peaks emerging at short $\Delta t$ under the thresholding procedure, implies that avalanche occurrence in the up-state is not always solely controlled by $r_{up}$. As a consequence, rescaling by $r_{up}$ does not lead to a good data collapse in the up-state of each of the analyzed samples (Fig. 7).

This result shows that avalanche activity in cortex slice cultures, as well as in those systems alternating up and down-state, can exhibit universal scaling features provided that the different time scales are taken into account, thus confirming that the lack of universality reported for anaesthetized rats has to be attributed to the slow oscillations characterizing their spontaneous activity (Steriade et al., 1993). It is worth to notice here, that the same rescaling works for the waiting time distributions in the up-states of different samples (Fig. 1, b), whereas it does not for down-states of different samples (Fig. 1, c). Therefore, while the power law appears to be a property of up-states in all samples, down states exhibit sample dependent features.

4 DISCUSSION

4.1 UP-DOWN STATE DYNAMICS, CRITICALITY AND TEMPORAL ORGANIZATION OF NEURONAL AVALANCHES

Several experimental evidences suggest that the brain behaves as a system acting at a critical point. This statement implies that the collective behavior of the network is more complex than the functioning of the single components. Moreover, the emergence of self-organized neuronal activity, with the absence of a characteristic scale in the response, unveils similarities with other natural phenomena exhibiting scale free behavior, as earthquakes or solar flares. For a wide class of these phenomena, self-organized criticality
(Bak, 1996), has indeed become a successful interpretive scheme. However, it is important to stress that the observation of a scale-free response is not a sufficient indication for the existence of temporal correlations among events. For instance, the waiting time distribution for the original sand pile model is a simple exponential (Sanchez et al., 2002), since avalanches are temporally uncorrelated.

A number of natural stochastic phenomena characterized by temporal correlations and clustering, provide similar non-exponential distributions, all with a monotonic functional behavior. Our data on cortex slice cultures, which are characterized by avalanche critical behavior (Plenz and Chialvo, 2009), exhibit a non-monotonic waiting time distribution. Our model, inspired by self-organized criticality, is able to capture this complex non monotonic behavior, exhibiting the same universal features found experimentally. Avalanches are temporally correlated in the up-state, whereas down-state are long term recovery periods where memory of past activity is erased. The model suggests that the crucial feature of this temporal evolution is the different single neuron behavior in the two phases, namely the ability to oscillate between a very depolarized and hyperpolarized state. The good agreement with experimental data indicates that the transition from an up-state to a down-state has a high degree of synchronization, whereas the onset of up-states is usually more gradual (J. Staley et al., 1998). Moreover it shows that alternation between up and down-states is the expression of an homeostatic regulation which, during a burst, is

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**Figure 6.** Distributions of waiting times in the up (a,c) and down-state (b,d) for numerical and experimental data in Fig.3 and different thresholds $s_c$ on avalanche size. (a) Distributions after rescaling by the mean rate in the up-state (Fig.3, lower panel). Numerical data are shifted to the left. (b) Distributions after rescaling by the mean rate in the down-state (Fig.3, lower panel). Numerical data are shifted to the left. (c) Distributions after rescaling by the mean rate in the up-state (Fig.3, upper panel). Numerical data are shifted to the left. (d) Distributions after rescaling by the mean rate in the down-state (Fig.3, upper panel). Numerical data are shifted to the left. The dashed line represents a power law with exponent -2.2.
activated to control the excitability of the system and avoid pathological behavior, driving it into the down-state. Network mechanisms in the up-state, where neurons mutually sustain their spiking activity, act as a form of short-term memory, which give rise to the initial power law regime in the waiting time distribution, a clear sign of temporal correlations between avalanches occurring close in time. Conversely, in the down-state, the system slowly goes back to the active state, with no memory of past activity. The optimal agreement between numerical and experimental data depends on the balance between excitation and inhibition in the system, controlled by a single parameter. We find that avalanche size and duration distributions also reproduce the experimental scaling behavior for the parameter value giving an optimal agreement with the experimentally measured waiting time distributions. Hence our model suggests that the critical state realizes the correct balance between excitation and inhibition slowly alternating up and down states.

### 4.2 Universal Scaling Features

Recently it has been shown that (Ribeiro et al., 2010) for freely behaving rats the waiting time distribution is monotonic and uniquely controlled by the average occurrence rate. However their avalanche size distributions exhibit a lognormal rather than power law behavior. Anaesthetized rats, conversely, do not exhibit universal scaling for the waiting time distribution, but the distributions of avalanche sizes are consistent with a power law behavior. As in anaesthetized rats, we find a power law for the size and no universal scaling for the waiting time distributions, which in our case are non-monotonic.

The different behavior between anaesthetized and freely behaving rats, as well as between cultures and alive rats, has to be attributed to the different temporal scales governing spontaneous activity in slice cultures and anaesthetized rats. Indeed numerical and experimental results show that the waiting time distribution for the down-state is uniquely controlled by the mean rate \( r_{dw} \). On the other hand, the
structure of up-states is more complex: By imposing different size thresholds we enlighten that bursty periods are made of bursts within bursts, as indicated by the appearance of more minima at short $\Delta t$. This result suggests that several time scales characterize up-states. Multiplicity of characteristic times is often observed in the dynamics of complex systems, where different temporal scales are associated to the relaxation of different spatial regions or structures. For instance, their existence is a well established property in glassy materials, polymers or gelling systems, where they originate from the relaxation of complex structures at different mesoscopic scales. As a consequence, avalanche occurrence at short time scales is in general controlled by more than one parameter. However, a power law behavior with an exponent $\mu \simeq -2$ appears to be a universal property of waiting time distributions across the analyzed samples.

**DISCLOSURE/CONFLICT-OF-INTEREST STATEMENT**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figure 8. Experimental waiting time distributions in the down-states for different samples and different thresholds $s_c$ on avalanche size. Distributions are rescaled by the mean avalanche rate $r_{dw}$. A good data collapse is observed in all analyzed samples, indicating that distributions are solely controlled by the mean rate $r_{dw}$.
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